Nutrition in Lipidaemias

Topic 22

Module 22.1

Dyslipidemia: Targeting the Management of Cardiovascular Risk Factors

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Learning Objectives

- To know the main types of dyslipidaemia;
- To learn the consequences of lipid accumulation in different tissues;
- To understand the pathogenesis of atherosclerosis;
- To learn the laboratory evaluation of dyslipidaemia;
- To learn the indications for treatment in patients with dyslipidaemia.

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Key Messages

- Dyslipidaemia is important due to its causal relation with atherosclerosis and cardiovascular disease;
- Plasma lipid concentrations are stratified according to the presence of different cardiovascular risk factors in an individual and may differ between different subjects;
- The traditional classification of hyperlipidaemia is based on the pattern of plasma lipoprotein elevation as observed in lipoprotein electrophoresis. However, most current clinical guidelines on hyperlipidaemia management are not based on electrophoresis results;
- Hyperlipidaemia may be divided into primary and secondary disorders. In the first case, genetic defects alter normal metabolism of lipoproteins. Other factors that modify lipoprotein metabolism, such as diabetes mellitus, increase lipoprotein concentrations in secondary hyperlipidaemia. Many patients suffer both primary genetic disorders and secondary causes: the primary genetic defect predisposes them to a more severe expression of the secondary lipid disorder associated with underlying pathologies such as obesity and diabetes;
- Elevated plasma lipids (cholesterol or triglycerides) can accumulate in macrophage reticuloendothelial cells in certain tissues. The clinical expression may be as Xanthelasmas, Tendon, Tuberous, Palmar, and Eruptive Xanthomas;
- Serum triglyceride concentrations exceeding 1000 mg/dL (11 mmol/L) may precipitate attacks of acute pancreatitis. The pathogenesis of hypertriglyceridaemic pancreatitis is unclear, but the release of free fatty acids may damage pancreatic acinar cells or capillary endothelium;
- Abnormalities in plasma lipoproteins are well known risk factors for atherosclerosis;
- Atherosclerosis preferentially affects various regions of the circulation with distinct clinical manifestations depending on the particular circulatory bed affected;
- The development of the atheromatous plaque involves fatty streak formation, lipoprotein oxidation, leukocyte recruitment, foam cell formation, smooth-muscle cell migration, microthrombi formation and calcification, vascular remodelling, plaque instability and rupture, and endothelial dysfunction;
- Clinical Guidelines recommend cholesterol screening for primary prevention of coronary heart disease starting in adults at 20 to 45 years depending on the particular guideline. Individuals should have a fasting lipid profile done every 5 years. It includes total cholesterol, cLDL, cHDL and triglycerides. Non-HDL cholesterol (total cholesterol minus HDL cholesterol) measures all cholesterol particles that are considered atherogenic and it has been proposed as a useful index;
- Recommendations on when to start medical therapy depend on LDL levels and also on other risk factors for CHD. Different organizations have established guidelines that vary slightly. They usually follow a step-based approach to individual risk assessment.
1. Definition

The term dyslipidaemia (DLP) designates different alterations of plasma lipids, including an increase in total cholesterol, cholesterol transported by low density lipoprotein (cLDL) and triglycerides, as well as a decrease of cholesterol transported by high density lipoprotein (cHDL). This term is slightly broader than hyperlipidaemia (HLP) which refers only to an increase of plasma concentrations of cholesterol and triglycerides. Actually, hyperlipidaemia is synonymous with hyperlipoproteinaemia. This may be due either to increased production or secretion of lipids into the circulation or to decreased clearance or removal from the circulation; in some cases, both processes coexist. These alterations may affect one or more classes of lipoproteins.

DLP is important due to its causal relation to atherosclerosis and cardiovascular disease (CVD), which are the major causes of death and disability in Europe. There are important regional differences with reduced prevalence in Western countries of Europe (1).

The cut-off point defining a particular lipid concentration as high has several interpretations. From an epidemiological point of view, HLP may be defined as a value over a particular percentile from population distributions, for example, the 90th to 95th percentile. However, from a clinical point of view, lipoproteins within the low normal or ideal (desirable) range, have the best association with the prevention of cardiovascular disease or to therapeutic benefit from lipid lowering drugs. Measurements which include concentrations of cLDL, cHDL and, to a lesser degree, triglycerides, are preferable to total cholesterol alone. High or low cLDL or cHDL, respectively, are directly and causally linked to an increased coronary risk.

