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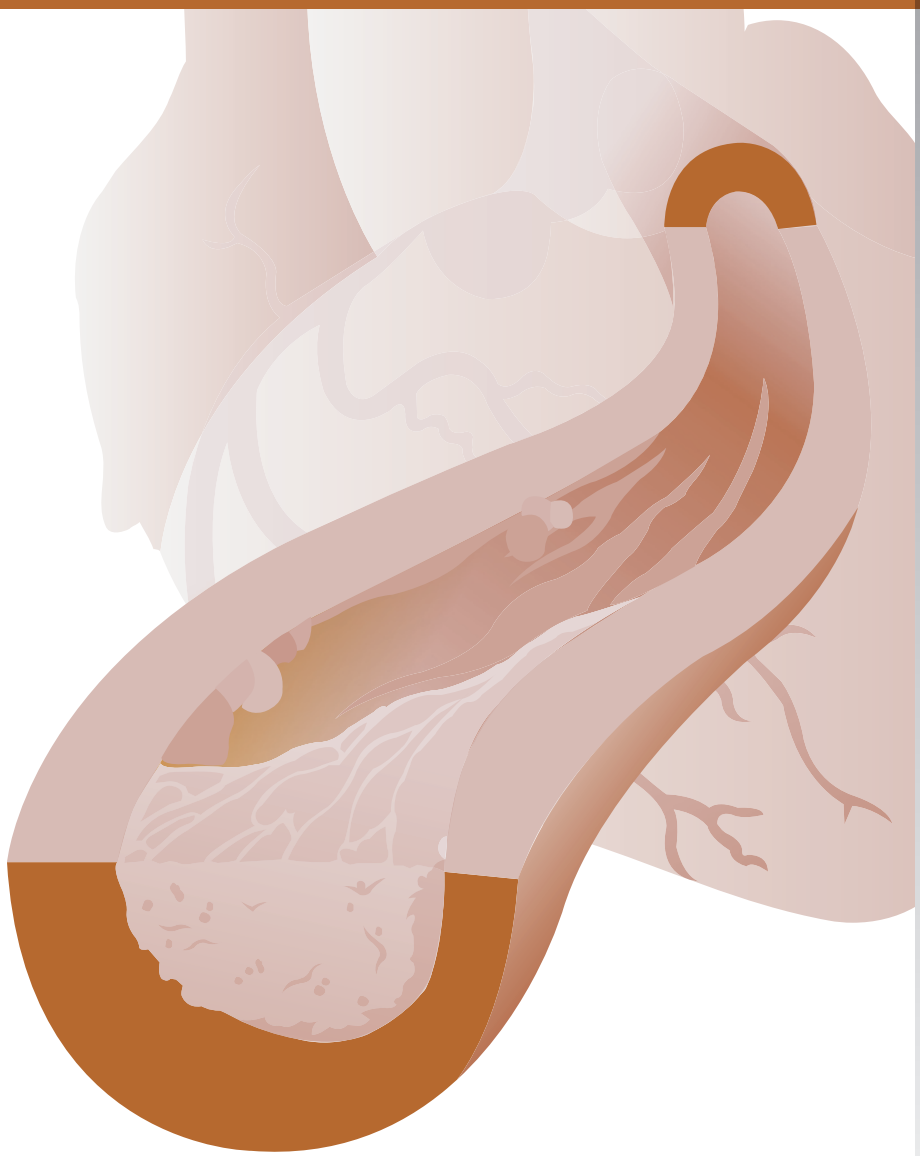

DYSLIPIDEMIA

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Dyslipidemia

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FOREWORD

Recent years have witnessed an explosion of knowledge in almost all the fields of medicine. Developments in one medical arena often have a significant impact on other disciplines.

Patients often have several coexisting conditions; hence, knowledge of diseases not directly related to one's area of expertise has assumed considerable importance.

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DYSLIPIDEMIA

INTRODUCTION

Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction and deficiency. They may manifest as one or more of the following: elevated total cholesterol, low-density lipoprotein cholesterol (LDL), and triglyceride levels or as decreased high-density lipoprotein cholesterol (HDL) level.

Dyslipidemia is closely associated with atherosclerosis and is a major causal factor in the development of ischemic diseases. Ischemic cardiovascular and cerebrovascular events are leading causes of morbidity and mortality. Knowledge of pathophysiology of dyslipidemia has grown dramatically in the last few years, leading to effective treatment strategies.

The purpose of this booklet is to update medical professionals on various aspects of dyslipidemia.

October 2005

LIPIDS AND LIPOPROTEINS

Lipids are a chemically diverse group of compounds that are poorly soluble in the aqueous environment of the cell. The main ones being cholesterol, triglyceride and phospholipid.

Cholesterol is essential for growth and viability of cells. It can be obtained from the diet or synthesized *de novo*. The absorption of triglyceride is essentially complete whereas that of cholesterol varies between 30-50%. Endogenous synthesis of cholesterol in the liver is controlled by the rate-limiting step involving the microsomal enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase.

Lipids are transported in plasma as components of lipoprotein complexes. Lipoproteins are spherical complex particles made up of hundreds of lipids and protein molecules. Proteins called apolipoproteins occupy the surface of lipoproteins. These serve as an additional interface between lipid and aqueous environments and play an important role in the regulation of lipid transport and lipoprotein metabolism.

