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Familial Dyslipidaemias

An Overview of Genetics, Pathophysiology and Management

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Contents

Abstract

Plasma lipid disorders can occur either as a primary event or secondary to an underlying disease or use of medications. Familial dyslipidaemias are traditionally classified according to the electrophoretic profile of lipoproteins. In more recent texts, this phenotypic classification has been replaced with an aetiological classification. Familial dyslipidaemias are generally grouped into disorders leading to hypercholesterolaemia, hypertriglyceridaemia, a combination of hypercholesterolaemia and hypertriglyceridaemia, or abnormal high-density lipoprotein-cholesterol (HDL-C) levels.

The management of these disorders requires an understanding of plasma lipid and lipoprotein metabolism. Lipid transport and metabolism involves three general pathways: (i) the exogenous pathway, whereby chylomicrons are synthesised by the small intestine, and dietary triglycerides (TGs) and cholesterol are transported to various cells of the body; (ii) the endogenous pathway, whereby very low-density lipoprotein-cholesterol (VLDL-C) and TGs are synthesised by the liver for transport to various tissues; and (iii) the reverse cholesterol transport, whereby HDL cholesteryl ester is exchanged for TGs in low-density lipoptrotein (LDL) and VLDL particles through cholesteryl ester transfer protein in a series of steps to remove cholesterol from the peripheral tissues for delivery to the liver and steroidogenic organs.

The plasma lipid profile can provide a framework to guide the selection of appropriate diet and drug treatment. Many patients with hyperlipoproteinaemia can be treated effectively with diet. However, dietary regimens are often insufficient to bring lipoprotein levels to within acceptable limits.

In this article, we review lipid transport and metabolism, discuss the more common lipid disorders and suggest some management guidelines. The choice of a particular agent depends on the baseline lipid profile achieved after 6–12 weeks of intense lifestyle changes and possible use of dietry supplements such as stanols and plant sterols. If the predominant lipid abnormality is hypertriglyceridaemia, omega-3 fatty acids, a fibric acid derivative (fibrate) or nicotinic acid would be considered as the first choice of therapy. In subsequent follow-up, when LDL-C is >130 mg/dL (3.36 mmol/L) then an HMG-CoA reductase inhibitor (statin) should be added as a combination therapy. If the serum TG levels are <500 mg/dL (2.26 mmol/L) and the LDL-C values are over 130 mg/dL (3.36 mmol/L) then a statin would be the first drug of choice. The statin dose can be titrated up to achieve the therapeutic goal or, alternatively, ezetimibe can be added. A bile acid binding agent is an option if the serum TG levels do not exceed 200 mg/dL

(5.65 mmol/L), otherwise a fibrate or nicotinic acid should be considered. The decision to treat a particular person has to be individualised.

It is generally accepted that dyslipidaemias are major causes of morbidity and mortality in the world, especially in developed countries.[1,2] Most of the serious health consequences of dyslipidaemias are attributed to cardiovascular disease (CVD) secondary to increased plasma cholesterol levels. Nevertheless, abnormalities in other lipid or lipoprotein moieties may contribute to the progression of CVD, may cause pancreatitis, and in some rare dyslipidaemias may be associated with lesser-known complications such as renal failure or haemolytic anaemia.

Dyslipidaemias can be broadly classified as either primary or secondary to a complicating event, be that organ failure or use of some medications[3-13] (table I). However, the overlap between these two categories is very common, such that it is more likely for people with dyslipidaemias to have their lipid disorder attributed to both a genetic predisposition and an additional aggravating secondary event such as weight gain, a change in diet, organ failure or use of medications. Thus, from a practical standpoint, it is imperative that every individual with dyslipidaemia is screened for secondary causes and, if possible, that those causes be ameliorated or eliminated.

Familial dyslipidaemias have been classified by Fredrickson according to the electrophoretic profile of lipoproteins (table II).[1,2] More recently, this phenotypic classification had been replaced with an aetiological classification (table III). In this article, the seminal features of more widely recognised fa-

Table I. Secondary causes of dyslipidaemia and associated lipid changes[3-13]

Cause	Changes
Diabetes mellitus	TG ↑, HDL-C ↓
Hypothyroidism	LDL-C ↑
Acromegaly	TG ↑
Anorexia nervosa	LDL-C ↑
Lipodystrophy	TG ↑, HDL-C ↓
Glycogen storage disorders	TG ↑
Nephrotic syndrome	Mixed hyperlipidaemia (LDL-C ↑ predominates)
Chronic renal failure	TG ↑
Obstructive liver disease	LDL-C ↑, lipoprotein X ↑
Alcohol	TG ↑
Immunoglobulin excess: paraproteinaemia	Mixed hyperlipidaemia
Medications:	
β-adrenoceptor antagonists (selective)	HDL-C ↓, TG ↑
thiazide diuretics	LDL-C ↑, TG ↑ or no change
glucocorticoids	LDL-C ↑or no change, TG ↑or no change, HDL-C ↑
ciclosporin	LDL-C ↑, TG ↑
interferons	TG ↑
antiviral medications (HIV protease inhibitors)	TG ↑, LDL-C ↑, HDL-C ↓
exogenous estrogens	TG ↑, HDL-C ↑, LDL-C ↓
retinoic acid derivatives	LDL-C ↑, TG ↑, HDL-C ↓

HDL-C = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **TG** = triglyceride; ↑ indicates increased levels; ↓ indicates decreased levels.

Table II. Fredrickson classification of familial dyslipidaemias

Fredrickson phenotype	Lipoprotein abnormality	Typical lipid levels
I	Chylomicrons	Total TG >99th percentile
II a	LDL	TC >90th percentile, may also see total TG ≥90th percentile
II b	LDL and VLDL	Depending upon type, TC and/or total TG ≥90th percentile
III	Remnants of VLDL and chylomicrons	TC and total TG >90th percentile
IV	VLDL	Total TG >90th percentile, depending upon type, may also see TC >90th percentile or low HDL
V	Chylomicrons and VLDL	Total TG >99th percentile

HDL = high-density lipoprotein; **LDL** = low-density lipoprotein; **TC** = total cholesterol; **TG** = triglycerides; **VLDL** = very low-density lipoprotein.

milial dyslipidaemias are described, and the pathogenesis of the lipid disorders as well as their management reviewed.

1. Overview of Lipid Transport and Metabolism

As lipids are insoluble in water, they are transported in lipoprotein complexes, with the core region containing cholesteryl ester (CE) and triglycerides (TGs) surrounded by an envelope containing phospholipids and free cholesterol.[2] Apoproteins are located on the surface monolayer and serve as cofactors for enzymes and as ligands for receptors. Although a handful of lipoprotein subclasses are qualitatively defined according to their density, and are described to characterise clinically recognisable dyslipidaemias (table II), there is a large degree of heterogeneity of size and density of these lipoprotein subclasses.

Lipid transport and metabolism involves three general pathways: (i) the exogenous pathway, whereby chylomicrons are synthesised by the small intestine, and dietary TGs and cholesterol are transported to various cells of the body; (ii) the endogenous pathway, whereby the very low-density lipoprotein-cholesterol (VLDL-C) and TGs are synthesised by the liver for transport to various tissues; and (iii) the reverse cholesterol transport, whereby high-density lipoprotein (HDL) in a series of metabolic steps facilitates the removal of cholesterol from the peripheral tissues for delivery to the liver and steroidogenic organs.

