Dyslipidemia

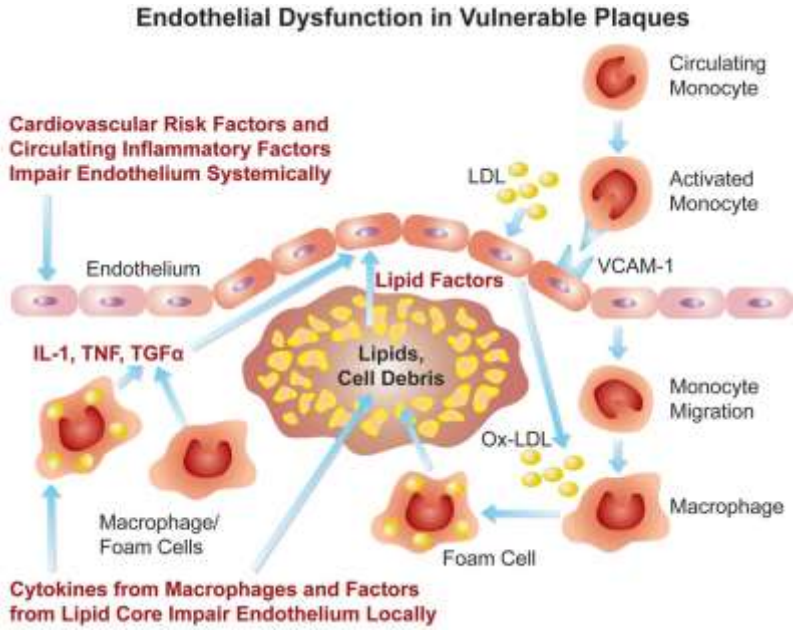
The term hyperlipidemia, which was formerly used to describe disorders of lipoprotein metabolism, is inappropriate. It is more appropriate to use the term dyslipidemia, which encompasses both abnormally high levels of specific lipoproteins, for example, LDL-C, and abnormally low levels of other lipoproteins, for example, HDL-C (1).
Dyslipidemia is defined as elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides; a low high-density lipoprotein (HDL) cholesterol; or a combination of these abnormalities. Abnormalities of plasma lipids can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease (2).

Epidemiology

Lipid and lipoprotein concentrations vary among different populations, with countries consuming a Western type of diet generally having higher TC and LDL-C levels than those where regular consumption of saturated fat is low (1). TC levels tend to increase with age (1). The prevalence of CHD in women is ultimately similar to that in men; it is just displaced by about 10 years. Whereas men begin to experience CHD events in their 50s and 60s, women experience it in their 60s and 70s. Eventually, CHD causes nearly as many deaths in women as it does in men (3).

Pathophysiology of atherosclerosis

Atherosclerosis is a low-grade inflammatory response due to injury of the vascular endothelium induced by lipoprotein retention (specifically LDLc (2)) and oxidation in the arterial wall (4).
Lipoproteins accumulate within intima of blood vessel wall forming initial lesion, the fatty streak (4). Once in the artery wall, LDL is chemically modified through oxidation and nonenzymatic glycation (2). Oxidized LDL cause an increased expression of cell-adhesion molecules on vascular endothelial cells leading to recruitment of monocytes into the intima (4). These monocytes then become transformed into macrophages that accelerate LDL oxidation (2).
The macrophages continue to accumulate lipoproteins and ultimately develop into lipid-laden foam cells. Accumulation of foam cells leads to formation of a lipid-rich core, which marks the transition to a more complicated atherosclerotic plaque (4).
Oxidized LDL provokes an inflammatory response mediated by a number of chemoattractants and cytokines (e.g., monocyte colony-stimulating factor, intercellular adhesion molecule, platelet-derived growth factor, transforming growth factors, interleukin- 1, and interleukin-6) (2).
Repeated injury and repair within an atherosclerotic plaque eventually lead to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells, such as T lymphocytes. Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis (2).



(Ref: 6)

In examining the coronary angiogram of a patient, evidence of stenosis (narrowing of the lumen) indicates the presence of older, more advanced lesions. When these lesions are seen, other lesions distal to the narrowing are likely to be present. They are younger and more susceptible to erosion or rupture, which can cause a thrombosis. In fact, the culprit lesion that results in an MI is usually not at the site of the greatest stenosis, but distal to it (3).

Lipid transport and lipoprotein metabolism

Cholesterol is an essential substance manufactured by most cells in the body. Cholesterol is used to maintain cell wall integrity and for the biosynthesis of **bile acids** and steroid hormones. Other major lipids in our body are triglycerides and phospholipids (4).
Cholesterol, triglycerides, and phospholipids are transported in the bloodstream as complexes of lipids and proteins known as lipoproteins (large carrier proteins) (2) because they are not readily soluble in serum and are rendered miscible by incorporation into lipoproteins (1).
These lipoproteins contain an oily inner lipid core made up of cholesterol esters and TGs and an outer hydrophilic coat made up of phospholipids and unesterified cholesterol. The outer coat also contains at least one protein (apolipoproteins), which provides the ligand for interaction with receptors on cell surfaces, acts as cofactors for various enzymes, and adds structural integrity (3).
There are six main classes of lipoproteins: chylomicrons, chylomicron remnants, very low-density lipoproteins (VLDL-C), intermediate-density lipoproteins (IDL-C), low-density lipoproteins (LDL-C) and high-density lipoproteins (HDL-C) (1).
Each lipoprotein has various proteins called apolipoproteins (Apos) embedded on the surface (4), of which apoproteins A-I, E, C and B are per-haps the most important. Apoprotein B exists in two forms: B-48, which is present in chylomicrons and associated with the transport of ingested lipids, and B-100, which is found in