Lipoproteins have been classified on the basis of their densities.

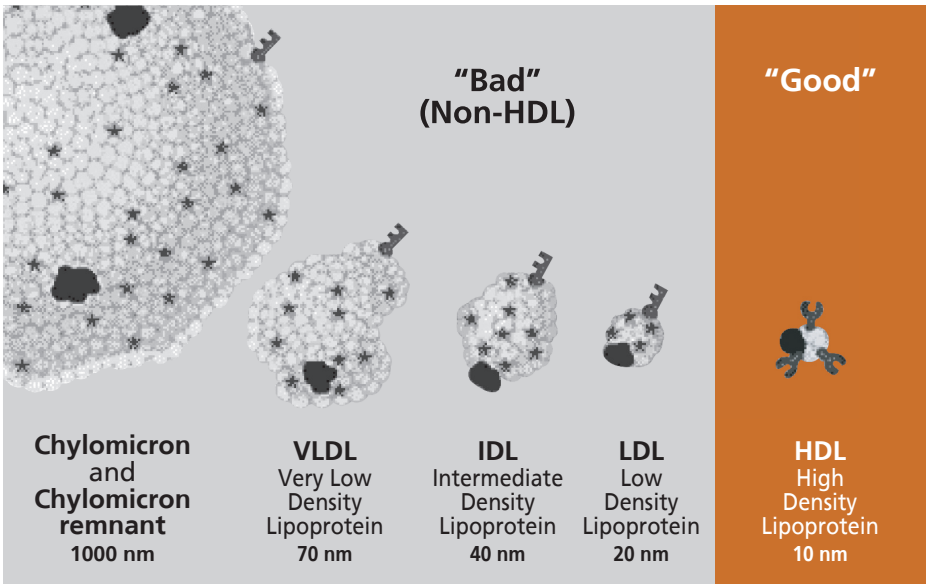
Table 1: Characteristics Of The Major Lipoprotein Classes

Lipoprotein	Density (g/dL)	Diameter (nm)	Lipid (%)		
			TG	Chol	PL
Chylomicrons	0.95	75-1200	80-95	2-7	3-9
VLDL	0.95-1.006	30-80	55-80	5-15	10-20
IDL	1.006-1.019	25-35	20-50	20-40	15-25
LDL	1.019-1.063	18-25	40-50	40-50	20-25
HDL	1.063-1.210	5-12	15-25	15-25	20-30

VLDL- Very Low Density Lipoproteins; IDL-Intermediate Density Lipoproteins; LDL-Low Density Lipoproteins; HDL-High Density Lipoproteins; TG-Triglyceride; Chol-free and esterified cholesterol; PL-Phospholipid
Note - The remaining composition is made up of apoproteins.

DYSLIPIDEMIA

Fig 1: Classification of Lipoproteins



Chylomicrons: These transport dietary triglyceride from the small intestine via the lymph into plasma.

Very Low Density Lipoproteins (VLDL): These carry endogenously synthesized cholesterol and triglycerides.

Low Density Lipoproteins (LDL): These are the principal vehicles for cholesterol transport and are taken up by LDL receptors on hepatocytes and peripheral cells, thus releasing the cholesterol component for cellular use.

High Density Lipoproteins (HDL): These mediate the reverse transport of cholesterol from peripheral tissues to the liver.

An elevated level of lipoproteins, except HDL, is the basis of all dyslipidemias.

LIPID GENERATION AND TRANSPORT

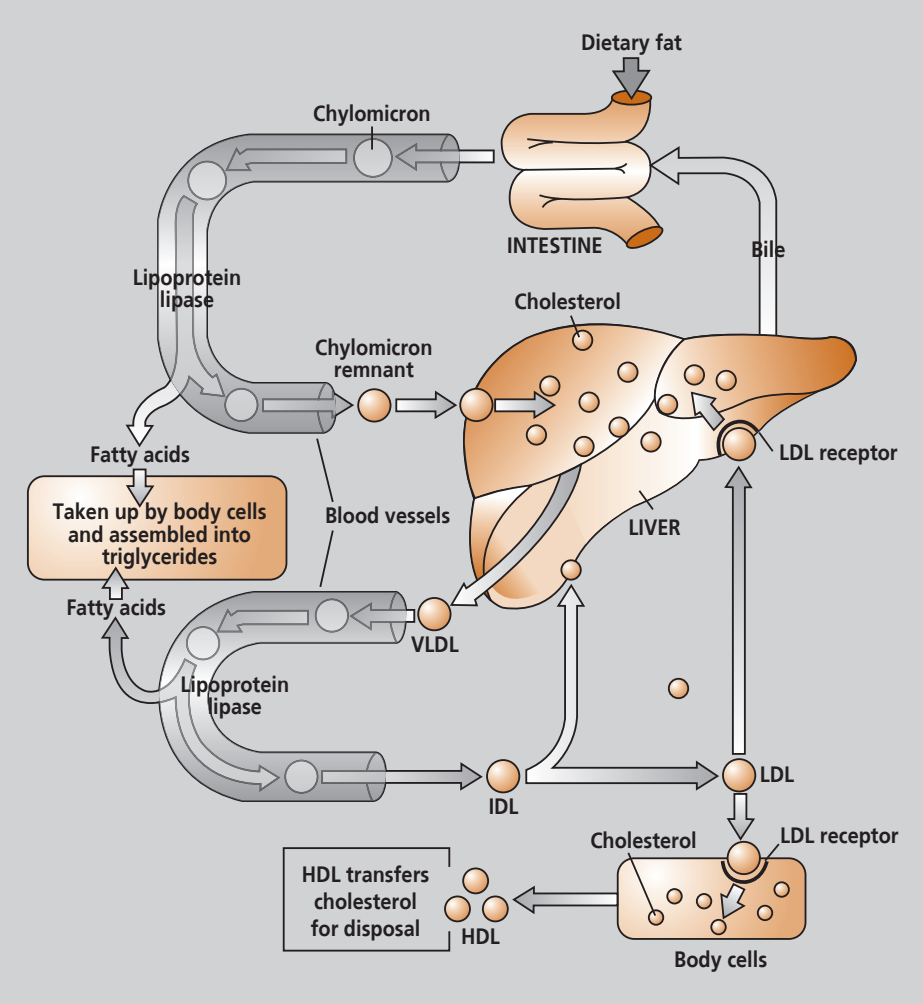
There are three main pathways responsible for the generation and transport of lipids within the body. These pathways include the exogenous pathway, the endogenous pathway, and the pathway of reverse cholesterol transport.