1.1 Exogenous Pathway

Dietary TGs are hydrolysed in the intestine to monoglycerides and free fatty acids (FFA) that form micelles and are then absorbed by the intestinal epithelium. Subsequently, the FFAs are re-esterified to form TG, and cholesterol is esterified by acetyl cholesterol acyltransferase. Droplets of TG combined with a small amount of CE and apopoprotein (apo) B48 acquire phospholipids, free cholesterol

Table III. Classification of familial dyslipidaemias according to predominant lipid abnormality and aetiology

Increased cholesterol	Increased TG	Increased TG and cholesterol	Decreased HDL	Increased HDL
Familial hypercholesterolaemia	Familial hypertriglyceridaemia	Familial combined hyperlipidaemia	Familial hypoalphalipoproteinaemia	Familial hyperalphalipoproteinaemia
Polygenic hypercholesterolaemia	Deficiency of lipoprotein lipase	Familial dysbetalipoproteinaemia	of unknown genetic defect	of unknown aetiology
Familial defective apoprotein B100	Deficiency of apoprotein CII		Apoprotein A1 deficiency	CETP deficiency
Familial combined hyperlipidaemia			LCAT deficiency	Apoprotein AI overexpression
			Fish-eye disease	
			Tangier disease	

CETP = cholesteryl ester transport protein; **HDL** = high-density lipoprotein; **LCAT** = lecithin cholesterol acyltransferase; **TG** = triglyceride.

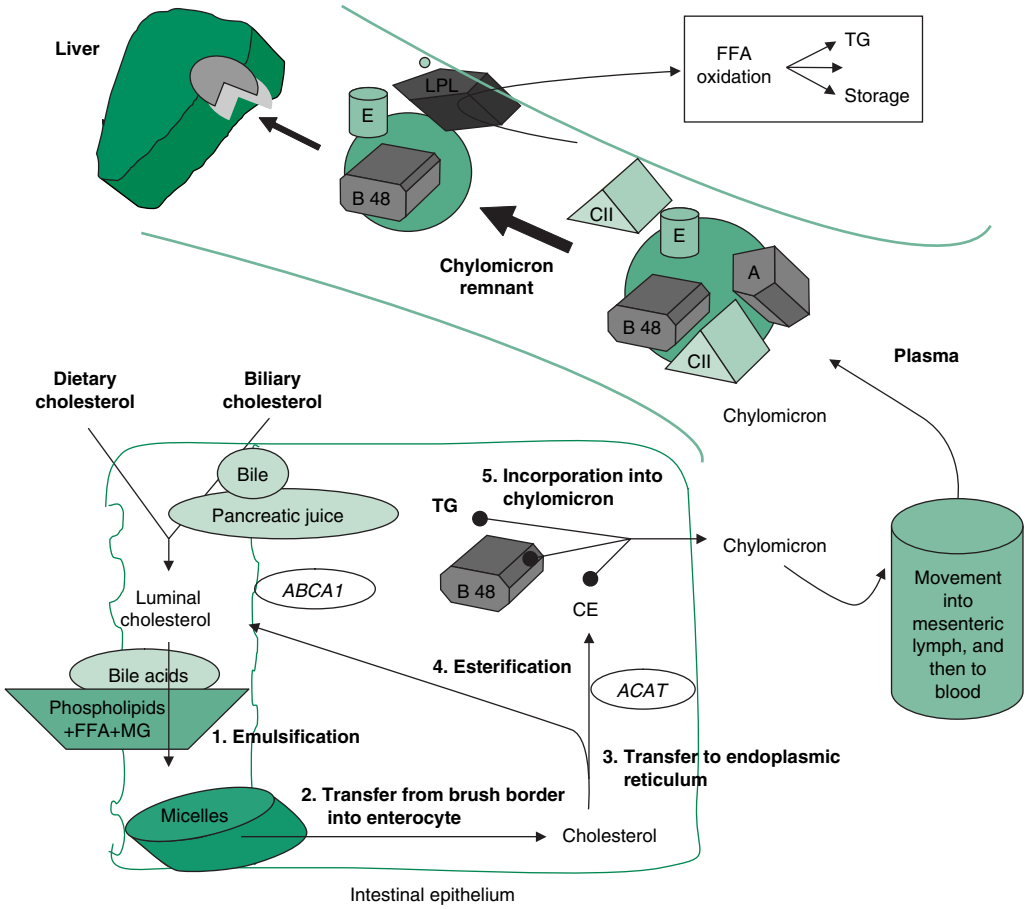

Fig. 1. Summary of the synthesis and metabolism of chylomicrons. Chylomicrons are synthesised by the small intestine to transport dietary triglyceride (TG) and cholesterol to various cells of the body. The TGs in these particles are hydrolysed within the plasma by lipoprotein lipase (LPL). The lipoprotein particles generated are referred to as chylomicron remnants, which are enriched in cholesterol and cleared by the liver. **ABCA1** = adenosine triphosphate-binding cassette transport subfamily A; **ACAT** = acetyl cholesterol acyltransferase; **A**, **B48, CII, E** = apolipoproteins A, CII, B48 and E; **CE** = cholesterol ester; **FFA** = free fatty acids; **MG** = monoglycerides.

and apo A and emerge into the extracellular space.[1] These later acquire apo C and E in exchange with HDL (figure 1).

Fatty acids derived from TGs of chylomicrons are delivered to tissues through hydrolysis by lipoprotein lipase (LPL), which is bound to capillary endothelium.[14] This pathway is facilitated by apo CII, which is a required cofactor for LPL. Chylomicron remnants are then removed by endocytosis in the liver. This process requires the presence of apo E.[15,16]

1.2 Endogenous Pathway

The liver exports TGs to peripheral tissues in the core of VLDL. These lipoproteins contain apo B100, CII and E. FFAs are delivered to tissues by the action of LPL.[17] Subsequently, VLDL remnants or intermediate-density lipoprotein (IDL) are either removed from blood via LDL receptor-related protein (LRP) and LDL receptor or transformed into LDL.[18] Apo B100 on LDL binds to its receptors, and LDL is taken into the cells to deliver cholesterol (figure 2). Remnant metabolism is mainly mediated