endogenously secreted VLDL-C and associated with the transport of lipids from the liver (1).
Dietary cholesterol and triglycerides are transported in the intestinal lymphatics as chylomicrons (large lipoproteins constituted from 80% of TG). When chylomicrons pass through blood capillaries in adipose tissue and skeletal muscle break down by enzyme lipoprotein lipase(bound to the endothelium of these capillaries) which is activated by apoprotein C-II on the surface of the chylomicron. VLDL-C (80% TG) is formed in the liver and transports triglycerides. The triglyceride content of VLDL-C is removed by lipoprotein lipase in a similar manner to that described for chylomicrons above, and forms IDL-C particles. The core of IDL-C particles is roughly 50% triglyceride and 50% cholesterol esters, acquired from HDL-C under the influence of the enzyme lecithin-cholesterol acyltransferase (LCAT). Approximately 50% of the body's IDL particles are cleared from serum by the liver. The other 50% of IDL-C are further hydrolysed and modified to lose triglyceride and apo-protein E1 and become LDL-C particles. LDL-C is the major cholesterol-carrying particle in serum. LDL-C is also the main lipoprotein involved in atherogenesis, although it only appears to take on this role after it has been modified by oxidation. HDL-C mediates the return of lipoprotein and cholesterol from peripheral tissues to the liver for excretion in a process known as reverse cholesterol transport (1). Thus it is evident that HDL-C plays a major role in maintaining cholesterol homeostasis in the body (1). (TG mainly from food, while cholesterol is mainly synthesized in the liver via VLDL)

Lipoprotein (a) Lp(a)

A raised level of Lp(a), appears to be a genetically inherited determinant of CVD. Lp(a) is a low-density lipoprotein-like particle synthesised by the liver. Raised concentrations of Lp(a), play a role in both atherogenesis and thrombosis. An important component of Lp(a) is apo(a), which is structurally and functionally similar to plasminogen and may competitively bind to fibrin and impair fibrinolysis. Concentrations of Lp(a) above 0.3 g/L increase the risk of coronary atherosclerosis and stroke (1).

Aetiology of dyslipidemia

Primary dyslipidaemia

The types and corresponding lipoprotein elevations include the following types: I (chylomicrons), IIa (LDL), IIb (LDL + VLDL), III (IDL), IV (VLDL), and V (VLDL + chylomicrons) (2).
The common familial (genetic) disorders can be classified as:

A. The primary hypercholesterolaemias such as familial hypercholesterolaemias in which LDL-C is raised (1). There is also familial defective apoB100 (4). While Polygenic hypercholesterolemia it is very common and caused by a combination of nutritional and genetic factors (LDL-C is 130 to 250 mg/dL) but it is not associated with tendon xanthomas (3).

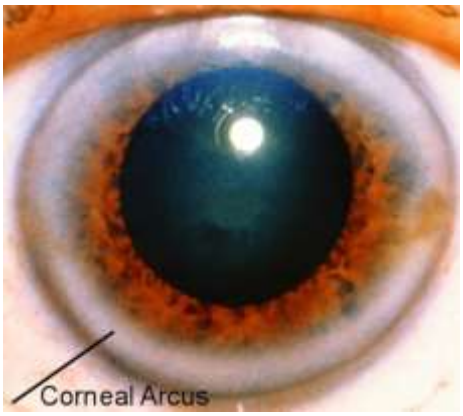
B. The primary mixed (combined) hyperlipidaemias in which both LDL-C and triglycerides are raised. Because it is associated with excessive synthesis of VLDL-C. In addition to increases in triglyceride and LDL-C levels, patients also typically have raised levels of apoB and elevated levels of small, dense LDL particles. It is associated with an increased risk of atherosclerosis) (1).
C. The primary hypertriglyceridaemias such as type III hyperlipoproteinaemia (dysbetalipoproteinemia) , familial lipoprotein lipase deficiency and familial apoC-II deficiency (which is the activator of lipoprotein lipase). (1) and Type V and IV (4)

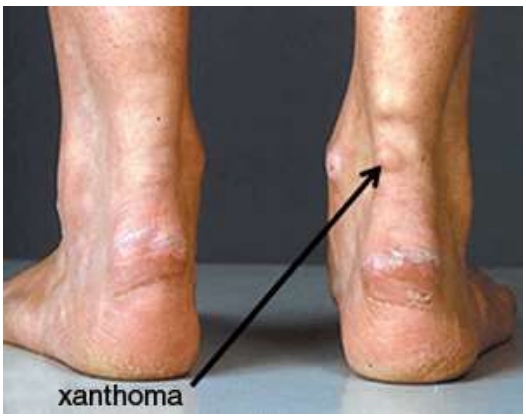
Atherogenic dyslipidemia, which usually accompanied by DM and central obesity, VLDL secretion increased along with decrease in LPL activity and decrease in VLDL removal, therefore TG conc. Increased while HDL decreased (5).

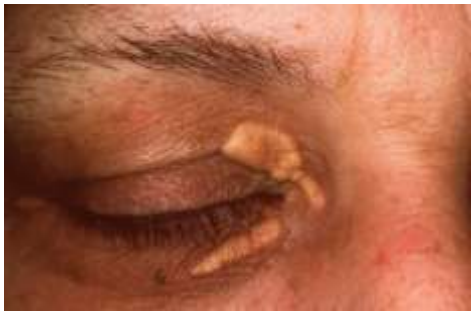
Familial hypercholesterolaemia (FH) (1)

Disorders that affect the number or affinity of LDL receptors are known as familial hypercholesterolemia (FH), while those that affect the ability of Apo B-100 to bind to the receptor known as familial defective Apo B-100 (4) (LDLc 250 – 450mg/dl(5)). These patients commonly present with corneal arcus of the eye and xanthomas of extensor tendons of the hand and Achilles tendon, and premature CHD (4).