The desirable plasma concentrations are stratified according to the presence of other cardiovascular risk factors in an individual and may therefore vary between different subjects. However, it is widely accepted that coronary risk increases with higher lipids across the complete range of values, with decreased risk as these values descend.

2. Classification

The pattern of plasma lipoprotein elevation is useful to classify (hyperlipidaemia) HLP. The Fredrickson classification has been very helpful to understand lipid disorders (Table 1) and some denominations of DLP are still based on the predominant pattern of lipoprotein elevation. However, this classification is based on electrophoresis of plasma lipoproteins, and although it has been used for many years, it has now fallen into disuse. This is due to the fact, on the one hand, that different lipoprotein patterns may occur in several family members with the same disorder and on the other hand, that most current clinical guidelines are not based on electrophoresis results.

Table 1
Classification of hyperlipidaemia according to Fredrickson

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Increased Lipoprotein</th>
<th>Plasma Cholesterol</th>
<th>Plasma Triglycerides</th>
<th>Atherogenesis</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Normal or ↑</td>
<td>↑↑↑↑</td>
<td>+</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>↑↑</td>
<td>Normal</td>
<td>+++</td>
<td>10</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL &amp; VLDL</td>
<td>↑↑</td>
<td>↑↑</td>
<td>+++</td>
<td>45</td>
</tr>
<tr>
<td>III</td>
<td>ILD</td>
<td>↑↑</td>
<td>↑↑↑↑</td>
<td>+</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Normal or ↑</td>
<td>↑↑</td>
<td>+</td>
<td>45</td>
</tr>
<tr>
<td>V</td>
<td>VLDL &amp; chylomicrons</td>
<td>↑↑</td>
<td>↑↑↑↑</td>
<td>+</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>
HLP may be divided into primary disorders (Table 2), in which genetic defects cause abnormal lipoprotein metabolism, and secondary disorders, in which acquired conditions (Table 3), such as obesity and diabetes, modify lipoprotein metabolism. Many patients suffer a combination of both primary genetic and secondary causes: the primary genetic defect predisposes them to a more severe expression of the secondary lipid disorder associated with the acquired pathology. At the same time, correction of the underlying disorder causing the secondary process also benefits the treatment of the primary genetic defect. In clinical practice, as shown in Table 2, it is useful to focus on the main plasma lipid disorder, either raised cholesterol, triglycerides, or both, to orientate the management of the patients (2).

**Table 2**

Classification of hyperlipidaemia according to main lipid disorder

<table>
<thead>
<tr>
<th>Type</th>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Prevalence</th>
<th>Increased Lipoprotein</th>
<th>Cardiovacular risk</th>
<th>Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated Hypercholesterolaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polygenic hypercholesterolaemia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>5/100</td>
<td>LDL</td>
<td>High</td>
<td>Angina</td>
</tr>
<tr>
<td>Familial hypercholesterolaemia</td>
<td>LDL receptor</td>
<td>AD</td>
<td>1/500</td>
<td>LDL</td>
<td>High</td>
<td>Angina Tendinous xanthoma Xanthelasma</td>
</tr>
<tr>
<td>Familial defective Apo B-100</td>
<td>Apo B</td>
<td>AD</td>
<td>1/1000</td>
<td>LDL</td>
<td>High</td>
<td>Tendinous xanthoma</td>
</tr>
<tr>
<td>Familial combined hyperlipidaemia</td>
<td>Unknown</td>
<td>AD</td>
<td>1/100</td>
<td>LDL &amp; VLDL</td>
<td>High</td>
<td>Angina</td>
</tr>
<tr>
<td><strong>Isolated Hypertriglyceridaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial deficit of LPL</td>
<td>LPL</td>
<td>AR</td>
<td>1/10^6</td>
<td>Q</td>
<td>?</td>
<td>Eruptive xanthoma Pancreatitis</td>
</tr>
<tr>
<td>Familial deficit of apoC-II</td>
<td>ApoC-II</td>
<td>AR</td>
<td>1/10^6</td>
<td>Q</td>
<td>?</td>
<td>Eruptive xanthoma Pancreatitis</td>
</tr>
<tr>
<td>Familial combined hyperlipidaemia</td>
<td>Unknown</td>
<td>AD</td>
<td>1/1000</td>
<td>LDL &amp; VLDL</td>
<td>High</td>
<td>Angina</td>
</tr>
<tr>
<td>Familial hypertriglyceridaemia</td>
<td>Unknown</td>
<td>AD</td>
<td>0.5-1/100</td>
<td>VLDL &amp; Q</td>
<td>Normal/high</td>
<td>Pancreatitis Angina</td>
</tr>
<tr>
<td><strong>Mixed Hyperlipidaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial dysbetalipoproteinaemia</td>
<td>ApoE</td>
<td>AR (AD rare)</td>
<td>1/10^4</td>
<td>IDL &amp; RQ</td>
<td>High</td>
<td>Palmar and tuberous xanthomas</td>
</tr>
<tr>
<td>Familial combined hyperlipidaemia</td>
<td>Unknown</td>
<td>AD</td>
<td>1/1000</td>
<td>LDL &amp; VLDL</td>
<td>High</td>
<td>Angina</td>
</tr>
</tbody>
</table>