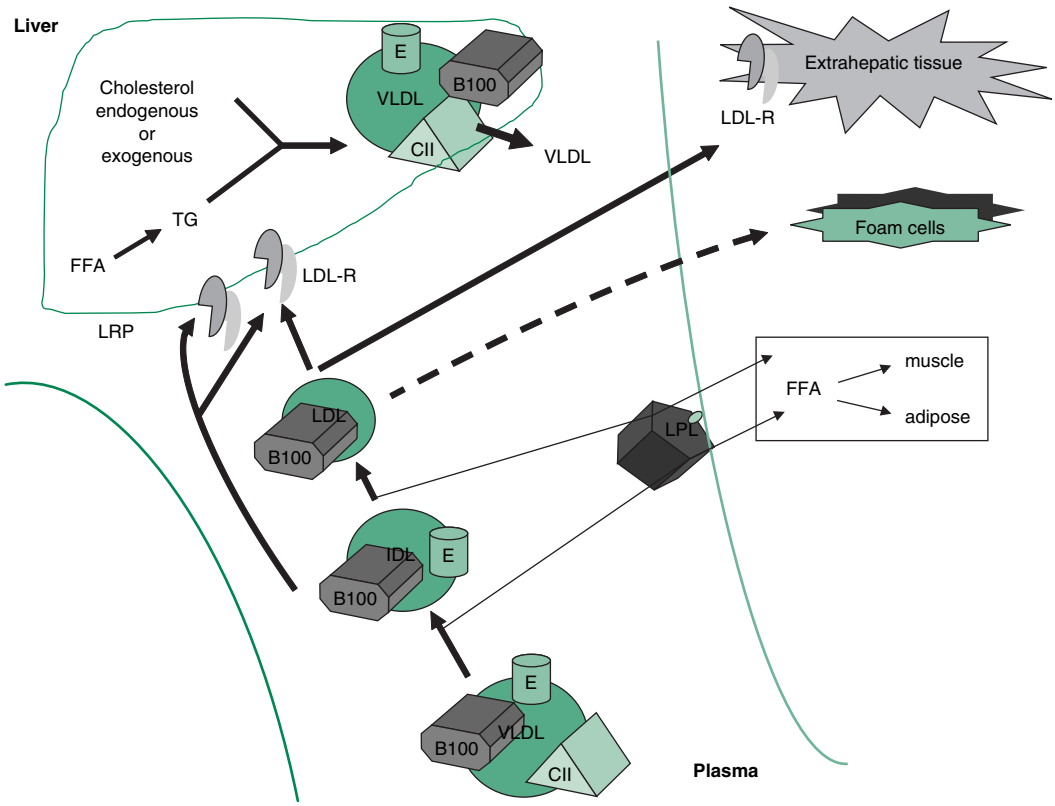

Fig. 2. Summary of the metabolism of very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs) and low-density lipoproteins (LDLs). VLDLs are synthesised by the liver to transport triglycerides (TGs) and cholesterol from the hepatocytes to various tissues of the body. In the plasma, the TGs in VLDLs are hydrolysed by lipoprotein lipase (LPL), generating a series of smaller, cholesterol-enriched lipoproteins: IDL and LDL. IDL may be transformed into LDL or removed from the plasma by the LDL receptor (LDL-R) and LDL receptor-related protein (LRP). The clearance of LDL is mediated by apolipoprotein B100. **CII**, **E** = apolipoproteins CII and E; **FFA** = free fatty acids.

by apo E, and conformational change that occurs with LDL formation results in apo B becoming the ligand for the receptor. Thus, remnant clearance is essentially an apo E-mediated process.

When the LDL receptor uptake pathway is overwhelmed, LDL may be removed from the circulation by an accessory pathway called the scavenger pathway.[19] This pathway favours the uptake of oxidised LDL particles. This process occurs in the reticulo-endothelial system and macrophages, which form lipid-laden foam cells within the intima of blood vessels. The formation of foam cells propagates an inflammatory reaction along with platelet and fibrin deposition, which finally leads to additional endothelial cell damage.

Lipolysis of TGs in LDL particles can result in small LDLs. These small, dense particles penetrate arterial intima more readily and are more susceptible to oxidation, leading to enhanced macrophage uptake and foam cell formation.

1.3 Reverse Cholesterol Transport

Adenosine triphosphate (ATP)-binding cassette transporter subfamily A member 1 (ABCA1) mediates translocation of cholesterol to cell membranes and release of cholesterol to β-HDL or discoidal

HDL. The latter interacts with lecithin cholesterol acyltransferase (LCAT) to esterify cholesterol and form HDL3, which then interacts with cell membranes to remove free cholesterol. Further esterification of cholesterol by LCAT generates HDL2, which is a very potent anti-atherosclerotic particle (figure 3).[2,20]

HDL-cholesterol (HDL-C) is returned to the liver by the hepatic scavenger receptor type 1,[21] or its CE is transferred by cholesteryl ester transport protein (CETP) to VLDL, LDL and IDL in exchange for TGs.[22,23] When the level of VLDL is normal, CETP-mediated transfer of CE is directed preferentially to LDL. When VLDL concentration increases, CE is preferentially transferred to larger VLDL particles, which become cholesterol rich and thus more atherogenic.[24]

HDL particles rich in TG undergo lipolysis by the enzyme hepatic lipase (HL). The lipid-deprived HDL is then cleared by the kidney through cubulin receptors (figure 3).

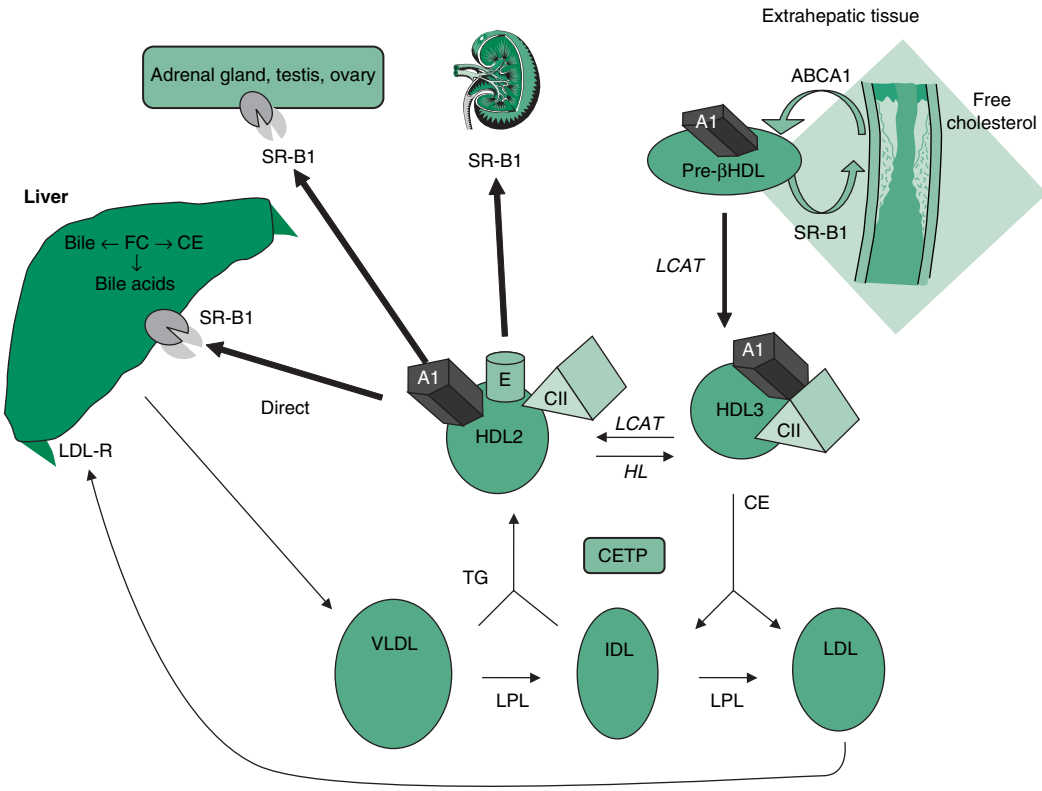

Fig. 3. Reverse cholesterol transport involving high-density lipoprotein (HDL). Adenosine triphosphate-binding cassette transport subfamily A (ABCA-1) mediates the transfer of excess cellular free cholesterol to pre-βHDL cholesterol. Plasma lecithin cholesterol acyltransferase (LCAT) converts free cholesterol in preβ-HDL to cholesteryl ester (CE), resulting in the formation of mature HDL-HDL2. HDL2 is transported to the liver by a direct or indirect pathway. In the direct pathway, selective uptake of CE by the liver occurs with the scavenger receptor type 1 (SR-B1). In the indirect pathway, the CE of HDL is exchanged for triglycerides (TGs) in low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) particles through CE transfer protein (CETP). Hepatic lipase (HL), found primarily on the endothelium of the hepatic sinusoids, hydrolyses HDL2 TGs and phospholipids to form small HDL3 particles. The enzyme lipoprotein lipase (LPL), bound to the surface of the capillary endothelium (especially in muscle and adipose tissue), hydrolyses TGs in chylomicrons and in VLDLs. **A1**, **CII**, **E** = apolipoproteins A1, CII and E; **FC** = free cholesterol; **IDL** = intermediate-density lipoprotiens; **LDL-R** = LDL receptor.