Exogenous (Dietary) Lipid Pathway: Following digestion and absorption of dietary fat, TG and cholesterol are packaged to form chylomicrons in the epithelial cells of the intestines. Chylomicrons circulate through the intestinal lymphatic system. In the blood, circulating chylomicrons interact at the capillaries of adipose tissue and muscle cells releasing TG to the adipose tissue to be stored and made available for the body's energy needs. The enzyme lipoprotein lipase (LPL) hydrolyzes the TG and free-fatty acids are released. Some of the components of the chylomicrons are "repackaged" into other lipoproteins.

Endogenous Pathway: The endogenous pathway involves the liver synthesizing lipoproteins. TG and cholesterol esters are generated by the liver and packaged into VLDL particles and then released into the circulation. VLDL is then processed by LPL in tissues to release fatty acids and glycerol. Once processed by LPL, the VLDL becomes a VLDL remnant. The majority of the VLDL remnants are taken up by the liver via the LDL receptor, and the remaining remnant particles become IDL, a smaller, denser lipoprotein than VLDL. The fate of some of the IDL particles requires them to be reabsorbed by the liver (again by the LDL receptor); however, other IDL particles are hydrolyzed by hepatic-triglyceride lipase to form LDL, a smaller, denser particle than IDL. LDL is the main carrier of circulating cholesterol within the body.

Reverse Cholesterol Transport: Reverse cholesterol transport refers to the process by which cholesterol is removed from the tissues and returned to the liver. HDL is the key lipoprotein involved in reverse cholesterol transport and the transfer of cholesteryl esters between lipoproteins.

Fig 2: **Lipid Synthesis, Metabolism and Transport**



TYPES OF DYSLIPIDEMIA

Primary dyslipidemia: Several monogenic disorders have been defined that lead to different type of dyslipidemias, but for many cases, the etiology is polygenic. These disorders affect plasma lipoprotein levels by overproduction of lipoproteins and/or decreased clearance.

Secondary dyslipidemia: Many medical conditions are associated with mild or even severe dyslipidemia even in the absence of underlying genetic disorder. Table 2 lists the common disorders causing lipid abnormalities.

Table 2: **Secondary Causes of Lipoprotein Abnormalities**

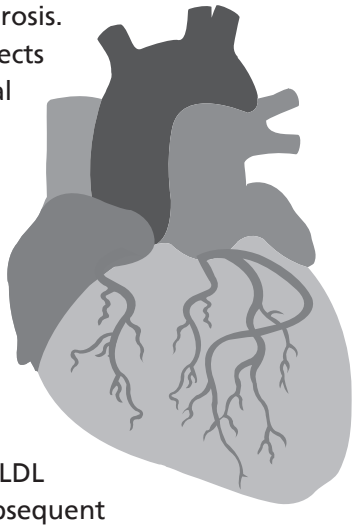
Hypercholesterolemia
Hypothyroidism; Obstructive liver disease; Nephrotic syndrome; Anorexia nervosa; Acute intermittent porphyria; Drugs: progestogens, cyclosporine, thiazides
Hypertriglyceridemia
Obesity; Diabetes mellitus; Pregnancy; Chronic renal failure; Lipodystrophy; Glycogen storage disease; Alcohol; Bypass surgery; Stress; Sepsis; Acute hepatitis; SLE; Monoclonal gammopathy; Drugs: estrogen, beta blockers, glucocorticoids, bile acid-binding resins, thiazides
Low HDL
Type-2 diabetes mellitus, Rheumatoid arthritis, Malnutrition, Obesity, Cigarette smoking, Beta blockers, Anabolic steroids

MANIFESTATIONS OF LIPID ABNORMALITIES

There may be no symptoms associated with dyslipidemia and it may come to notice only during routine health check-up. Person might be obese or have an early onset of chest pain. Sometimes, lipid abnormalities may be diagnosed for the first time after a person suffers a myocardial infarction or stroke. Painless nodules called xanthomas may be seen on tendons, elbows or buttocks. These are due to intra- and extra-cellular deposition of cholesterol.