AD: Autosomal Dominant; AR: Autosomal Recessive
Table 3
Clinical Disorders associated with Secondary Hyperlipidaemia

<table>
<thead>
<tr>
<th>Endocrine Disorders</th>
<th>Non Endocrine Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Oestrogen therapy</td>
<td>Uraemia</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>Biliary obstruction or cholestasis</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Monoclonal gammopathy</td>
</tr>
<tr>
<td>Lipodystrophy (congenital or acquired)</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Werner’s syndrome</td>
<td>Glycogen storage disease</td>
</tr>
</tbody>
</table>

3. Clinical Manifestations

Most patients with DLP are initially asymptomatic, although some of them show skin abnormalities, develop pancreatitis or have clinical manifestations of atherosclerosis, such as hypertension, coronary heart disease, cerebrovascular disease and peripheral artery disease.

3.1 Skin

Elevated plasma lipids (cholesterol or triglycerides) can accumulate in macrophage reticuloendothelial cells in certain tissues, particularly skin, tendons, eye, liver, and spleen.

*Xanthelasmas* are small, raised, yellowish macules that typically appear on or near the eyelids. Occasionally, they also occur in patients with normal plasma cholesterol levels, possibly as the result of abnormal uptake of lipoproteins by tissue macrophages. Xanthelasmas may regress when therapy decreases cholesterol concentrations. They are seen in familial hypercholesterolaemia, familial defective apo-B100, and type III hyperlipoproteinaemia.

*Tendon xanthomas* are nodular accumulations of cholesterol that are deposited in tissue macrophages of different tendons, particularly the Achilles tendon and extensor tendons in the hands, knees, elbows and buttocks. They may be small, and therefore detailed examination is needed to avoid overlooking them. They appear in the HLP mentioned just before, but they are particularly common in familial hypercholesterolaemia.

*Tuberous xanthomas* are subcutaneous nodules that develop in the skin over areas predisposed to repeated trauma such as the elbows and knees. The size may be variable, as well as their number in any given location. These xanthomas are most often seen in type III hyperlipoproteinaemia and also occur in familial hypercholesterolaemia.

*Palmar xanthomas* are cutaneous deposits in the palmar and digital creases of the hands. This type of xanthoma is very characteristic of type III hyperlipoproteinaemia and high plasma levels of β-VLDL.

*Eruptive xanthomas* are deposits of triglycerides in dermal histiocytes predominantly distributed in the abdominal wall, the back, the buttocks, and other pressure contact areas. They appear as small, yellowish, round papules with a pale centre and erythematous base. When they are visible, plasma triglyceride levels are high (over 1000 mg/dl or 11.3 mmol/L). As triglyceride levels fall with treatment, these xanthomas tend to vanish. They also appear in patients with LPL deficiency (2).
3.2 Eye

**Corneal Arch or Arcus Senilis:** it is an arc-shaped corneal deposit of cholesterol. It is characteristic of familial hypercholesterolemia, but it also appears in normal individuals older than 45 years. Therefore, its presence is not pathognomonic.

**Lipaemia retinalis:** retinal vessels appear creamy white or yellowish. This fundoscopic finding occurs only with extreme hypertriglyceridaemia, i.e. exceeding 4000 mg/dl. This sign appears in patients with familial deficiency of LPL or Apo C-II.