2. Familial Dyslipidaemias

Traditionally, lipid disorders were classified according to the Fredrickson classification system based on lipoprotein electrophoresis patterns (table II). In more recent texts, the dyslipidaemias are classified according to their known or suspected causes (table III). An exhaustive review of the topic is beyond the scope of this overview, and the discussion will be limited to some of the more commonly encountered lipid disorders.

2.1 Familial Disorders of Hypercholesterolaemia

2.1.1 Familial (Monogenic) Hypercholesterolaemia

By conventional definition, familial (monogenic) hypercholesterolaemia (FH) is an autosomal dominant disorder caused by a mutation in LDL receptor gene. Because the underlying molecular defect is not readily recognisable in clinics, FH can be more broadly defined as a clinical syndrome of predominant LDL hypercholesterolaemia with premature atherosclerosis and tendon xanthomas. The phenotypic expression would depend on whether the person is a homozygote or heterozygote. Thus, clinically diagnosed FH could be explained either by LDL receptor mutations or, less commonly, by either an apo B mutation (which does not have gene-dose effect), the homozygous state of proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene mutation, or could be secondary to autosomal recessive hypercholesterolaemia (ARH).

Low-Density Lipoprotein Receptor Mutations

There are more than 700 mutations in the LDL receptor that have so far been described. A database of mutations can be found at the University College of London Internet site.[25] Heterozygosity for FH occurs with a frequency of about one in 500 in the population and is more prevalent in some ethnic groups, including Ashkenazi Jews, people in the Middle East, and French Canadians, with a frequency of up to one in 67.[26] There is also a prominent and well described founder effect in the Afrikaner population of South Africa.[26] Homozygosity is rare, occurring at a frequency of one in a million.[27]

The lack of LDL receptors or dysfunctional receptors impairs the clearance of LDL, leading to an increase in the plasma cholesterol levels.[27] However, the pathophysiology of LDL receptor defects is somewhat more complex than a simple clearance problem. In addition, there appears to be some overproduction or oversecretion of apo B-containing lipoproteins. The excess plasma LDL-cholesterol (LDL-C) is taken up by scavenger receptors on macrophages, leading to deposition of lipid-laden foam cells.

Heterozygous subjects typically have plasma total cholesterol levels >300 mg/dL (7.76 mmol/L) and LDL-C >250 mg/dL (6.47 mmol/L), and homozygous subjects have plasma cholesterol levels ranging from 600 mg/dL to 1000 mg/dL (15.52 to 25.86 mmol/L) with LDL-C between 550 and 950 mg/dL (14.22 and 24.57 mmol/L).[28]

The characteristic physical finding in affected individuals is the presence of tendon xanthomas, the prevalence of which increases with age. Other common physical findings include xanthelasmas and premature arcus cornea. Homozygous individuals frequently have planar xanthomas, which are often noticed by the age of 6 years. These individuals are more susceptible to valvular and supravalvular aortic stenosis, with symptoms of cardiac disease occurring before the age of 10 years.[29] When children are diagnosed early and treated optimally, the manifestations of CVD can be substantially delayed. The overall CVD risk for people with FH varies depending on other co-existing CVD risk factors.

Treatment of heterozygous FH consists of a diet low in total and saturated fat (approximately 20% and 6% of calories, respectively) and cholesterol (<100 mg/day). In general, dietary therapy in lean

FH patients has a limited effect. HMG-CoA reductase inhibitors (statins) are effective, but combinations of two or three drugs are often needed. Effective combinations usually include a statin with ezetimibe, a bile-acid binding agent (bile acid sequestrant [BAS]) and nicotinic acid (niacin).

The age at which treatment should begin is controversial. A rational approach may be to use diet and BAS in early years and add a statin later in adolescence.[30] There is good safety data for BAS in children, but the tolerance for these agents (especially cholestyramine) is often poor. This leads to poor compliance and failure of therapy. There are good data on statin safety in children, and if treatment is considered necessary many experts who see large numbers of children with FH would prescribe a statin even before children reach adolescence.[26]

In homozygous individuals, the most effective treatment is removal of LDL-C by plasmapharesis. In addition, experimental therapies include liver transplant, porto-caval shunt and gene therapy.[27,31] Recent studies in mice have also suggested that antisense oligonucleotides can be considered as potential future therapy for homozygous individuals.[32]

Familial Defective Apoprotein (Apo) B100

This disorder is caused by a mutation in apo B100, which impairs the ability of LDL to bind to its receptor. It occurs with a frequency of one in 500 individuals and phenotypically is similar to FH, but usually milder in its manifestation because the apo E-mediated clearance of remnant particles is normal.[33]

The diagnosis is suggested by the presence of increased LDL-C, tendon xanthomas, xanthelasmas and premature CVD. However, these individuals tend to have mildly elevated cholesterol levels and, therefore, xanthomas are very rare. Treatment is similar to that of heterozygous FH.

Other Mutations with FH Phenotype

ARH is a rare disorder caused by loss of function of an adaptor protein (ARH protein) required for receptor-mediated hepatic uptake of LDL. The phenotype in this condition tends to be milder than that seen in those patients with homozygous LDL receptor mutations.[34]

Mutations in the gene *PCSK9* can cause either hypercholesterolaemia or hypocholesterolaemia.[35] *PCSK9* encodes proprotein convertase subtilisin/kexin type 9 or neural apoptosis regulated convertase, which is a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis. This proprotein convertase causes degradation of cell surface LDL receptors. Autosomal dominant hypercholesterolaemia has been attributed to mutations in this gene.[35]

It is noteworthy that the metabolic defect in these patients is mainly related to an overproduction of apo B100, although the LDL clearance is also modestly reduced.[36]

Additional environmental or genetic factors may contribute to the phenotype caused by *PCSK9* missense mutations in humans.[37]

2.1.2 Polygenic Hypercholesterolaemia

Most patients with moderate to severe hypercholesterolaemia may have either multiple mild metabolic abnormalities that synergistically raise LDL-C levels, or the phenotype is the result of one of many potential metabolic abnormalities that raise LDL-C levels.[26] These conditions do not yet have clearly defined genetic abnormalities.

2.2 Familial Disorders of Hypocholesterolaemia

2.2.1 Abetalipoproteinaemia

Abetalipoproteinaemia (ABL) is an inherited disease which is characterised by the virtual absence of apo B-containing lipoproteins from plasma. Patients

with ABL present in childhood with diarrhoea and fat malabsorption, and in their teens or later years of life develop retinitis pigmentosa and spinocerebellar ataxia. They also have acanthocytosis and fat-soluble vitamin deficiencies. Undetectable plasma apo B levels confirm the diagnosis. The condition is the result of mutations in microsomal TG transfer protein with an inability to secrete apo B in plasma. A variant of this syndrome is normo-triglyceridaemic abetalipoproteinaemia where chylomicron formation and apo B48 are normal but apo B100 is lacking.[38]

2.2.2 Hypobetalipoproteinaemia

Familial hypobetalipoproteinaemia (FHB) is a syndrome in which the plasma LDL-C levels are abnormally low. It is caused by mutations in the apo B gene that prevent the translation of a full-length apo B100 molecule. The clinical phenotype and the serum lipid profile are similar to those seen with ABL.