FH can be caused by various "gain-of-function" mutations in the gene encoding for Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9).WhenPCSK9is secreted into the plasma, it binds to the cell-surface LDL receptors, leading to endocytosis, intracellular degradation, reduced number of LDL receptors, and increased LDL-C (to approximately 300 mg/dL) (3).
Heterozygous familial hypercholesterolaemia is more common than homozygous FH. It is caused by mutations that affects the LDL receptor gene. Patients with FH may have serum levels of LDL-C two to three times higher than the general population, so CVD presents about 20 years earlier than in the general population, with some individuals, particularly men, dying from atherosclerotic heart disease often before the age of 40 years. Familial hypercholesterolaemia is transmitted as a dominant gene, with siblings and children of a parent with FH having a 50% risk of inheriting it (1).







Homozygous FH is extremely rare (1 per million) and associated with an absence of LDL receptors and almost absolute inability to clear LDL-C. Myocardial infarction has been reported in homozygous children as early as 1.5–3 years of age. Up to the 1980s, sudden death from acute coronary insufficiency before the age of 20 years was normal (1).

Hypertriglyceridaemia

It was found that TGs (150 – 500mg/dl) independently predicted CHD risk, even after adjustment for other lipid risk factors. Paradoxically, very high TG levels (>500 mg/dL) are not commonly associated with an increased CHD risk, but do cause an increased risk of pancreatitis, especially when levels exceed 1,000 mg/dL (3).

Clinical presentation

Most patients are asymptomatic for many years. Signs on physical examination depend on lipoprotein abnormality (2).

Secondary dyslipidaemia

Dyslipidaemias that occur secondary to a number of disorders (DM, hypothyroidism, CKD, cholestasis, nephritic syndrome, alcohol abuse, anorexia nervosa, bulimia and pregnancy), dietary indiscretion or as a side effect of drug therapy (BB, steroid, isotretinoine, alcohol, androgens, ciclosporin, estrogen and progesterone, thiazide diuretics, and valproate) account for up to 40% of all dyslipidaemias. Fortunately, the lipid abnormalities in secondary dyslipidaemia can often be corrected if the underlying disorder is treated, effective dietary advice implemented or the offending drug withdrawn. On occasion, a disorder may be associated with dyslipidaemia but not the cause of it. For example, hyperuricaemia (gout) and hypertriglyceridaemia co-exist in approximately 50% of men. In this particular example, neither is the cause of the other and treatment of one does not resolve the other. There are, however, two notable exceptions to the rule with this example: nicotinic acid and fenofibrate. Both drugs reduce triglyceride levels but nicotinic acid increases urate levels while fenofibrate reduces them by an independent uricosuric effect (1).

Secondary hypertriglyceridaemia may be secondary to the use of medicines or it may be a component of the metabolic syndrome or type 2 diabetes mellitus (1).

Example on drugs and their negative effect on lipid profile (1).

Androgens, testosterone and isotretinoine decrease HDL and increase LDL and VLDL (1,3)

BB increase VLDL and decrease HDL, b-Blockers with intrinsic sympathomimetic activ-ity appear to have little or no effect on VLDL-C or HDL-C. Pindolol has intrinsic sympathomimetic activity but is rarely used as an antihypertensive agent since it may exacerbate angina. Alternatively, the combined α- and b-blocking effect of labetalol may be of use since it would appear to have a negligible effect on the lipid profile (1). Selective BB cause less negative effect on TG and HDL (less increase in TG and less decrease in HDLc) (3).

Diuretics: Thiazide cause slight increase in total cholesterol, but with high (30 – 50%) increase in TG and increase 1% in HDLc, while loop diuretics affect only on HDLc (decrease by up to 15%). Indapamide and metolazone have no effect on lipid profile. (3). Use of a thiazide for less than 1 year has been reported to increase TC by up to 7% with no change in HDL-C. However, there is evidence that the short-term changes in lipids do not occur with the low doses in current use. Studies of 3–5 years' duration have found no effect on TC (1).

Hepatic microsomal enzyme inducers

Drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin and griseofulvin increase hepatic microsomal enzyme activity and can also increase serum HDL-C. The administration of these drugs may also give rise to a slight increase in LDL-C and VLDL-C. The overall effect is one of a favourable increase in the TC:HDL-C ratio. It is interesting to note that patients treated for epilepsy have been reported to have a decreased incidence of CVD (1).

Diseases that lead to secondary dyslipidemia

DM: In patients with type 1 diabetes, HDL-C may appear high but for reasons which are unclear, it does not impart the same degree of protection against CVD as in those without diabetes. Patients with type 1 diabetes have a two- to three-fold increased risk of developing CVD. While Patients with type 2 DM have increased triglycerides and decreased HDL-C. Levels of TC may be similar to those found in non-diabetic individuals (1).

Hypothyroidism: increase LDL (because of reduced LDL receptor activity) , increase TG and decrease HDL due to reduced lipoprotein lipase activity (1).

Obesity: Chronic, excessive intake of calories leads to increased concentrations of triglycerides and reduced HDL-C (1).

Metabolic syndrome (occurs if 3 of the following is present: impaired fasting glucose, hypertension, increased waist circumference, increased TG, and decreased HDL) is associated with substantial increased risk for CHD (5).

HDL may be lowered by smoking, obesity, a sedentary lifestyle, and drugs such as *β*-blockers (2).

Dyslipidemia after renal transplantation

Ciclosporin is primarily used to prevent tissue rejection in recipients of renal, hepatic and cardiac transplants. Its use has been associated with increased LDL-C levels, hypertension and glucose intolerance.

Diagnosis

A fasting lipoprotein profile including total cholesterol, LDL, HDL, and triglycerides should be measured in all adults 20 years of age or older at least once every 5 years (2).

Measurement of plasma cholesterol, triglyceride, and HDL levels after a 12-hour or longer fast is important, because triglycerides may be elevated in nonfasting individuals; fasting state minimize interference with TG values from chylomicrons (2). Total cholesterol is only modestly affected by fasting (2). Patients must also be seated for at least 5 min prior to drawing a blood sample (1).