3.3 Pancreatitis

After gallstones and alcoholism, hypertriglyceridaemia is the third most common identifiable, non-iatrogenic cause of acute pancreatitis, causing around 5% of all cases. Serum triglyceride concentrations exceeding 1000 mg/dL (11 mmol/L) may precipitate such attacks of acute pancreatitis, although the pathogenesis is unclear. It is possible that the release of free fatty acids may damage pancreatic acinar cells or capillary endothelium.

The association between hypertriglyceridaemia due to inherited lipid disorders and acute pancreatitis can occur in early childhood, particularly in children who are homozygous for lipoprotein lipase or apolipoprotein C-II (apo C-II) deficiency.

Most adults with hyperchylomicronaemia have a mild form of genetically inherited type I or type V hyperlipoproteinaemia and an additional condition known to raise serum lipids (e.g., alcohol abuse, obesity, insulin resistance, diabetes mellitus, hypothyroidism, pregnancy, oestrogen or tamoxifen therapy, glucocorticoid excess, nephrotic syndrome, or beta-blocker therapy).

Several patterns of hypertriglyceridaemia-induced pancreatitis have been described (3). The first is a patient with poorly controlled diabetes and a history of hypertriglyceridaemia; treatment with insulin corrects the elevated levels of triglycerides. The second is an alcoholic patient who is found to have hypertriglyceridaemia on hospital admission. Alcohol causes a moderate rise in serum triglyceride concentration in a “dose-dependent” manner. Alcoholic patients with severe hyperlipidaemia often have a coexisting primary genetic disorder of lipoprotein metabolism (4). The third is a non-diabetic, non-alcoholic, non-obese person who has drug- or diet-induced hypertriglyceridaemia. Drug-induced disease is more likely to occur if there is underlying hypertriglyceridaemia (5).

The clinical manifestations of hypertriglyceridaemia-associated disease are similar to those of other causes of acute pancreatitis: abdominal pain, nausea, and vomiting are the major symptoms. However, the serum amylase concentration may not be substantially elevated at presentation (6).

3.4 Cardiovascular Disease

Abnormalities in plasma lipoproteins are well known risk factors for atherosclerosis. It is the leading cause of death and disability in the developed world. Central to the pathogenesis of atherosclerosis is the deposition of cholesterol in the arterial wall. Nearly all lipoproteins are involved in this process. Low-density lipoprotein (LDL), particularly the small, dense form, is considered the main culprit, followed by remnant lipoprotein and very-low-density lipoprotein (VLDL). Most of the cholesterol in blood plasma is normally carried in LDLS and there is a strong and graded positive association between
total as well as LDL cholesterol and risk of cardiovascular disease. When HLP occurs in combination with other risk factors early cardiovascular disease is commonplace. Atherosclerosis preferentially affects various regions of the circulation with distinct clinical manifestations depending on the particular circulatory bed affected: angina pectoris and myocardial infarction, strokes and transient cerebral ischaemia, peripheral vascular disease leading to intermittent claudication and gangrene, mesenteric ischaemia and renal artery stenosis. Atherosclerosis manifests itself focally not only in space, but in time as well. Atherosclerotic plaques grow discontinuously with quiescent periods followed by others with more rapid progression. Clinical expressions of atherosclerosis mirror this time-frame. They may be chronic, as in stable, effort-induced angina pectoris or intermittent claudication. Alternatively, the presence of atherosclerosis may be revealed by an acute clinical event such as myocardial infarction or cerebrovascular accident. On the other hand, atherosclerosis may be a post mortem finding without any prior clinical manifestation (7).

The development of the atheromatous plaque has been comprehensively studied. The main steps are (7, 8, 9):