CONSEQUENCES OF LIPID ABNORMALITIES

Dyslipidemia is a major risk factor for atherosclerosis. Atherosclerosis is a disease process that affects the coronary, cerebral and peripheral arterial circulation.

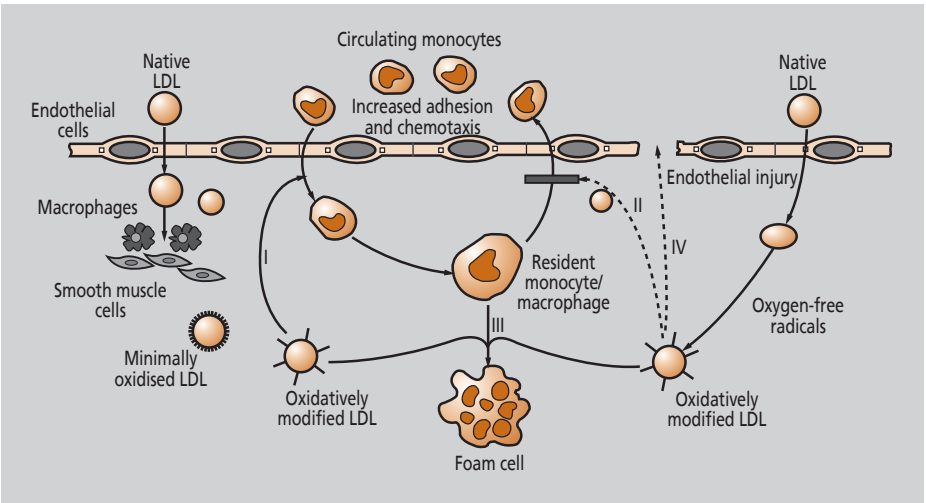


Coronary Heart Disease (CHD)

The etiology of atherosclerosis is multifactorial but the cause-effect relationship between dyslipidemia and atherosclerosis has been shown in many studies and trials.

It has been shown that reducing the plasma LDL cholesterol levels sharply reduces the risk of subsequent clinical CHD in both patients with pre-existing CHD and in patients free of CHD. There is no doubt about the atherogenicity of LDL. Evidence suggests that oxidative modification of LDL within the artery is necessary for mediating its atherogenicity.

Fig 3. Oxidation of Low-Density Lipoprotein



Angiographic studies have shown that intensive cholesterol lowering regimens slow progression of coronary lesions and in some cases, even lead to significant regression of lesions.

While LDL cholesterol is a strong risk factor for coronary artery disease (CAD), it is not only the amount of LDL that is important but also the type of LDL. LDL exists as **small dense LDL** and **large buoyant LDL.** Small dense LDL is more atherogenic or more toxic to the endothelium. It is more likely to enter the vessel wall, become oxidized and trigger the atherosclerotic process. Large buoyant LDL is not as toxic to the blood vessel wall and much less prone to trigger the atherosclerosis development. Small dense LDL is prevalent in diabetic dyslipidemia.

High serum **triglyceride** levels are associated with the risk of developing cardiovascular disease independently of other major measured risk factors. Earlier studies have shown that the association between triglycerides and cardiovascular risk diminishes after adjustment for total cholesterol and, more importantly, HDL cholesterol. However, in a recent study in the Asia-Pacific region, it has been shown that serum triglyceride level is an independent determinant of cardiovascular risk across a broad population group within the Asia-Pacific region. Even a slight increase in the triglyceride level could lead to increased risk of CAD.

Chylomicrons and **VLDL** are not directly atherogenic, probably, because they are too large to penetrate into the artery. However, catabolic products of chylomicrons and VLDL are atherogenic.

Higher plasma levels of **HDL** are associated with lower risk of CHD. It is widely believed that HDL protects against atherosclerosis by facilitating reverse cholesterol transport, that is, the ability of HDL to accept excess cholesterol from tissues and return it to the liver either directly or via other lipoproteins.

Increased risk of CHD has been found in people with increased levels of **Lp (a)**. Lp (a) is a LDL particle to which an additional large protein termed apo (a) is attached.

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An atherogenic lipoprotein pattern, characterized by a predominance of small dense LDL, moderately elevated plasma triglycerides and low HDL levels, is the most powerful risk factor for CAD.

Stroke

Stroke is a term that describes a clinical event caused either by occlusion or hemorrhage in the arterial supply to the central nervous system resulting in tissue infarction. It is one of the most devastating consequences of vascular disease. Atheroma formation is the root of pathogenesis of thrombo-embolic stroke.

Observational studies suggest that dyslipidemia particularly high LDL-C, low HDL-C and high TG are important risk factors for thrombo-embolic stroke.