Two determinations, 1 to 8 weeks apart, with the patient on a stable diet and weight, and in the absence of acute illness, are recommended to minimize variability and to obtain a reliable baseline (2). However if LDL-C is so high a repeat test is not likely to change the assessment. And thus a second test is optional (3).
Agarose-gel lipoprotein electrophoresis is useful to determine which class of lipoproteins is affected (2).

In general, lipid profile measurement should be deferred for 2 weeks after a minor illness and for 3 months after a myocardial infarction, serious illness or pregnancy (1). The lipid profile obtained during 24 hour of hospitalization for ACS can be interpreted in a normal manner. Profiles drawn after 24 hours are generally lower, however, than pre-event levels and remain so for several weeks (3).

Once the TC, HDL-C and triglyceride values are known it is usual to calculate the value for LDL-C using the Friedewald equation (1):

LDL-C(mg/dl) = Total Chol – (HDL-C + TG/5)
LDL-C(mmol/L) = Total Chol – (HDL-C + TG/2.2)

The Friedewald equation should not be used in non- fasting individuals, it is less reliable in individuals with diabetes and is not valid if the serum triglyceride concentration >4 mmol/L (1).

Most labs who measure LDL-C done so through the above equation. This calculated value includes cholesterol carried by true LDL particles, as well as IDL particles. It also includes cholesterol carried by these lipoprotein (a) [Lp (a)] particles (12)

The value for non-HDL-C is obtained by subtracting the value for HDL-C from TC. Non-HDL cholesterol, can be measured from a *non-fasting* blood sample and it should be used in preference to low density lipoprotein (LDL) cholesterol as the

treatment goal for lipid lowering therapy (12,13). Because it represents the total of cholesterol circulating on apoprotein B particles, that is, both LDL and triglyceride-rich lipoproteins, and represents the main atherogenic particles (1). Besides that in about 30% of cases, the presence of other lipoproteins are concurrently elevated and the assessment of LDL-C alone may underestimate a patient's risk. In these cases, it is helpful to know how much cholesterol is being carried by all of these particles. Although apolipoprotein B-100 can be measured directly, measurement of non–HDL-C is more practical, reliable, and inexpensive and correlates well with apolipoprotein B-100. Moreover, LDL-C can be incorrectly calculated in the presence of postprandial hypertriglyceridemia, whereas non–HDL-C is reliable when measured in the nonfasting state (3).
An increased number of lipoprotein particles (i.e., an increased apolipoprotein B-100 concentration) is a strong predictor of CHD risk (3).
However, it should be emphasized that goal thresholds apply to both non–HDL-C and LDL-C, because discordance may occur, and effective management of atherogenic cholesterol would ideally result in achieving goal levels for both (12).

Risk Assessment
Primary prevention
Primary prevention is done for patients without evident CHD (3). Risk assessment can be done either by charts or by using specific designed calculators like: Framingham, Assign (mainly for Scotland patients), and QRISK2. They usually measure risk for the next 10 years (1). Those with a cardiovascular risk >20% over 10 years are deemed to require treatment according to current national and international guidelines (1),
However, 10-year risk estimates may provide false reassurance over the long term, especially in young individuals and women with high lifetime risk. As cardioprotective drugs have become cheaper and have been shown to be safe and efficacious over the longer term, there is an opportunity to extend their use beyond the current 10-year CVD risk threshold, like lifetime risk. (13)

QRISK2 is a new tool that takes into account additional risk factors like RA, CKD, AF and also focus on patient ethinicity and smoking behavior (1).

Risk factors for developing CHD (3)

1. Age: Man ≥45 years
2. Woman ≥55 years
3. Family history of a premature CHD (definite MI or sudden death before 55 years in father or other male first-degree relative or before 65 years in mother or other female first-degree relative) (3) which increase risk by 1.5 – 2 fold (1).
4. Current cigarette smoking (3); individuals who have stopped smoking within 5 years of assessment should be considered as current smokers(1)
5. Hypertension (≥140/90 mm Hg or on antihypertensive drugs)
6. Low HDL-C (<40 mg/dL)

Note: some references consider obesity (high BMI, or waist circumference) **as a risk factor (1).**
DM considered as CHD equivalent (risk greater than 20% in the next 10 years) (3).

Patients with high level (more than 3mg/liter) of hs CRP is considered at high risk of CHD (3).
Risk assessment is not required when the individual is 75 years of age or older, or they have pre-existing CVD. These individuals are already assumed to have a 10-year risk of at least 20% (1).

Secondary prevention
Patients with CVD (MI, angina, ACS, CABG, TIA, stroke, or peripheral vascular disease) and levels of TC >4 mmol/L and LDL-C >2 mmol/L are the ones most likely to benefit from treatment with lipid-lowering agents (1).

Treatment
Desired Outcome
The goals of treatment are to lower total cholesterol, LDL cholesterol (2) and non-HDLc (12) in order to reduce the risk of first or recurrent events such as MI, angina, heart failure, ischemic stroke, or other forms of peripheral arterial disease (2). Using treatment goals, compared with prescribing moderate- to high-intensity statins without treatment targets, will not result in under treatment as was suggested by ACC/AHA 2013 guidelines. Moreover, treatment goals facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives, thus supporting efforts to maximize long-term adherence to the treatment plan (12).

Decision on treatment should be based on the following (12)

Table 3 Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

Risk category	Criteria	Treatment goal: Non-HDL-C, mg/dL LDL-C, mg/dL	Consider drug therapy: Non-HDL-C, mg/dL LDL-C, mg/dL
Low	• 0–1 major ASCVD risk factors • Consider other risk indicators, if known	<130 <100	≥190 ≥160
Moderate	• 2 major ASCVD risk factors • Consider quantitative risk scoring • Consider other risk indicators*	<130 <100	≥160 ≥130
High	• ≥3 major ASCVD risk factors • Diabetes mellitus (type 1 or 2)† ○ 0–1 other major ASCVD risk factors and ○ No evidence of end-organ damage • Chronic kidney disease stage 3B or 4† • LDL-C of ≥190 mg/dL (severe hypercholesterolemia)† • Quantitative risk score reaching the high-risk threshold†	<130 <100	≥130 ≥100
Very high	• ASCVD • Diabetes mellitus (type 1 or 2) ○ ≥2 other major ASCVD risk factors or ○ Evidence of end-organ damage*	<100 <70	≥100 ≥70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Note: Apo B is secondary optional goal. Target for Apo B is less than 90mg/dl in all cases except for those with very high risk goal will be less than 80mg/dl (12).