- Fatty streak formation: Hypercholesterolaemia promotes accumulation of LDL particles in the intima of the vascular wall. The lipoprotein particles often associate with constituents of the extracellular matrix;
- Lipoprotein oxidation: Lipoproteins in the intima are separated from plasma antioxidants and are altered by oxidative modification. In patients with diabetes non-enzymatic glycation of lipoproteins and other matrix proteins may contribute to the development of the plaque;
- Leukocyte recruitment: Oxidized lipoproteins may elicit a local inflammatory response that generates different molecular signals that attract lymphocytes and monocytes to the site of the accumulation of LDL particles. These cells and vascular wall cells produce adhesion molecules that maintain the attraction of leukocytes to the nascent plaque;
- Foam cell formation: The mononuclear phagocytes in the evolving fatty streak differentiate into macrophages. They multiply and exhibit increase expression of receptors for modified lipoprotein. Therefore, these cells acquire a scavenger role. They accumulate lipids and are transformed into foam cells, in which lipid droplets are deposited in the cytoplasm;
- Smooth-muscle cell migration: some of these cells travel to the atherosclerotic lesion and accumulate within the expanding intima. They are subjected to positive and negative stimuli from different pro-inflammatory cytokines, synthesized by local macrophages and vascular wall cells. The usual outcome is that migrated cells produce increased amounts of extracellular matrix that expands the intima and leads to the advanced atherosclerotic lesion. Fibrous tissue accumulates in the fatty streak;
- Associated factors: various diseases and hormones may contribute to the development of the atheromatous plaque: diabetes mellitus, hypertension, smoking, sex hormones, proteins related to coagulation and fibrinolysis, such as plasminogen-activator inhibitor 1 (PAI-1) and lipoprotein (a);
- Microthrombi: In advanced fatty streaks limited endothelial denudation occurs. The extracellular matrix is very thrombogenic. Platelets are attracted to these microscopic breaches in endothelial integrity and microthrombi are organized in such sites. Activated platelets release numerous factors that can promote the fibrotic response. However, these microthrombi may be clinically silent due to local fibrinolysis and endothelial repair;

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• Mineralization: Advanced atheromatous plaques may accumulate calcium. Osteocalcin, osteopontin and bone morphogenetic proteins are involved in bone formation and in atherosclerotic plaques as well;

• Plaque evolution: The atherosclerotic plaque development is not linear, but is punctuated by contradictory events, such as import and export of lipoproteins and inflammatory cells, proliferation and apoptosis of smooth-muscle cells, deposition and remodelling of extracellular matrix, etc. Late lesions are more fibrous, while initial lesions are more cellular;

• Plaque-vessel relationship: Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as compensatory enlargement, a type of vascular remodelling. Initially, the plaque usually grows outward and therefore does not represent an obstacle to flow through the vessel thereby decreasing tissue perfusion. Eventually, the plaque causes flow-limiting stenosis that may be manifest as exercise-dependent ischaemia, for example angina pectoris or intermittent claudication (10, 11);

• Plaque instability and rupture: Acute cardiovascular events are frequently triggered by a non-occlusive plaque that has not previously caused chronic symptoms of ischaemia, but has become unstable. Either a fracture in the plaque or a superficial erosion of the endothelium initiates the coagulation cascade and prompts the development of a thrombus. Consequently, the vessel’s lumen is blocked by the thrombosis and the blood flow is severely limited. It has been proved that unstable plaques contain more lipid and inflammatory cells, but fewer smooth-muscle cells than stable ones. This is probably due to an ongoing inflammatory response at sites of plaque rupture. The more local inflammation the less extracellular matrix and fibrous tissue, facilitating the rupture (12);

• Endothelial dysfunction: Disordered endothelial vasomotor function of the coronary arteries is common in patients with angina, and results in diminished vasodilatation or even vasoconstriction in response to various stimuli, including exercise.

4. Management of Dyslipidaemia

Different institutions and scientific societies have proposed guidelines that direct the diagnosis and therapy of dyslipidaemia. We will review some points based on the guidelines issued by the American College of Cardiology and American Heart Association (ACC/AHA), European Society of Cardiology and European Society of Atherosclerosis (ESC/EAS) and National Institute for Clinical Excellence of United Kingdom (NICE) (13-15). Other Associations have also produced Guidelines, such as the American Association of Clinical Endocrinologists and American College of Endocrinology or U.S. Department of Veterans Affairs and U.S. Department of Defense (16, 17), but we do not comment on them in detail.

4.1 Laboratory Evaluation of Dyslipidaemia

Lipid disorders are evaluated by measuring different parameters. The fasting profile includes total cholesterol, cLDL, cHDL and triglycerides. LDL-C is used as the primary lipid analysis. Analysis of HDL-C is also recommended before treatment. If it is impossible to obtain fasting levels, then only the total cholesterol and HDL provide reliable information (18). The results of these tests must be evaluated along with the other risk factors in each individual. Special tests, such as C-reactive protein (CRP) measurement, can be considered to define a subset of patients that is at excess risk for Coronary Heart Disease (CHD) (19). A scoring system that adds highly sensitive CRP and
family history of premature CHD has been described – the CAD score (www.reynoldsriskscore.org). If a patient is at average risk for a lipid-related event over the next 1 to 2 years, laboratory tests should be repeated every 1 to 2 years, because total cholesterol and LDL cholesterol tend to increase with age. If a patient, due to his or her risk stratification, needs drug therapy, before starting it, he/she should have baseline liver function tests (LFTs), creatinine kinase (CK) and thyrotropin (TSH) documented, especially if the individual is believed to be at increased risk for adverse muscle events. Follow-up tests should include LFTs 6 to 12 weeks after initiation of therapy, every 6 months for 1 year, and on a yearly basis thereafter. CK should be monitored if indicated by symptoms, but routine periodic retesting is not recommended (20).