Truncated species of apo B (e.g. apo B37 [1728 amino acids], apo B46 [2057 amino acids]) can occasionally be identified in the plasma of individuals with FHB.[39] In some variants, TG levels can be as high as 100 mg/dL (1.13 mmol/L).

Those who are heterozygotes for FBH are usually asymptomatic. The LDL-C in these people is 25–50% of those of healthy individuals, and consequently they have protection against CVD.[38] Homozygous individuals with FBH have extremely low LDL-C levels and have several clinical problems secondary to fat malabsorption and fat-soluble vitamin deficiency.

2.2.3 Mutations in the PCSK9 Gene

Mutations that disrupt the normal function of the *PCSK9* gene, which has a regulatory role in LDL receptor turnover, could result in an increased number of LDL receptors and hypocholesterolaemia.[40] Such mutations may also increase the cholesterol-lowering effect of statins.[40]

2.3 Familial Disorders of Hypertriglyceridaemia

Hypertriglyceridaemia is commonly the result of both a genetic predisposition and an additional aggravating cofactor such as insulin resistance in centrally obese patients. Hypertriglyceridaemia in combination with insulin resistance and central obesity is far more frequent than familial hypertriglyceridaemia. Obesity or insulin resistance-induced hypertriglyceridaemia is associated with polymorphisms in the apo A1/CIII/AIV/AV gene cluster.[41,42] This observation highlights gene-environment interactions that determine the expression of the dyslipidaemic phenotype.

2.3.1 Familial Hypertriglyceridaemia

The mode of inheritance of familial hypertriglyceridaemia is unknown, but the metabolic defect is characterised by excess TG enrichment of VLDL, chylomicrons or both in the presence of near-normal apo B production.[43] This leads to large, TG-rich VLDL particles. Whether these large, TG-rich VLDL particles are atherogenic is not clear.

Generally, this condition is mild and asymptomatic, unless a secondary factor contributes to increased TG production, leading in adulthood to pancreatitis and eruptive xanthomas. The disorder can be diagnosed only if elevated serum TG levels are found in half of the first-degree relatives at risk, and it can be difficult to distinguish from familial combined hyperlipidaemia (FCH). Serum TG levels are usually in the 200–500 mg/dL (2.26−5.65 mmol/L) range. HDL-C is decreased and LDL-C levels are normal.[29]

In addition to dietary fat restriction, secondary disorders should be screened for and treated. Drugs that lower TG levels and are commonly used in the management of this condition include fibric acid derivatives (fibrates) such as fenofibrate and gemfibrozil, or nicotinic acid.

2.3.2 Deficiency of Lipoprotein Lipase

This is a rare recessive disorder that results from mutation in the LPL gene or its cofactor apo CII. The prevalence of this dyslipidaemia is estimated to be one in a million

In patients with severe disease, the plasma can be visibly lipaemic, with TG levels ranging from 2000 to 25 000 mg/dL (22.6 to 282.5 mmol/L). Lipaemic plasma is found in the majority of patients, especially at time of diagnosis when no dietary changes have been made as yet.

The condition usually presents in childhood with pancreatitis, eruptive xanthomas and lipaemia retinalis. Neonatal pancreatitis can occur with familial LPL deficiency.[44] Hepatomegaly and splenomegaly are frequently present and are the result of TG accumulation in reticuloendothelial cells.[26] There is no evidence of increased risk of CVD in this lipid disorder, although some case reports have suggested that this may occur.[45]

The definitive diagnosis of LPL deficiency is established by demonstrating the absence of lipase activity in plasma after intravenous heparin administration.[46]

The mainstay of treatment is a diet very low in fat (<10% of total calories, ~15–30 g/day in adults). Drug therapy is largely ineffective, although fibrates and nicotinic acid may lower VLDL production modestly.

2.3.3 Deficiency of Apo CII

Apo CII deficiency is a rare autosomal recessive inborn error of metabolism. Since apo CII is a cofactor of LPL, its deficiency state clinically resembles LPL deficiency.

The biochemical findings in homozygous individuals include severe fasting hypertriglyceridaemia and chylomicronaemia. Heterozygous carriers are typically normolipidaemic.[47]

A transient normalisation of plasma TG levels and a marked improvement in the clinical course is achieved by infusion of plasma containing apo CII in these patients.[48] However, transgenic mice overexpressing the human apo CII gene are hypertriglyceridaemic, suggesting that apo CII has additional roles in the metabolism of plasma TGs that extend beyond activating LPL.[49] In these mice, the clearance of VLDL was delayed, whereas the production of VLDL was unaffected. VLDL prepared from these transgenic animals showed markedly decreased binding to heparin, raising the possibility that apo CII modulates the interaction of lipoproteins with cell surface glycosaminoglycans.[49]

2.4 Familial Disorders of Combined Hypertriglyceridaemia and Hypercholesterolaemia

2.4.1 Familial Combined Hyperlipidaemia

FCH is the most common form of hyperlipidaemia, occurring in 1–2% of the population. It is inherited as an autosomal dominant trait with unknown genetic cause.

The association between the upstream stimulatory factor 1 gene and FCH is intriguing and requires further study.[50]

The metabolic defect is unclear, but overproduction of apo B may be a contributing factor to the increased production of VLDL. In addition, the clearance of TG-rich lipoproteins may be impaired in some individuals.[51]

The phenotype may be the same as that of familial hypertriglyceridaemia. The predominant lipid abnormality may also vary in a single person over time. In general, it should be suspected in patients with moderate hypertriglyceridaemia or hypercholesterolaemia or both, especially in the setting of a family history of premature CVD.[52]

FCH is often associated with low HDL-C levels and increased serum level of small, dense LDL particles. This lipid phenotype is not unique to FCH and can be seen in other lipid disorders as well. Affected individuals have a high prevalence of the

dysmetabolic syndrome with its associated hypertension, diabetes mellitus and obesity. The risk of premature CVD in these individuals is increased by 2- to 5-fold.

The diagnosis is usually made on the basis of plasma total cholesterol and/or TG levels >90th percentile adjusted for age and sex. Some studies have suggested that an elevated apo B levels might be the common hallmark of FCH within an individual, and that the diagnosis of FCH can best be predicted by absolute apo B levels combined with TG and total cholesterol levels adjusted for age and sex.[53] However, one important limitation of using apo B measurements as a diagnostic criterion for FCH is the need for a standardised test for apo B.

The variations in metabolic phenotypes of FCH were shown in a study of 72 hyperlipidaemic FCH relatives.[54] This analysis showed bimodal distribution of LDL size associated with distinct phenotypes: type A with large buoyant LDL and type B with small dense LDL. Individuals with large LDL showed a hypercholesterolaemic phenotype, and those with small, dense LDL had hypertriglyceridaemia and low HDL-C phenotype with moderately elevated apo B levels.[54]

In FCH, multiple genetic defects in the expression of LDL receptor have been described. These include abnormalities in synthesis of the receptor in endoplasmic reticulum, abnormalities of transport to Golgi apparatus or a defective clustering in coated pits.

The treatment of this dyslipidaemia consists of weight reduction and a low-fat diet. This will help correct the metabolic abnormalities such as obesity and insulin resistance. Drug therapy should be directed at the predominant lipid abnormality.

2.4.2 Familial Dysbetalipoproteinaemia

Familial dysbetalipoproteinaemia is a disorder that often remains undiagnosed. The prevalence rate in the general population ranges from 0.2% to 1.0%. It is also referred to as type III dyslipidaemia in the Fredrickson classification.