Peripheral Artery Disease (PAD)

Peripheral artery disease is most commonly a manifestation of systemic atherosclerosis in which the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque. High lipoprotein concentrations are important in the development of PAD. There is growing evidence that atherosclerosis in the peripheral circulation should be considered in the same manner as atherosclerosis in the coronary circulation. Patients with PAD, even in the absence of a history of myocardial infarction or stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with a history of coronary or cerebrovascular disease.

ASSESSMENT OF LIPID PROFILE

Since 1988, the National Cholesterol Education Program (NCEP) has provided guidelines to health professionals so that they can best lower the cholesterol levels and, thereby, reduce the risk of cardiovascular complications and death. The third iteration of the NCEP guidelines, the Adult Treatment Panel III (ATP III), was released in May 2001 and modified in 2004.

According to these guidelines, all adults over the age of 20 should have a 12-hour fasting lipid profile performed every 5 years. Since serum lipids vary from day to day, 2-3 measurements should be done days or weeks apart before initiating therapy.

To properly evaluate and treat the patients, a full cholesterol profile with the major sub-components is needed.

LDL-C: The key measure in the lipid profile is LDL-C. Treatments that reduce LDL-C have been shown to reduce CHD risk by 25% to 45% over 5 years.

Small dense LDL-C: All procedures estimating small dense LDL are time-consuming, labor intensive and expensive, thus restricting the use of small dense LDL as a cardiovascular marker. An easy clinical tool to determine the elevated small dense LDL is the triglycerides/HDL ratio. According to a study in Indians, triglycerides/HDL ratio > 3.0 could serve as a surrogate marker of small dense LDL in Asians.

HDL-C: The concentration of high-density lipoprotein cholesterol (HDL-C) is inversely related to CHD risk; HDL-C level of less than 40 mg/dL is considered a CHD risk factor.

Low HDL-C is often a marker for other risk factors, including increased remnant lipoproteins; obesity; insulin resistance; diabetes; physical inactivity; and genetic disorders.

Triglycerides: Triglyceride levels >200 mg/dL increases the risk of CHD. Very high triglyceride levels (i.e., > 500 mg/dL) indicate the presence of chylomicrons in addition to VLDL particles. Patients with very high triglyceride levels, especially those in whom triglycerides exceed 1,000 mg/dL, are at increased risk for pancreatitis.

The relationship between cholesterol levels and CHD risk is continuous over a broad range, therefore, ATP III adopts the classification of cholesterol levels as shown in table 3.

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Table 3: ATP III Classification of LDL, Total and HDL Cholesterol and Triglycerides (mg/dL)

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

MANAGEMENT OF DYSLIPIDEMIA

The basic principle of cholesterol management is that the intensity of treatment should match the level of CHD risk. Once the fasting lipoprotein profile has been determined and CHD risk factors assessed, a history of clinical CHD or CHD equivalent events should be obtained.

On the basis of CHD, CHD risk equivalents and major risk factors (other than LDL cholesterol), ATP III has identified risk categories that modify the goals and modalities of LDL-lowering therapy. LDL cholesterol is not

counted among the risk factors used to classify in the risk categories because the purpose is to modify the treatment of LDL cholesterol based on the category.

Once the patient has been placed in the appropriate category, the treatment goal and the approach to achieve that goal should be decided.

There is a significant correlation between LDL lowering and reduction in coronary events, including death. Therefore ATP III has recognized that LDL lowering is the primary surrogate end point toward reductions in cardiovascular events and mortality.

The recommended LDL-C goals for the risk categories and the cutpoints at which therapeutic lifestyle changes (TLC) and drug therapy should be initiated are shown in table 4.

Table 4: ATP III LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories and Proposed Modifications (in brackets) Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-year risk > 20%)	< 100 mg/dL (optional goal: < 70 mg/dL)	≥ 100 mg/dL	≥ 100 mg/dL (< 100 mg/dL: consider drug options)
Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)	< 130 mg/dL (optional goal: < 100 mg/dL)	≥ 130 mg/dL	≥ 130 mg/dL (100-129 mg/dL; consider drug options)
Moderate risk: 2+ risk factors (10-year risk < 10%)	< 130 mg/dL	≥ 130 mg/dL	≥ 160 mg/dL
Lower risk: 0-1 risk factor	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

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Note:

- CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

- CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery]), diabetes, and 2 + risk factors with 10-year risk for hard CHD > 20%.

  Risk factors include cigarette smoking, hypertension (BP $\geq$ 140/90 mmHg or on antihypertensive medication), low HDL cholesterol (< 40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men $\geq$ 45 years; women $\geq$ 55 years).

- Almost all people with zero or 1 risk factor have a 10-year risk < 10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

- Very high risk favors the optional LDL-C goal of < 70 mg/dL, and in patients with high triglycerides, non-HDL-C < 100 mg/dL.

- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g. obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

- When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

- If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

Therapeutic Lifestyle Changes (TLC)

ATP III has recommended a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated therapeutic lifestyle changes (TLC). Its essential features are:

- Reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/day)
- Therapeutic options for enhancing LDL lowering such as plant stanols sterols and increased viscous fiber
- Weight reduction
- Increased physical activity

In most patients, TLC is implemented before initiating drug therapy. However, in high-risk patients, drug therapy may be initiated simultaneously with TLC. If the patient does not achieve the LDL-C goal at 12 weeks after starting the TLC program, then drug therapy may be started.