Triglycerides: moderate increase of triglycerides is a risk factor for CVD. Triglyceride levels add information about risk, and their measurement is indicated for diagnosis and choice of treatment. Severe hypertriglyceridaemia (> 900 mg/dl or 10 mmol/L) is also a risk factor for pancreatitis, as we have seen. High fasting triglycerides (>150 mg/dL or >1.7 mmol/L) are markers of increased risk, although they do not constitute target levels for therapy. Postprandial concentrations of triglycerides are also good predictors of CVD risk, but measurement is not well standardized and therefore is not routinely used in clinical practice. It is not uncommon to find the combination of low concentrations of HDL cholesterol with elevated triglycerides, particularly in high-risk patients with type 2 diabetes, abdominal obesity, insulin resistance, and little physical activity (1).

Other measurements are being considered as emerging or potential risk factors for CHD (14):

- Non-high-density lipoprotein cholesterol or Non-HDL cholesterol (total cholesterol minus HDL cholesterol) measures all cholesterol particles that are considered atherogenic. It captures information on triglyceride-rich remnant lipoprotein that LDL-C does not. Non-HDL-C can be calculated, especially in subjects with high TG avoiding the limitations of Fridewald estimation. Non-cHDL should have an upper limit just 30 mg/dL (0.8 mmol/L) higher than the goal for cLDL. Non-cHDL is a secondary target of therapy in patients with triglycerides over 200 mg/dL. Non-cHDL is more readily available than measurements of apoB and apoA1.
- The total cholesterol to HDL cholesterol ratio may be more predictive of CHD than total cholesterol or LDL cholesterol. Among men, a ratio of 6.4 or greater was associated with greater risk of CHD than the individual parameters mentioned.
- Lipoprotein (a) or Lp(a) consists of an apoprotein (a) molecule bound by a sulfhydryl link to the apolipoprotein B moiety of an LDL particle. Apoprotein (a) has homology with plasminogen and may inhibit fibrinolysis by competing with plasminogen. Elevated Lp(a) levels predict CHD events, particularly in patients with dyslipidaemia or low cHDL. There is no randomized intervention showing that reducing Lp(a) decreases CVD risk. The European Guidelines state that Lp(a) measurement should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD. Individuals with: Premature CVD, Familial hypercholesterolaemia, a family history of premature CVD and/or elevated Lp(a), Patients with recurrent CVD despite optimal lipid-lowering treatment, and ≥5% 10-year risk of fatal CVD according to SCORE, should be considered for lipoprotein(a) screening (14).

Small, dense low-density lipoprotein particles are associated with increased serum concentrations of apo B and triglycerides and reduced serum HDL. Epidemiological studies have noted an association between small, dense LDL and CHD. However, routine screening for LDL particle size or concentration has not been validated.
Apolipoproteins: Apolipoprotein A1 (apoA1) is the major apoprotein of HDL as apo B is of LDL. ApoB can be substituted for LDL cholesterol measurement or non-HDL cholesterol and it is a similar risk marker to LDL cholesterol. There appears to be less laboratory error in the determination of apoB than LDL cholesterol, particularly in patients with hypertriglyceridaemia. When the triglyceride level is greater than 150 mg/dL or the HDL-C level is less than 40 mg/dL, AACE believes that the apo B or the apo B to apo AI ratio may be particularly useful in assessing residual risk in patients at risk for coronary artery disease. ApoB values lower than 80 and 90 mg/dL are recommended targets for subjects with very high or high CVD risk, respectively (16). Apolipoproteins may be a better indicator of atherogenicity than the lipids measured conventionally. The apoB:apoA1 ratio is one of the strongest risk markers, but apoproteins are not available to all physicians, are more costly than currently used lipid variables, and do not add more information. There is controversy regarding their usefulness. Some groups have found these are not much better than measurements of cholesterol fractions in clinical practice. More than 3300 middle-aged, white participants without cardiovascular disease in the Framingham Offspring Study were followed for a median of 15 years. A total of 291 first CHD events occurred, 198 of them in men and 93 in women. In men, elevations in non-HDL cholesterol, apo B, total cholesterol:HDL ratio, LDL:HDL ratio, and apo B:apo A-1 ratio were all significantly associated with increased CHD risk to a similar degree. Elevated apo A-1 and HDL were likewise associated with reduced CHD risk. In men, total cholesterol:HDL and apo B:apo A-1 ratios both improved classification of 10-year risk for CHD; however, the difference between the two was not significant. In women, neither lipid ratio improved CHD risk reclassification. The authors concluded that the overall performance of apo B:apo A-I ratio for prediction of CHD was comparable with that of traditional lipid ratios but did not offer incremental utility over total cholesterol:HDL-C. These data do not support measurement of apo B or apo A-I in clinical practice when total cholesterol and HDL-C measurements are available (21). However, the 2008 INTERHEART study, done in 52 countries, reported that the non-fasting ApoB:ApoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and the authors claim that it should be introduced into worldwide clinical practice (22).