The cause is a mutation in apo E that results in defective binding to the lipoprotein receptors. In most instances, this condition is inherited as an autosomal recessive trait that requires a secondary exacerbating metabolic factor for expression. Only a subset of E2/E2 homozygous individuals will express the clinical syndrome. This apo E mutation will lead to the accumulation of cholesterol-rich remnants of VLDL, IDL and chylomicrons.[1,55] These cholesterol-rich remnants appear as a β-VLDL band on lipoprotein electrophoresis and lead to deposition of cholesterol in macrophages with foam cell formation and accumulation.

Clinically, individuals with this dyslipidaemia have skin xanthomas and atherosclerotic vascular disease, especially peripheral vascular disease.[56] The presence of planar palmar xanthomas makes the diagnosis highly likely. Tuberous xanthomas are also common, but are less helpful diagnostically because they are also found in FH and other rare disorders of sterol metabolism. Most patients with dysbetalipoproteinaemia have xanthomata that are best described as tuboeruptive.

Dysbetalipoproteinaemia is somewhat different from most other familial dyslipidaemias in the sense that there is often delayed manifestation of the phenotype in the form of often normal or low lipid levels in youth with a 'metabolic switch' in adulthood and severe dyslipidaemia thereafter.

The diagnosis should be suspected in patients with moderately severe elevations in both plasma TG and cholesterol levels. Typically, the plasma cholesterol and TG levels are in the range of 300–400 mg/dL (3.39–4.52 mmol/L), and the VLDL-C/TG ratio is usually more than 0.3 (normally the ratio is <0.2). HDL-C levels are usually normal and LDL-C levels are almost always reduced.[55]

The expression of dysbetalipoproteinaemia is influenced by coexisting conditions such as obesity,

insulin resistance, diabetes and, less commonly, hypothyroidism and alcohol consumption.[56,57] These confounding problems should be identified and treated. Dietary therapy should be aimed at restricting total fat and cholesterol. If dietary therapy and treatment of coexisting metabolic conditions do not yield satisfactory results, drug therapy should be initiated using statins, nicotinic acid or fibrates.

2.4.3 Familial Hepatic Lipase Deficiency

The main physiological function of HL is to remove TGs and phospholipids from chylomicron and VLDL remnants. It also facilitates the conversion of VLDL to LDL and the metabolism of HDL2 to HDL3.[1] People with HL deficiency have severe hypertriglyceridaemia secondary to accumulation of VLDL remnants and modestly elevated LDL-C, but HDL-C levels in these individuals are either normal or elevated.[58] Overall, HL deficiency may result in a lipoprotein pattern that is associated with low heart disease risk.[59]

2.5 Familial Causes of Low High-Density Lipoprotein-Cholesterol (HDL-C)

2.5.1 Familial Hypoalphalipoproteinaemia of Unknown Genetic Defect

Familial hypoalphalipoproteinaemia is an autosomal dominant disorder with an unknown genetic defect.[60] Sequence variations in the heterozygote state of LCAT, ABCA1 and apo AI are associated with HDL-C levels in the lower fifth percentile of the population.[61]

It is found more frequently in some ethnic groups such as those of the Indian subcontinent. It is manifested by low plasma HDL-C (<30 mg/dL [0.78 mmol/L] in men or <40mg/dL [1.04 mmol/L] in premenopausal women) and an increased risk of premature CVD.[60] There are no characteristic physical findings, but there is often a family history of low HDL-C and premature CVD.

Treatment includes raising the HDL-C levels with weight loss and exercise. Estrogen therapy for postmenopausal women,[62] nicotinic acid, fibrates and thiazolidinediones can also modestly increase the HDL-C levels.

2.5.2 Apoprotein AI Deficiency

Apo AI deficiency is caused by a mutation in apo AI gene that leads to low HDL-C levels (<10 mg/dL [0.26 mmol/L]).

Clinical manifestations include premature CVD, xanthomas and corneal opacities.[63] Raising HDL-C levels in these patients is usually difficult and, therefore, the treatment should be directed towards lowering non-HDL-C levels.

A rare variant, apo AI Milano, has been recognised where there is a substitution of cysteine for arginine in the apo AI. This is an autosomal dominant disorder that despite low HDL-C levels is associated with longevity.[64]

2.5.3 Lecithin Cholesterol Acyltransferase Deficiency

LCAT deficiency is a rare recessive disorder that results in decreased esterification of cholesterol to CE on HDL particles and thus leads to accumulation of free cholesterol in peripheral tissues (cornea, red blood cell membranes and renal glomeruli), causing corneal opacities, normochromic anaemia and renal failure in young adults.[65] Similarly, accumulation of cholesterol in vascular tissues causes premature CVD.

A number of mutations have been described. Plasma cholesterol levels are variable, HDL-C levels are low, and the ratio of free cholesterol to esterified cholesterol in plasma is increased.[66]

Increasing plasma activity of LCAT is an ideal treatment, but it is not practical at the present time. Current treatment consists of preventive strategies with dietary fat restriction and symptomatic treatment (e.g. renal transplant).

2.5.4 Fish-Eye Disease

Fish-eye disease is a variant of LCAT deficiency caused by a mutation of the LCAT gene, but the phenotype is less severe than in LCAT deficiency.[67] It is characterised by low HDL-C levels and corneal opacities, but there is no anaemia, renal failure or premature CVD.

2.5.5 Tangier Disease

Tangier disease is a rare autosomal recessive disorder that is associated with enhanced catabolism of plasma HDL-C. Mutations in *ABCA1* have been linked to this disease, causing massive amounts of CE accumulation in macrophages.[68] The phenotype is characterised by orange tonsils, corneal deposits, hepatomegaly and splenomegaly, peripheral neuropathy and some increase in risk of CVD.[69] Low LDL-C and HDL-C levels with mild hypertriglyceridaemia are often present. There is no specific treatment for this condition.

2.6 Familial Causes of High HDL-C

2.6.1 Familial Hyperalphalipoproteinaemia of Unknown Genetic Defect

Marked elevation in plasma HDL-C levels is typical of hyperalphalipoproteinaemia (HALP), which is characterised by HDL-C levels >90th percentile for an age- and sex-matched general population.[70] Primary HALP can be of unknown aetiology or can arise from genetic deficiency of plasma CETP, as well as from increased production of apo AI, which is a major HDL apoprotein.[70]

2.6.2 Cholesteryl Ester Transport Protein Deficiency

CETP deficiency is a hereditary syndrome in which plasma HDL-C levels are increased. It is the most important and frequent cause of HALP in Asian populations.[71] Features include marked elevations of plasma HDL-C levels in homozygotes (usually 100 mg/dL [2.59 mmol/L]) and moderate elevation (70–100 mg/dL [1.81–2.59 mmol/L]) in heterozygotes.