Drug Therapy

The goal of lipid modifying drug therapy is to lower the LDL-C level to the recommended level. When drugs are prescribed, attention to TLC should always be maintained and reinforced.

Currently available drug classes that affect lipoprotein metabolism are listed in table 5.

Table 5: Drugs Affecting Lipoprotein Metabolism

Drug Class	Mechanisms	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG-CoA reductase inhibitors (Statins) Simvastatin (Simcard) * Atorvastatin (Atorlip) * Rosuvastatin Lovastatin Pravastatin Fluvastatin	↓ Cholesterol synthesis caused by partial inhibition of HMG-CoA reductase	LDL ↓ 18-55% HDL ↑ 5-15% TG ↓ 7-30%	Myopathy Increased liver enzymes	**Absolute:** • Active or chronic liver disease **Relative:** • Pregnancy and lactation
Fibric acids (Fibrates) Fenofibrate (Fenolip)* Bezafibrate Clofibrate Gemfibrozil	↑ activity of lipoprotein lipase; ↓ release of free fatty acids from peripheral adipocytes	LDL (may be increased in patients with high TG) ↓ 5-20% HDL ↑ 10-20% TG ↓ 20-50%	Dyspepsia Gallstones Myopathy	**Absolute:** • Severe renal disease • Severe hepatic disease
Nicotinic acid (Niacin)	↓ production of VLDL; ↓ mobilisation of free fatty acids from peripheral adipocytes	LDL ↓5-25% HDL ↑15-35% TG ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	**Absolute:** • Chronic liver disease • Severe gout **Relative:** • Diabetes • Hyperuricemia • Peptic ulcer disease
Cholesterol Absorption Inhibitors (CAI) Ezetimibe	Selective cholesterol absorption inhibition by blocking a sterol transporter that moves cholesterol into the wall of the small intestine	LDL ↓17% HDL-minimal change TG-minimal change	Angioedema Headache	Hypersensitivity
Bile acid Sequestrants (BAR) Cholestyramine Colestipol (Not available in India)	↓ intrahepatic cholesterol by nonspecific binding of bile acids; ↑ activity of LDL receptors	LDL ↓15-30% HDL ↑3-5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	**Absolute:** • Dysbetalipo-proteinemia • TG > 400 mg/dL

Symbols: ↑ increase; ↓ decrease, * manufactured by Cipla

1. HMG-CoA reductase inhibitors (Statins): Statins are the most powerful drugs for lowering LDL cholesterol. They are considered as the first line of treatment for dyslipidemia.

Statins are competitive inhibitors of HMG-CoA reductase, the rate limiting step in cholesterol synthesis. In response to decreased cholesterol production, the number and activity of LDL receptors are upregulated, stimulating removal of circulating LDL. Intermediate density and very low-density lipoprotein (VLDL) are removed as well, contributing to lowering triglyceride-rich lipoprotein levels. Statins also have modest effect on HDL levels.

This class of drugs has been shown to reduce total mortality, major coronary events, progression of atherosclerosis, CHD mortality, need for revascularisation, and incidence of stroke in large scale, randomized clinical trials of CHD subjects and those at high risk of CHD.

Statin therapy has also been shown to substantially reduce the increased cardiac event risk found in patients of arterial inflammation who undergo coronary stenting.

Cholesterol-independent effects of statins have been described most extensively in relation to effects of statins in restoring endothelial function that may promote plaque stability through modulation of macrophage activation, immunological effects and antiplatelet and antithrombotic actions.

Evidence suggests that these drugs are safe and generally well tolerated. The two main side effects are hepatic dysfunction and myopathy. Both are relatively uncommon and appear to be associated with high plasma drug levels due to high dosage or drug-drug interactions.

2. Fibric acid derivatives (Fibrates): The fibrates are PPAR-α ligands, which improve plasma lipoprotein catabolism, primarily by effects on hepatocytes. Once activated, PPAR-α forms heterodimers with the retinoic acid receptor, activating numerous genes, including lipoprotein lipase, apo A1, apo A2 and genes involved in fatty acid oxidation. The primary clinical effect is a reduction in plasma TG of 30-40% and an increase in HDL-C of 8-15%. Relatively minor changes in LDL-C concentrations occur although newer agents such as fenofibrate may reduce LDL-C by 15-20%. There is a phenotypic change in

LDL with reduced synthesis of small dense atherogenic LDL particles as well as reduced synthesis of atherogenic TG-rich lipoprotein particles.

In addition to favourable effects on lipid profile, fibrates reduce the risk of atherosclerosis and coronary heart disease by reducing plasma fibrinogen and uric acid levels. Increased levels of fibrinogen are associated with an increased risk of atherosclerosis and coronary heart disease. Hyperuricaemia is common in patients with dyslipidemia and has been implicated as a possible risk factor for coronary heart disease.

Fibrates are generally well tolerated. The most common complaints are pertaining to the gastrointestinal system.