4.2 Selection of Patients for Treatment

The selection of patients for treatment begins by an assessment of cardiovascular risk. There are numerous calculators published in the literature, such as SCORE (ESC/EAS), ASCVD (ACC/AHA) and QRISK-3 (NICE). In general, the tools look at the risk of developing cardiovascular events, but SCORE gives an estimation of the risk of death caused by a cardiovascular event.

In the SCORE model risk estimation is based on age, sex, smoking habits, systolic blood pressure (SBP), and either total cholesterol or cholesterol:HDL ratio. There are two sets of SCORE charts: the low-risk chart is for countries such as Belgium, France, Greece, Italy, Luxembourg, Portugal, Spain, and Switzerland, (Fig. 1 and 2). Relative risk is calculated by comparing an individual's risk category with that of a non-smoking person of the same age and gender with blood pressure \(</= 140/90\) mm Hg and total cholesterol \(</= 5\) mmol/L (< 190 mg/dL) (23, 24).
Fig. 1 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at high CVD risk. These countries are Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia FYR, Moldova, Russia, Ukraine, and Uzbekistan. The chart shows the 5 risk factors that are included in SCORE: age, sex, smoking, systolic blood pressure, and total cholesterol.
Fig. 2 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at low CVD risk. These countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom. The chart shows the 5 risk factors that are included in SCORE: age, sex, smoking, systolic blood pressure, and total cholesterol.

The ASVCD measure has been criticized because it overestimates the risk in certain populations, especially in the elderly, and this may lead to an excessive number of individuals being treated with lipid reducing drugs without clear benefit (25). Ideally, health care providers should use the calculator of risk that best applies to the population they take care of. A barrier for this goal is the lack of national representative cohorts in most countries that could allow the development of a national standard. For this reason a less calculator-reliant approach could be proposed (26).

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In asymptomatic adults without evidence of CVD, diabetes, CKD or familial hypercholesterolaemia, total risk estimation using a risk estimation system is recommended when they are >40 years of age. Although including all the classical factors, the ASCVD and SCORE calculators do not include other risk factors such as family history of premature CVD (men: <55 years; women: <60 years), obesity or central obesity, physical inactivity, atrial fibrillation, left ventricular hypertrophy, chronic kidney disease, obstructive sleep apnoea syndrome, autoimmune and other inflammatory disorders, treatment for human immunodeficiency virus (HIV) infection, psychosocial stress and major psychiatric disorders, and social deprivation. The QRISK-3 does include some of these risk factors. Despite these comments about the limitations of risk estimators/calculators, they may have a major impact in primary prevention in determining how many people will be treated with drugs.