The relationship between reduced CETP function and the susceptibility to atherosclerosis is complex with both longevity[71] and increased CVD risk[72,73] reported. Some investigators have considered that this disorder represents a 'longevity syndrome', because plasma lipid profiles in CETP deficiency are characterised by high plasma HDL-C levels and relatively low LDL-C levels.[72] In the Japanese population of Omagari, the intron 14 splicing defect in the CETP gene was found to be a frequent cause of CETP deficiency, but the condition was not associated with longevity and instead appeared to be pro-atherogenic.[74]

2.6.3 Apo AI Overexpression

Several animal studies have shown that apo AI prevents atherosclerosis development. Infusion of apo AI containing lipoproteins in rabbits inhibits lesion formation,[75] and overexpression of human apo AI in apo E-deficient mice[76] and human apo(a)- transgenic mice[77] protects against atherosclerosis. Somatic adenovirus-mediated apo AI gene transfer was associated with a 2-fold increase of HDL-C levels and 2-fold decrease in the development of atherosclerotic lesions over a 6-week period in transgenic mice.[78]

Increased production of apo AI in humans has been associated with high HDL-C levels, absence of CVD and longevity.[79]

2.7 Other Dyslipidaemias

Another dyslipidaemia that is not commonly recognised is increased plasma lipoprotein (a) [Lp{a}] concentration.[80] This disorder consists of large LDL particles in which the apo B protein is covalently bonded to apo(a). The latter is a protein of unknown function that shares high-sequence homology with plasminogen. Some studies have suggested that elevated Lp(a) levels are associated with an increased risk of CVD.[80]

There are no characteristic physical findings in this disorder. Elevated Lp(a) [> 30 mg/dL] is usually

suspected in patients with premature CVD. Some ethnic or racial groups (e.g. the African American population) appear to have higher levels of Lp(a). Treatment includes nicotinic acid, which lowers Lp(a) by 30–40%, and estrogen therapy for postmenopausal women, which lowers Lp(a) by about 20%.

3. Management Guidelines

Management of any lipid disorder starts with thorough evaluation to identify and possibly ameliorate secondary causes that may be contributing to the abnormal lipid metabolism. Currently, the management of dyslipidaemias is based on their predominant phenotypic feature rather than on their precise underlying aetiology. The cornerstone of the management of lipid disorders is lifestyle modification, including increased physical activity and dietary restrictions.[81] The overall lipid-lowering efficacy of such intervention is modest. In some individuals, and especially with certain forms of dyslipidaemia, dietary modifications can have a significantly favourable effect. An example of the latter is the lowering of serum TG levels in hypertriglyceridaemic individuals with a reduction in dietary fat intake. In some hypercholesterolaemic individuals, dietary changes, notably a reduction in saturated fat and cholesterol intake or increased consumption of sterols to block cholesterol absorption, can have a robust effect. However, on average, the reduction in LDL-C levels with such dietary changes is in the order of 10–15%. It is noteworthy that lifestyle interventions have favourable effects independent of their lipid-lowering effect. Examples of the latter include the effect of smoking cessation and possibly the effect of diets high in omega-3 polyunsaturated fatty acids. In addition, many people with dyslipidaemia are overweight and benefit from calorie restriction.

Lipid alterations can be effected by a number of dietary approaches that differ with respect to the degree and type of underlying lipid abnormality. The Adult Treatment Panel III (ATP III) dietary recommendation for predominantly high LDL-C phenotypes is to limit the intake of saturated fat to <7% of total calories and cholesterol to <200 mg/day, with intake of polyunsaturated fat being up to 10% of total calories, monounsaturated fat up to 20% of total calories and protein 20% of total calories.[82] Carbohydrates should be limited to 50% of total calories and preferably 20–30 g/day of fibre should be consumed. If severe hypertriglyceridaemia is present, the recommendation is to start with a fat-free diet until the plasma TG level is <1000 mg/dL (11.3 mmol/L), then to follow a maintenance diet with total fat content <10% of total calories.[82]

Light to moderate amounts of alcohol have no acute effect on glucose and insulin levels, although excessive amounts of alcohol (three or more drinks per day) can contribute to hyperglycaemia.[83] In small clinical trials and some observational studies, light to moderate amounts of alcohol (one to two drinks per day; 15–30g of alcohol) improve insulin sensitivity and raise HDL-C levels, but do not raise TG levels. However in some susceptible individuals, alcohol, especially when consumed in excessive amounts, will contribute to hypertriglyceridaemia.[82,83]

There are several classes of pharmacological agents for the treatment of dyslipidaemias[84-90] (table IV). Statins, competitive inhibitors of HMG-CoA reductase, lead to decreased cellular cholesterol synthesis, causing activation of sterol regulatory element binding protein, a transcription factor that upregulates hepatic LDL-receptor activity and thus decreases serum LDL-C levels.[84] Statins may also affect additional pathways of lipid metabolism because they have some efficacy in LDL receptor-deficient homozygous FH patients.

Fibrates act by activating the nuclear transcription factor peroxisome proliferator-activated receptors α (PPARα), modestly upregulating the expres-

Table IV. Pharmacological agents for the treatment of dyslipidaemias

Drug or drug class	Effects on lipid levels	Adverse effects	Specific agents (trade name) and dosage
HMG-CoA reductase inhibitors (statins)	LDL-C ↓ 18–55% HDL-C ↑ 5–15% TG ↓ 7–30%	Hepatotoxicity, myopathy, ↑ creatine kinase levels	Rosuvastatin (Crestor®) 5–40mg orally once daily Fluvastatin (Lescol®) 20–40mg orally nightly Fluvastatin extended release (Lescol XL®) 80mg orally nightly Simvastatin (Zocor®) 5–80mg orally every evening Pravastatin (Pravachol®) 10–80mg orally once daily Atorvastatin (Lipitor®) 10–80mg orally once daily Lovastatin (Mevacor®) 10–80mg orally nightly Lovastatin extended-release (Altoprev®) 10–60mg orally nightly
Ezetimibe	LDL-C ↓ 15–20% HDL-C ↑ 1% TG ↓ 8%	No major adverse effects	Zetia®, 10mg orally once daily
Ezetimibe combined with simvastatin	LDL-C ↓ 30–60% HDL-C ↑ 9% TG ↓ 20%	As above	Vytorin™ 10/10mg to 10/80mg orally once daily
Nicotinic acid (niacin)	LDL-C ↓ 5–25% HDL-C ↑ 15–35% (↑ Apoprotein A1) TG ↓ 20–50% Small, dense LDL ↓	Flushing, hyperglycaemia, hyperuricaemia, hepatotoxicity	Nicotinic acid 1–2g orally two or three times daily Extended-release nicotinic acid (Niaspan®) 1000–2000mg orally nightly Sustained-release nicotinic acid (Slo-Niacin®) 250–750mg orally once or twice daily
Combination of a statin and nicotinic acid	LDL-C ↓ 30–42% HDL-C ↑ 20–30% TG ↓ 32–44%	As above for individual agents	Lovastatin/nicotinic acid (Advicor®) 20–500mg to 20–1000mg orally nightly
Fibrates (fibric acid derivatives)	LDL-C ↓ 5–20% HDL-C ↑ 10–15% TG ↓ 20–50% Small, dense ↓ LDL-C	Dyspepsia, gallstones, hepatotoxicity, myopathy	Fenofibrate, micronised (Antara™) 43–130mg orally once daily Fenofibrate, micronised (Lofibra™) 67–200mg orally once daily Fenofibrate (Tricor®) 48–145mg orally once daily Gemfibrozil (Lopid®) 600mg orally twice daily Bezafibrate (Bezalip®, Bezagen®, Fibrazate®, Liparol™, Zimbacol®) 200mg orally twice daily; Bezalip® Mono 400mg once a day
Bile acid binding agents (or sequestrants)	LDL-C ↓ 10–20% HDL-C ↓ 1–2% TG ↓ possible ↓ 10%	Gastroinestinal distress, constipation	Cholestyramine (Questran) 4–24g orally daily, two or three times daily Colestipol (Colestid®) 5–30g orally once or twice daily Colesevelam (Welchol®) 1.875–3.75g once or twice daily
Omega-3 fatty acid	TG ↓ 25–30% LDL-C ↓ 5–10% HDL-C ↑ 1–3%	Fishy aftertaste, gastrointestinal disturbances	Omacor® (1g) 4g orally daily; OTC: fish oil, Promega, Cardio-Omega 3, Marine Lipid Concentrate, MAX EPA®, SuperEPA 1200, 2–4g per day of EPA + DHA

DHA = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **OTC** = over the counter; **TG** = triglyceride.

sion of LDL receptors and apo AI gene, and downregulating the expression of the apo CII and apo CIII genes. Fibrates also increase the buoyancy of LDL particles.[91] Decreased expression of apo CIII rather than apo CII (an activator of LPL) seems to be the most important change in apo C proteins.[91,92] Upregulation of LPL seems to be an important feature regarding the TG-lowering potency of fibrates.[93] The lipid-lowering effects of fibrates are multiple and complex.