The 2013 ACC/AHA guidelines did not support treating patients to specific LDL-C or non-HDL-C goals. a. An approach of "treating to goal" has not been found to result in improved ASCVD outcomes; it may lead to the patient receiving inappropriate therapy. This current guideline does not recommend such goals as performance measures (5, 14).

• Four distinct statin benefit groups were identified (5,14):

1. Patients with clinical ASCVD or those without ASCVD but with LDLc ≥ 190 mg/dL use (high-intensity statin like Atorvastatin (40*a*)–80 mg Or Rosuvastatin 20 (40) mg)
2. Patients without ASCVD, but with or without diabetes, aged 40 to 75 years, and with an LDL-C between 70 and 189 mg/dL and 10 years risk less than 7.5% use (moderate-intensity statin like atorvastatin 10(20), Rosuvastatin 5(10), simvastatin 20 – 40, lovastatin 40, fluvastatin XL 80mg, Or pitavatstin 2 – 4 mg) while those with risk ≥ 7.5% use high intensity statin :

Low intensity statin like, simvastatin 10, lovastatin 20, fluvastatin 40, pitavastatin 1or pravastatin 10 -20mg are not included in the recommendation of ACC/AHA 2013 guideline (5)

Non Pharmacological treatment

Begin therapeutic lifestyle changes (TLCs) on the first visit, including dietary therapy (decrease intake of total fat ≤ 30% of total energy intake (TEI), saturated fat ≤ 10% TEI, Trans fat ≤ 0.5% TEI and cholesterol ≤ 300mg/day while increase fiber intake and fish oil, also consume large amount of fruit and vegetables as a natural antioxidants (1,2)), weight reduction, and increased physical activity. Advise overweight patients to lose 10% of body weight (2). Avoid alcohol or ensure moderate alcohol intake (14 – 21 Unit/ week) (1). Encourage physical activity of moderate intensity 30 minutes a day(2) [it can be taken in 10min bouts (1)] for most days of the week (2) [5 days a week (1)]. Assist patients with smoking cessation and control of hypertension. If all recommended dietary changes were instituted, the estimated average reduction in LDL would range from 20% to 30%. (2).
Therapeutic lifestyle changes and exercise should be considered in all patients; additional therapeutic interventions should not be delayed in high-risk patients (5). It is usually advised to start with dietary and life style modification for 3 – 6 months in patients who are in need for primary prevention, start pharmacological therapy if the goal is not reached (1).

Exercise decrease TG and increase HDLc (3). Diet modification should always be encouraged in a patient with dyslipidaemia but is rarely successful alone in bringing about a significant improvement in the lipid profile (1).

Pharmacological treatment

General notes

There are five main classes of lipid-lowering agents available: Statins, Fibrates, Bile acid binding agents, Cholesterol absorption inhibitors, and Nicotinic acid and derivatives (1).

• Four drugs effectively reduce LDL-C: statin, resin, ezetimibe, and niacin. When two or more agents are combined, an additive LDL-C-lowering effect is achieved. Side effects are the major limiting factor in combining drugs (5).

The choice of lipid-lowering agent depends on the underlying dyslipidaemia, the response required and patient acceptability (1).

• Statins are the drugs of first choice to lower cholesterol and reduce CHD risk (5). because of their great ability to reduce LDL-C, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, and low risk of side effects (3).

• No effective drugs substantially and specifically increase HDL-C. The 2013 ACC/ AHA guidelines recommend aggressive LDL-C lowering with a statin in patients with a low HDL-C (5).

Other newer classes include:

Microsomal triglyceride transfer protein (MTp) inhibitors : Inhibit absorption of lipid and reduce hepatic secretion of lipoproteins (VLDL), thereby reducing atherosclerotic plaque formation (1). Like Juxtapid (lomitapide) oral capsule; which is approved at 2012 For the treatment of homozygous familial hypercholesterolemia (15).

PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibodies like :

Praluent (alirocumab) ; who is indicated for use as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (15)

Repatha (evolocumab) which is indicated for use as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous or homozygous familial hypercholesterolemia. Both are approved at 2015 and used SC once every 2 weeks (15).

ApoB 100 inhibitors like Kynamro (mipomersen sodium); indicated For the treatment of homozygous familial hypercholesterolemia as an adjunct to lipid-lowering medications and diet. It is given SC. Approved January 2013 (15)

Statins

Statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) (2).

They lower LDL-C by approximately 20% to 46% with initial doses and 35% to 60% with maximal doses. Statins also reduce TG levels by 15% to 45% and increase HDL-C modestly (5% to 8%). The LDL-C lowering achieved is dose dependent and log linear. Low dosages produce substantial LDL-C–lowering effects, and with each doubling of the daily dose, LDL-C is lowered an additional 6% to 7% on average (3).

Statins are POM drugs, the evidence base to support the use of 10 mg simvastatin (OTC dose) and achieve long-term cardiovascular benefit is limited (1).

Mechanism of action

Statins act by inhibition of HMG-CoA reductase in the liver and the subsequent inhibition of the formation of mevalonic acid, the rate- limiting step in the biosynthesis of cholesterol. This results in a reduction in intracellular levels of cholesterol, an increase in expression of hepatic LDL receptor, and enhanced receptor-mediated catabolism and clearance of LDL-C (1) and VLDL remnant particle from circulation, this would account for their ability to reduce serum TG levels as well as cholesterol levels (3).