3. **Nicotinic acid (Niacin):** This agent decreases LDL, triglycerides and lipoprotein (a), and increases HDL levels. Unfortunately, intolerance due to flushing limits its use. Tolerance to this adverse effect does appear to develop with continued therapy. Because of its ability to affect the entire lipid profile, niacin is an attractive treatment for mixed dyslipidemia, especially in combination with other agents.

4. **Selective cholesterol absorption inhibitors:** Selective cholesterol absorption inhibitors are thought to act by interfering with the cholesterol transport in the intestinal brush border, thereby blocking absorption of dietary and biliary cholesterol. Ezetimibe is a recently approved drug falling in this category of drugs.

Studies have shown that ezetimibe reduces LDL levels by 17% as monotherapy, and further lowers LDL level by 25% when added to ongoing statin therapy. As monotherapy, ezetimibe has only minimal effects on HDL and triglyceride levels, but when combined with a statin it appears to further increase HDL levels and lower triglyceride levels by an additional 14%.

5. **Bile acid sequestrants (BAR):** These agents lower LDL and may mildly increase triglyceride levels. The possibility of increasing triglyceride levels is a concern in patients with high or borderline-high levels. The agents work by sequestering bile acids in the intestine, preventing their reabsorption and interrupting their enterohepatic circulation. Since systemic absorption is limited, serious adverse effects are rare.

6. Other Therapies: Other lipid lowering agents are stanol esters and omega-3 fatty acids. Patients with severe hyperlipidemia may require lipid apheresis.

COMBINATION THERAPY

Although statins remain first-line therapy for most patients to lower LDL, combination therapy is the next logical step in achieving goals in patients with mixed dyslipidemia or elevated LDL despite statin therapy. At least 30% of patients may need combination therapy to normalise their lipid levels. For patients with high LDL, low HDL, and high triglyceride levels, the combination most often used is a statin plus fibrate or niacin.

Despite the small but added risk of hepatotoxicity or myositis, use of a statin in combination with either fibrate or niacin is both safe and effective in achieving goal LDL levels and improving HDL and triglyceride levels, particularly for patients with CHD or at equivalent risk. At low doses of statins, the benefits overweigh the risk. Fenofibrate is preferred over gemfibrozil when used in combination with statins due to lesser risk of side effects.

For patients at highest risk of a CHD event, it is desirable to have another drug that can be used safely in combination with statins to achieve target LDL levels. Ezetimibe may have a role in these cases as there appears to be no significant increase in side effects compared with placebo.

Some of the combinations available are:
Atorvastatin + Ezetimibe **(Atorlip EZ)**
Atorvastatin + Fenofibrate **(Atorlip F)**

SPECIFIC DYSLIPIDEMIAS

Hypertriglyceridemia: Elevated triglycerides are an independent risk factor for CHD. Causative factors associated with hypertriglyceridemia include:

- Obesity
- Physical inactivity
- Cigarette smoking

- Excess alcohol intake
- High carbohydrate diet
- Certain diseases (type 2 diabetes, chronic renal failure, nephrotic syndrome)
- Certain drugs (e.g. corticosteroids, estrogens etc.)
- Genetic disorders

Whereas reduction of LDL cholesterol is the primary target of treatment to reduce the risk of CHD, reduction of non-HDL cholesterol (total cholesterol minus HDL cholesterol) is considered as a secondary target of therapy in persons with elevated triglyceride levels. Non-HDL cholesterol represents cholesterol carried on all the potentially proatherogenic particles. Its derivation does not require lipid profile to be done in the fasting state, which is not the case with triglycerides.

The goal for non-HDL cholesterol is set at 30 mg/dL higher than that for LDL cholesterol.

Table 6: Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL-C Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD > 20%)	< 100	< 130
Multiple (2+) Risk Factors and 10-year risk ≤ 20%	< 130	< 160
0-1 Risk Factor	< 160	< 190

Dietary modifications and exercise remain the initial therapeutic approaches; however, pharmacological intervention may be required in many patients with hypertriglyceridemia. Drugs used to manage hypertriglyceridemia are fibrates, nicotinic acid (niacin) and to a lesser extent, statins. Fibrates have a higher potency, reducing the TG level by 20-55%. Niacin, the other drug used has to be given in very high doses, which can produce intolerable side-effects, and makes compliance a problem.

Low HDL-C: Low HDL-C is also a strong independent predictor of CHD. It has several causes, many of which are associated with insulin resistance.

- Obesity
- Type 2 Diabetes mellitus
- High carbohydrate diet
- Physical inactivity
- Cigarette smoking
- Certain drugs (beta-blockers, anabolic steroids, progestational agents).

Fibrates and nicotinic acid are the drugs available for raising HDL cholesterol. However, treatment for isolated low HDL cholesterol is reserved for persons with CHD and CHD equivalent risks.

Dyslipidemia and Diabetes: Insulin deficiency and hyperglycemia in Type-1 diabetes mellitus produces lipid abnormalities, which can be usually corrected with insulin therapy.

Type-2 diabetes mellitus is associated with abnormal lipid metabolism, even when glycemic control is good and nephropathy absent. Diabetic patients tend to have higher triglyceride, lower high-density lipoprotein cholesterol (HDL), and similar low-density lipoprotein cholesterol (LDL) levels compared with nondiabetic patients. However, diabetic patients tend to have a higher concentration of small dense LDL particles, which are associated with higher CHD risk. In diabetics, the relative risk of CHD is greatly increased at every level of cholesterol. As per American Diabetes Association (ADA), combination therapy may be often necessary to control all lipid abnormalities in patients with diabetes.