The primary action of nicotinic acid is to inhibit the mobilisation of FFA from peripheral tissues, thereby reducing hepatic synthesis of TGs and secretion of VLDL.[84] It also decreases the assembly

and increases the degradation of apo B, thereby further lowering VLDL and LDL levels. In addition, nicotinic acid inhibits hepatic uptake of apo AI and enhances plasma pre-βHDL, causing an increase in plasma HDL-C levels.[84,86] Recently, nicotinic acid receptor has been discovered (HM74A).[94] This is a G protein-coupled receptor that has a role in prostaglandin synthesis and PPAR activation.[95,96]

BAS bind bile acids in the intestine, interrupt the enterohepatic circulation of bile acids and increase the conversion of cholesterol into bile acids in the liver.[84] This leads to an increase in hepatic synthesis of cholesterol, along with an increase in the secretion of VLDL, causing a modest elevation of serum TG levels. This latter feature limits the utility of this class of agents in individuals with combined hypercholesterolaemia and hypertriglyceridaemia.[84]

Ezetimibe inhibits the intestinal absorption of cholesterol and related phytosterols.[97] The effect of ezetimibe is additive to the LDL-C lowering achieved with statins. When used as monotherapy, ezetimibe reduces LDL-C levels by 15–20%, with a non-significant increase in HDL-C levels.[97]

Decreased HDL-C levels constitute a major risk factor for coronary heart disease. However, at the present time, there are no therapies that substantially increase plasma HDL-C levels. Nicotinic acid can raise HDL-C levels by up to 30%.[84] Inhibition of CETP has been proposed as a strategy to raise HDL-C levels. Torcetrapib, a potent inhibitor of CETP, is currently being investigated in clinical trials. In a recent phase III study, plasma HDL-C levels increased by 46–106% in the group that received torcetrapib. Relative to placebo, torcetrapib also reduced TG and LDL-C levels.[98] The relation of CETP activity to the risk of CVD remains controversial, and additional clinical trials are being conducted to evaluate the effect of this drug on atherosclerotic plaques, as measured by various imaging modalities.

The choice of a particular agent depends on the baseline lipid profile achieved after 6–12 weeks of intense lifestyle changes and possible use of dietary supplements such as stanols and plant sterols.[82] A simplified algorithm of drug therapy of dyslipidaemia in adult subjects is shown in figure 4. The values of serum lipid profile are not intended to represent goals of therapy but rather are suggested as trigger points for initiation or modification of drug choices.[99] If the predominant lipid abnormality is hypertriglyceridaemia with serum TG concentration >500 mg/dL (5.65 mmol/L), then omega-3 fatty acids would be considered as the first choice of therapy. This approach is often effective when administered at the correct dosage and carries relatively small risk. As a cautionary note, it is prudent to keep in mind that omega-3 fatty acids are effective in moderate hypertriglyceridaemia, but may be inappropriate in chylomicronaemia when there is a profound lipolytic defect such as in LPL deficiency. An effective alternative is the use of a fibrate or nicotinic acid. In subsequent follow-up, when LDL-C levels are >130 mg/dL (3.367 mmol/L), then a statin should be added as a combination therapy.

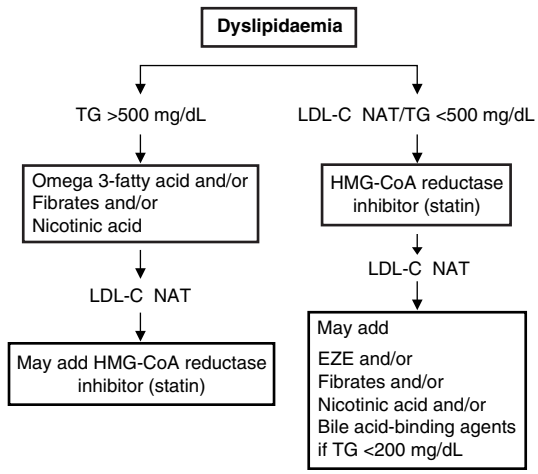

Fig. 4. A simplified algorithm of drug therapy of dyslipidaemias in adults. Triglyceride (TG) levels of 200 and 500 mg/dL (2.26 and 5.56 mmol/L) are equivalent to 2.26 and 5.65 mmol/L, respectively. **EZE** = ezetimibe; **LDL-C** = low-density lipoprotein-cholesterol; **NAT** = not at target.

Other options to be used in combination with a fibrate or nicotinic acid could include ezetimibe.[98] However, the combination of ezetimibe with fibrates or nicotinic acid is not well studied and does not have US FDA approval and, as such, should be closely monitored.

In general, if the serum TG levels are <500 mg/dL (5.65 mmol/L) and the LDL-C values are >130 mg/dL (3.37 mmol/L), then a statin should be the first drug of choice. The statin dose can be titrated up to achieve the therapeutic goal, or alternatively ezetimibe can be added. BAS are an option if the serum TG levels do not exceed 200 mg/dL (2.26 mmol/L), otherwise a fibrate or nicotinic acid should be considered (figure 4).

The decision to treat a particular patient has to be individualised. Patients with established CVD invariably need treatment. Other patients will need global risk assessment to determine the desirable goal of LDL-C level. In individuals with FH, treatment is indicated irrespective of global risk assessment, since the latter will severely underestimate the true clinical risk in these patients.

The use of drug combination as first-line therapy is becoming more popular with the advent of fixed-dose combination pills. However, the clinical experience with this approach is limited. The combination of a statin with a fibrate or nicotinic acid increases the risk of rhabdomyolosis and, therefore, a low dose of statins or a fibrate with the lowest drug interaction potential, such as fenofibrate, should be used.

The use of nicotinic acid to treat dyslipidaemia in patients with type 2 diabetes has been discouraged because of the potential increase in insulin resistance. It appears that if the dose of nicotinic acid is limited to <2 g/day, the effect on insulin resistance is modest.[100] It is noteworthy that some of the newly available insulin sensitisers such as pioglitazone have significant favourable effects on serum TG and HDL-C levels, and these effects are independent of their effects on blood glucose control.[101]

The goals of therapy should also be individualised. The guidelines suggested by the ATP III of the National Cholesterol Education Program (NCEP) are helpful in clinical practice.[82] Unfortunately, a significant number of patients fail to achieve these goals. The task of achieving the lipid therapy goals in a larger number of patients will be greatly facilitated with the advent of more powerful agents that can be used safely in combination with other agents with distinct mechanisms of actions.

4. Conclusions

Dyslipidaemias continue to be a major cause of morbidity and mortality, despite the significant advances in pharmacological therapies. The individual pharmacological therapies usually achieve a 30% reduction in cardiovascular events. To make further inroads in reducing the burden of CVD, more aggressive and early interventions will be needed. Combination therapy targeting all aspects of abnormal lipid metabolism, including reducing TG levels and increasing HDL-C levels, will be necessary to achieve further reductions in CVD.

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