All the statins require the presence of LDL receptors for their optimum clinical effect, and consequently they are less effective in patients with heterozygous FH because of the reduced number of LDL receptors. However, even in the homozygous patient

where there are no LDL receptors they can bring about some reduction of serum cholesterol, although the mechanism is unclear (1).
The reduction in LDL-C occurs in a dose- dependent manner, with a lesser and dose-independent effect on VLDL-C and triglycerides (1). A reduction in TC and LDL-C is usually seen with all statins within 2 weeks, with a maximum response occurring by week 4 and maintained thereafter during continued therapy (1).
Statins are more effective for secondary (patients with CVD) than primary prevention (without CVD) (1).

Monitoring of statin effectiveness: Patients receiving statins should have a fasting lipid panel 4 to 8 weeks after the initial dose or dose changes (2).

Rosuvastatin provides the most substantial LDL-C lowering, followed by atorvastatin, simvastatin, pitavastatin, lovastatin, pravastatin, and fluvastatin in descending order (3). The efficacy of many statins is greater if administered in the evening to coincide with the nighttime upturn in endogenous cholesterol biosynthesis; atorvastatin, and rosuvastatin with a longer half-life and more potent LDL-C lowering, may be administered without regard to time of day. The bioavailability of lovastatin is improved by administration with food; thus, it is recommended for dosing with the evening meal (3). Lovastatin and rosuvastatin may prolong the international normalized ratio in patients receiving warfarin anticoagulants concurrently; this effect is not caused by pravastatin (3).

Despite overwhelming evidence of statin benefit, effectiveness is frequently compromised by poor adherence with up to 50% of patients discontinuing treatment within 12 months and 75% within 3 years. Patient factors that influence this include perception of risk, side effects of medication, expected treatment duration and socio-demographic factors (1).

Rosuvastatin is the most potent of the statins but there are concerns about rosuvastatin safety profile and rhabdomyolysis in particular, when used at the higher dose of 40 mg/day. The maximum dose should not exceed 20 mg/day because of their increased predisposition to myopathy and rhabdomyolysis (1).

Therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in patients with very high or high risk. The maximum tolerated statin dosage should generally be used before add-on therapy is considered (12).

If fibrate is used with statin, Consider use of fenofibrate in conjunction with a low- or moderate-intensity statin when triglycerides are ≥ 500 mg/dL and the benefits of reductions in ASCVD risk or triglycerides are deemed to outweigh risks for adverse effects (14).

To date, there is limited evidence demonstrating that adding a second or third drug to background statin therapy produces incremental benefit on the risk of CHD. The safest and most effective combination to lower LDLc is statin plus ezetimibe (3).
Triple therapy used rarely: The addition of niacin to statin and ezetimibe regimen

should be initiated with lowdoses that are slowly titrated upward to allow tolerance to develop at each dosage level (3).

Adverse effects of statins

Many side effects appear mild and transient. The commonest include GIT symptoms, altered liver function tests and muscle aches. Less common are hepatitis, rash, headache, insomnia, nightmares, vivid dreams and difficulty concentrating. Myopathy leading to myoglobulinuria secondary to rhabdomyolysis is also a rare but serious potential adverse effect of all the statins that can occur at any dose (1). Statins may increase risk for type 2 diabetes, but benefits of statin therapy far outweigh the risks in the aforementioned patient populations (14).

Statins can cause an elevation in transaminase enzyme levels of more than three times the upper limit of normal (ULN) in a dose-dependent manner. The transaminase level can return to normal spontaneously even with continued statin therapy. If ALT or AST is one to three times the ULN during statin therapy, there is no need to discontinue the statin. If ALT or AST exceeds three times the ULN during statin therapy, monitor the patient and repeat the transaminase measures. There is no need to discontinue the statin. If a patient's transaminase levels continue to rise or if there is further objective evidence (i.e., hepatomegaly, jaundice, elevated direct bilirubin, related symptoms) of liver injury, the statin should be discontinued. Rechallenge with the same or a different statin after enzymes have returned to normal limits is acceptable. The estimated incidence of statin-associated liver failure is 1 per million person-years of use. There is some evidence that patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy and may improve liver function tests (3).

Myositis defined as muscle weakness and an increase in serum CPK more than 10 times the ULN, occurs in a dose-dependent manner. The statin should be withdrawn until CPK levels return to normal. Occasionally, symptoms of myalgia are bothersome or intolerable to the patient, even with a normal CPK or one that is elevated but less than 10 times the ULN. In these cases, the statin should be discontinued. Once symptoms subside, statin therapy can be restarted at the same or reduced dose, or with a different statin. Alternate day and even once-weekly dosing of statins have been used in patients who have statin intolerance caused by myopathy (3).
The risk of myopathy is increased when there are underlying muscle disorders, renal impairment, untreated hypothyroidism, alcohol abuse, or the recipient is aged over 65 years or female or in case of co prescribing statins with interacting drugs like fibrates, nicotinic acid, ketokenazole, ciclosporin, erythromycin and clarithromycin (1).

With grapefruit one should completely avoid simvastatin while one should avoid drinking large quantity of grapefruit juice with atorvastatin (1).

If the patient requires a short course of therapy with a potentially interacting drug (e.g., erythromycin), the statin should be discontinued during this period and restarted when the course has been completed (3). If an interacting drug must be used long term

(e.g., cyclosporine) with a statin, the lowest effective dose of the statin should be selected, with careful monitoring of muscle symptoms (3).
Statin induced myopathy may respond to either Vitamin D supplementation or Q10 enzyme (3).

Monitoring of statin side effects

Liver function test should be done at baseline (2). Routine monitoring of creatine kinase and hepatic transaminase levels is not necessary (unless the patient's symptoms indicate a possibility of myopathy or hepatotoxicity) (14).

Statin therapy for stroke patients

Statin therapy is recommended for patients with ischaemic stroke. Its introduction should be delayed for 2 weeks post-stroke, but there is no need to discontinue statins in patients already on therapy (13). Statin therapy should be avoided in individuals with a history of haemorrhagic stroke, particularly in those with inadequately controlled hypertension unless there is a compelling indication, such as concomitant coronary artery disease (13).