Both ADA and NCEP ATP III guidelines recommend an aggressive treatment programme for dyslipidemia in patients with diabetes. Table 7 shows the lipoprotein goals in diabetic patients.

Table 7: **ADA Guidelines for Lipoprotein Goals and Therapy In Diabetic Patients**

Lipoprotein Goals	Level (mg/dL)
LDL	<100 (< 70 mg/dL in patients with CVD)
HDL -Men -Women	>40 >50
Triglycerides	<150

DYSLIPIDEMIA

Nonpharmacologic interventions (diet and exercise) are first-line therapies and are used with pharmacologic therapy when necessary. Lowering LDL levels is the first priority in treating diabetic dyslipidemia. Therefore, statins are the drugs of first choice for lipid lowering actions and reducing risk of CAD in these patients. For elevated triglyceride levels, hyperglycemia must be controlled first.

However, current therapeutic use of statins as monotherapy still leaves many patients with mixed atherogenic dyslipidemia at high risk for coronary events. A combination statin/fibrate therapy may be often necessary to control all lipid abnormalities in patients with diabetes. Fibrates provide additional important benefits, particularly on triglyceride and HDL-C levels. The combined therapy concentrates on all the components of the mixed dyslipidemia that often occurs in persons with diabetes.

Current evidence and guidelines mandate that diabetic dyslipidemia be treated aggressively, and lipid goals can be achieved in most patients with diabetes when all available drugs are considered and, if necessary, used in combination.

Dyslipidemia and Metabolic Syndrome: Patients with metabolic syndrome have atherogenic dyslipidemia characterised by borderline-high to high triglyceride levels, low HDL-C, and increased small dense LDL. They also have other risk factors for CHD, eg. excess body fat distributed mostly around the abdomen, insulin resistance with impaired fasting glucose or diabetes, elevated blood pressure, a proinflammatory state, and a prothrombotic state.

In patients with the metabolic syndrome, any elevation in the LDL-C level accentuates their CHD risk.

Weight loss and increased physical activity are the two primary interventions used in treating the metabolic syndrome but drug therapy may be required in some cases.

Statins are the first-line therapy for all patients whose LDL-C levels are above goal. Because statins have lesser effects on TG and HDL-C, monotherapy may not be sufficient to correct lipid abnormalities of patients with the

metabolic syndrome. Consequently, combination therapy may be necessary to reduce CAD risk in these patients. Both fibrates and niacin can be used in combination with statins to correct the atherogenic dyslipidemia associated with metabolic syndrome. Fibrates also improve other features of metabolic syndrome viz. hyperinsulinemia and hypertension.

Dyslipidemia and Chronic Renal Disease: Cardiovascular disease is the leading cause of death for patients with chronic renal disease. Many factors contribute to the increased cardiovascular morbidity and mortality in patients with renal disease, one of the major ones being dyslipidemia. While the nature of dyslipidemia differs in patients with different types of renal disease, the typical pattern of lipoprotein abnormality predisposes to cardiovascular disease.

There is a growing body of evidence suggesting that the presence of dyslipidemia accelerates renal deterioration.

Routine cholesterol screening of patients with renal disease should be done. Initiation of dietary modification and dyslipidemia therapy should be a part of the management. Statins are generally the first agent of choice for lipid regulation in renal disease patients.

DYSLIPIDEMIA IN SPECIAL POPULATIONS

Elderly: Most new CHD events and coronary deaths occur in older persons. Lipid lowering agents may not delay eventual mortality in this population. However, morbidity and the quality of life can be improved. TLC has been suggested as the first line of therapy for primary prevention of CHD in the elderly. However, LDL lowering drugs can be considered in older persons who are at higher risk. Statins are the preferred first-line therapy for dyslipidemia in the elderly with established CHD.

Women: In women, onset of CHD is delayed by some 10-15 years as compared to men. It was believed that the gender difference in CHD was due to protective effect of estrogen in women. Recent evidence doubts the usefulness of hormone replacement therapy to reduce CHD risk in postmenopausal women. Women should be treated similar to men,

however the late onset of CHD in women should be considered while deciding therapy for dyslipidemia.

Children and Adolescents: The most common causes of dyslipidemias in children are genetic disorders, obesity and adverse diet. Total cholesterol levels are generally 40 mg/dL higher in adults than in childhood. Lipid levels should be measured initially in children only in the presence of a strong family history. Resins are generally recommended as the first-choice treatment in this age group. Statins can also be considered.

CONCLUSION

Dyslipidemia is one of the most important modifiable risk factors for CHD. Therefore, determination of cause of dyslipidemia, evaluation of the individual patient's health and risk status, focus on treatment goals and a clear understanding of the mechanism and effects of lipid lowering agents are necessary. Although LDL levels are considered as the primary goal in the management of dyslipidemia, evidence suggests that HDL and triglyceride levels are also associated with coronary risk and should not be ignored. If desired levels cannot be reached with monotherapy, then combination therapy should be considered.

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