Contraindications
Statins should not be used in patients with active liver disease or those who are (or hope to become) pregnant because of potential hazards to the fetus (3).

Statin pleiotropic properties

Statin pleiotropic effects may also play a part in reducing morbidity and mortality from CVD. These effects include plaque stabilisation, inhibition of thrombus formation, decrease platelet activation and activity, reduced serum viscosity, anti-inflammatory, antioxidant activity and increased endothelial nitric oxide release (1).

Fibrates

Members of this group include bezafibrate, ciprofibrate (1), fenofibrate, clofibrate and gemfibrozil (2). They are thought to act by binding to peroxisome proliferator-activated receptor α (PPAR-α) on hepatocytes. This then leads to changes in the expression of genes involved in lipoprotein metabolism (1). Fibrate can enhance the activity of LPL (3)
Consequently, fibrates reduce triglyceride and increasing HDLc (1) by 10 – 15%(2). A reciprocal rise in LDL may occur, and total cholesterol values may remain relatively unchanged(2) . They are not recommended for LDL-C lowering only (5). Fibrates take 2–5 days to produce an effect on VLDL-C, with their optimum effect present after 4 weeks. In addition to their effects on serum lipids and lipoproteins, the fibrates may also have a beneficial effect on the fibrinolytic and clotting mechanisms. The fibrates also produce an improvement in glucose tolerance, although bezafibrate probably has the most marked effect (1). Clofibrate is less effective than gemfibrozil or niacin in reducing VLDL production (2).

Fibrates can be used first line in patients with isolated severe hyper-triglyceridaemia. In individuals with mixed hyperlipidaemia, fibrates may be considered when a statin or other agent is contraindicated or not tolerated (1).

Statins are first-line lipid-lowering agent for diabetic patients because of a lack of clear evidence that fibrates prevent CVD in diabetes (1).

Adverse effects of fibrates

Mild and vary between members of the group (1). Gastro-intestinal symptoms such as nausea, diarrhoea and abdominal pain are common (1) occur in 3 – 5%of patients (2) but transient, and often resolve after a few days of treatment (1). Rash, dizziness, and transient elevations in transaminase levels and alkaline phosphatase may also occur. Gemfibrozil and probably fenofibrate enhance gallstone formation rarely (2).

Myositis has been described (1) and it seems to be more common in patients with renal insufficiency (2). Fibrates are known to significantly increase the effect of anticoagulants (2).

Bile acid binding agents (resins) BARs

Both colestyramine and colestipol usage is limited (1). by taste and inconvenient preparations (5) Colesevalam is the most recent of the bile acid binding agents but has never had a first-line indication. They are not absorbed from GIT They bind bile acids in the intestine, prevent re-absorption and produce an insoluble complex that is excreted in the faeces. The deple-tion of bile acids results in an increase in hepatic synthesis of bile acids from cholesterol. The depletion of hepatic cholesterol upregulates the hepatic enzyme 7-α-hydoxylase which increases the conversion of cholesterol to bile acids. This increases LDL receptor activity in the liver and removes LDL-C from the blood. Hepatic VLDL-C synthesis also increases and it is this which accounts for the raised serum triglycerides (1). So they may aggravate hypertriglyceridemia in patients with combined dyslipidemia (2).

Colestyramine, colestipol available as sachet powder mixed with liquid and used twice daily (1). Colestipol may have better palatability than cholestyramine because it is odorless and tasteless. Tablet forms may help improve adherence (2). However there is limited evidence to suggest it may achieve a higher adherence than colestyramine or colestipol (1).

Colesevelam is also US Food and Drug Administration (FDA) approved for use in improving glycemic control in type 2 diabetes. (3).

Adverse effects

Bloating, flatulence, heartburn and constipation are common complaints (1). Constipation can be managed by increasing fluid intake, increasing dietary bulk, and using stool softeners (2).

Long-term use of bile acid binding agents may also interfere with the absorption of fat soluble vitamins and supplementation with vitamins A, D and K is recommended (1).
BARs are known to interact with many drugs primarily by interfering with absorption (so other drugs should be taken 1 hour before bile acid binding agents or 4 hours after them) (1) like warfarin, thyroxin, … (2).

Cholesterol absorption inhibitors

Ezetimibe reduces LDL-C but has little effect on TG or HDL-C. It interferes with cholesterol absorption from the intestinal lumen (5).
Because cardiovascular outcomes with ezetimibe have not been evaluated, it should be reserved for patients unable to tolerate statin therapy or those who do not achieve satisfactory lipid lowering with a statin alone (2). When added to a statin, ezetimibe lowers LDL-C more than with a statin alone (1) produce additive effect (3).
Bile acid resins and ezetimibe reduce LDLc by 15 – 20% only (3).
Ezetimibe is well tolerated; ~4% of patients experience GI upset (3,4). It can cause arthralgias, cough, and fatigue (3).

Nicotinic acid and derivatives

Niacin is a low-cost agent that has a long history of use and evidence that it reduces CHD events (5).
Niacin (nicotinic acid) is a water-soluble B vitamin. Its metabolite, nicotinamide, has no effect on cholesterol and should not be used as a substitute to lower side effects such as flushing free (3).
Niacin inhibits the mobilization of free fatty acids from peripheral adipose tissue to the liver, which results in reduced synthesis and secretion of VLDL particles by the liver (3) this in turn reduces synthesis of LDL. Niacin also increases HDL by reducing its catabolism (2). It also lowers apolipoprotein B and Lp(a) (1).
It should be slowly titrated to avoid side effects (increase dose every 3 – 7 days) (3).
It is licensed for use in combination with a statin, or by itself if the patient is statin intolerant or a statin is in appropriate (2). The principal use of niacin is for mixed dyslipidemia or as a second-line agent in combination therapy for hypercholesterolemia (2).
It is the best therapy available to raise HDL-C and one of the best at lowering TGs (3).
Niacin is the only drug that can lower Lp(a), but no studies have shown that giving niacin to these patients reduces CHD risk (3).

The commonest side effect of nicotinic acid is flushing (2) [it is related to niacin metabolism by nicotinamide pathway (3)]. Flushing (prostaglandin mediated) occurs in over 90% of patients. It is cited as the major reason for discontinuation of treatment in 25–40% of patients. A number of strategies have been devised to overcome this problems including co-administration of aspirin 325 mg shortly before niacin ingestion (2). Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects (2). Concomitant alcohol and hot drinks should be avoided at the time of niacin ingestion (2). Other strategies include the use of extended-release formulations (1). Less common side effects of nicotinic acid include postural hypotension, diarrhoea, exacerbation of peptic ulcers, hepatic dysfunction, gout and increased blood glucose levels (1). by 10% to 20%, (5). GI intolerance is

also a common problem (2). Niacin-associated hepatitis is more common with sustained release preparations, and their use should be restricted to patients intolerant of regular- release products (2).
Niacin is contraindicated in patients with active liver disease, and it may exacerbate preexisting gout and diabetes (2).

Niaspan is a prescription-only, extended-release niacin formulation with pharmacokinetics intermediate between prompt- and sustained-release products. It has fewer dermatologic reactions and a low risk of Hepatotoxicity (2) when compared with sustained release preprations (3). Combination with statins can produce large reductions in LDL and increases in HDL (2). Daily doses of extended release niacin should not exceed 2,000 mg/day to reduce the risk of liver side effects (3). Niacin-induced hepatotoxicity appears to be completely reversible when the drug is discontinued (3).

Acipimox is structurally related to nicotinic acid, has similar beneficial effects on the lipid profile and a better side effect profile but appears to be less potent (1).

Fish oil (omega 3)

Fish oil lowers TG and has no effect on LDL-C (5) or may elevate LDL-C (2). Prescription-grade omega-3 fatty acid has EPA and DHA. Dietary fish oil supplements have variable concentrations of EPA and DHA; products should be carefully selected (5). They are effective to lower TG and VLDL, however the effect is inconsistent and significant increases in LDL-C have also been reported to accompany the use of fish oils. Data from several studies suggest that omega-3 fatty acids protect against CHD mortality (1).Omega-3 fatty acids have antiarrhythmic properties, ability to reduce blood pressure and heart rate, stimulate endothelial-derived nitric oxide, increase insulin sensitivity, decrease platelet aggregation and decrease proinflammatory eicosanoids (1). Which account for their cardioprotective effect (2). Pregnant women are advised to limit their intake of oily fish to two portions per week because of the potential accumulation of low level pollutants in the fish (1).

Complications of fish oil supplementation such as thrombocytopenia and bleeding disorders have been noted, especially with high doses (EPA 15–30 g/day) (2).

Treatment of hypertriglyceridaemia

Very high triglycerides are associated with pancreatitis and other adverse consequences. Management includes dietary fat restriction (10–20% of calories as fat), weight loss, alcohol restriction, and treatment of coexisting disorders (eg, diabetes). Drug therapy includes **gemfibrozil** or **fenofibrate**, **niacin**, and higher-potency statins (**atorvastatin**, **pitavastatin**, **rosuvastatin**, and **simvastatin**). Successful treatment is defined as reduction in triglycerides to less than 500 mg/dL (5.65 mmol/L) (2).

Table: Lipid-lowering effects of the three generations of statins (16) للاطلاع

Generation	Statins	Change in LDL	Change in HDL	Change in total cholesterol	Change in triglycerides
1st	Lovastatin, pravastatin, fluvastatin	−21% to −42%	+2% to +12%	−16% to −34%	−6% to −27%
2nd	Simvastatin, atorvastatin	−26% to −60%	+5% to +16%	−19% to −45%	−12% to −53%
3rd	Rosuvastatin	−45% to −63%	+8% to +14%	−33% to −46%	−10% to −35%

Reference

1. Clinical Pharmacy by Rodger Walker 2012
2. Pharmacotherapy handbook 2015
3. Applied therapeutics 2013
4. Pharmacotherapy principle and practice 2013
5. Handbook of applied therapeutics 2015
6. Ganz P, Hsue PY. Endothelial dysfunction in coronary heart disease is more than a systemic process. Eur Heart J. 2013 Jul;34(27):2025-7
7. Vincent Launay-Vacher, etal. Statins' dosage in patients with renal failure and cyclosporine drug–drug interactions in transplant recipient patients: review. nternational Journal of Cardiology 101 (2005) 9–17
8. Stefano Bellosta, etal. **Atherosclerosis: Evolving Vascular Biology and Clinical Implications**: **Safety of Statins. Focus on Clinical Pharmaco-kinetics and Drug Interactions. Circulation.**2004; 109: III-50-III-57
9. Debasish Maji, Shehla Shaikh, etal. Safety of statins. Indian J Endocrinol Metab. 2013 Jul-Aug; 17(4): 636–646.
10. Simonson SG, Raza A, Martin PD, et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered anantirejection regimen including cyclosporine. Clin Pharmacol Ther. 2004;76:167–177.
11. Asberg A[1]. **Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients.** Drugs. 2003;63(4):367-78.
12. Terry A. Jacobson, etal. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1—Full Report. Journal of Clinical Lipidology (2015)
13. **JBS3 Board**. **Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3).** *Heart* 2014;**100**:ii1-ii67 doi:10.1136/heartjnl-2014-305693
14. Stone NJ, etal. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, Journal of the American College of Cardiology (2013).
15. https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/1/cardiology-vascular-diseases Accessed October 2015
16. Navin K Kapur[1] and Kiran Musunuru. Clinical efficacy and safety of statins in managing cardiovascular risk. Vasc Health Risk Manag. 2008 Apr; 4(2): 341–353.