4.3 Intervention Strategies

ESC/EAS Guidelines (14)
The ESC/EAS Guidelines define the intervention strategies for individuals as a function of total CV risk and LDL-C level (Table 4). Interventions range from lifestyle advice to multiple concomitant drug therapies. LDL-cholesterol is the primary target, with different recommendations according to the risk. For primary prevention, a mnemonic rule has been developed as “European heart telephone number 035140530”, which represents:

- 0 - No tobacco;
- 3 - walk 3 km daily or 30 mins of any moderate activity;
- 5 - portions of fruit and vegetables a day;
- 140 (mm Hg) - Systolic Blood Pressure;
- (90 (mm Hg) - Diastolic Blood Pressure);
- 5 (mmol/L) - total cholesterol;
- 3 (mmol/L) - LDL cholesterol;
- 0 - Avoidance of overweight and diabetes.
Table 4
Intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level according to the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2016) (1)

<table>
<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 mg/dL &lt;1.8 mmol/L</td>
<td>70 to &lt;100 mg/dL 1.8 to &lt;2.6 mmol/L</td>
</tr>
<tr>
<td>&lt;1</td>
<td>Lifestyle advice</td>
</tr>
<tr>
<td>≥1 to &lt;5</td>
<td>Lifestyle advice</td>
</tr>
<tr>
<td>≥5 to &lt;10, or high-risk</td>
<td>Lifestyle advice, consider drug if uncontrolled</td>
</tr>
<tr>
<td>≥10 or very high-risk</td>
<td>Lifestyle advice, consider druga</td>
</tr>
<tr>
<td>Class/Level</td>
<td>I/C</td>
</tr>
</tbody>
</table>

aInpatients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels.

ESC/EAS Guidelines defines four categories or risk:
- Very High Risk: Subjects with any of the following:
  1) Documented CVD, clinical or unequivocal on imaging. 2) DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. 3) Severe CKD (GFR <30 mL/min/1.73 m²). 4) A calculated SCORE >10%.
- High-risk: Subjects with:
  1) Markedly elevated single risk factors, in particular cholesterol >8mmol/L (>310mg/dL) (e.g. in familial hypercholesterolaemia) or BP≥180/110 mmHg. 2) Most other people with DM (with the exception of young people with type 1 DM and without major risk factors who may be at low or moderate risk). 3) Moderate CKD (GFR 30–59 mL/min/1.73 m²). 4) A calculated SCORE ≥5% and <10%.
- Moderate-risk:
  1) SCORE is ≥1% and <5% at 10 years. Many middle aged subjects belong to this category.
- Low-risk:
  1) SCORE <1%.
Regarding considerations of treatment, normalised LDL-C and non-HDL are recommended as the primary and secondary targets for treatment, respectively. If other analyses are not available, lowering TC should also be considered as a treatment target. On the contrary, neither HDL-C nor the ratios apoB:apoA1 and non-HDL-C:HDL-C are recommended as targets for treatment.

After having defined the categories of risk and the lipid measurements that are targets for treatment, the ESC/EAS Guidelines recommend the following targets for each category and lipid:

- Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
- High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
- Low to moderate risk: LDL-C <3 mmol/L (115 mg/dL).
- Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100,130 and 145mg/dL) for very high-, high- and moderate-risk subjects, respectively.
- HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48mg/dL) in women indicates lower risk.
- TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

The European Guidelines emphasize that other risk factors should also be controlled in patients evaluated for treatment of dyslipidaemia, such as body weight, with the goal of a BMI of 20–25 kg/m², waist circumference <94 cm (men) and <80cm (women), blood pressure, <140/90 mmHg, and glycaemic control, HbA1c: <7% (<8.6 mmol/L).

Among the lifestyle objectives it reinforces the importance of no exposure to tobacco in any form, a healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish, and physical activity consistent with of 2.5–5 h moderately vigorous physical activity per week or 30–60 min most days. A more detailed explanation of lifestyle measures can be seen in Tables 5 and 6. As a general comment that serves for the three guidelines, all of them are based on RCTs, with the consequence that drug treatments receive a higher grading than lifestyle measures, which may have a significant benefit but which are more difficult to study in RCTs.
Table 5
Effect of lifestyle changes on Total Cholesterol and LDL Cholesterol Levels according to the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias (14)

<table>
<thead>
<tr>
<th>Lifestyle interventions to reduce TC and LDL-C levels</th>
<th>Magnitude of the effect</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce dietary trans fat</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce dietary saturated fat</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Increase dietary fibre</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Use functional foods enriched with phytosterols</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Use red yeast rice supplements</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce excessive body weight</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce dietary cholesterol</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>Increase habitual physical activity</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>Use soy protein products</td>
<td>+/-</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifestyle interventions to increase HDL-C levels</th>
<th>Magnitude of the effect</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce dietary trans fat</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Increase habitual physical activity</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce excessive body weight</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce dietary carbohydrates and replace them with unsaturated fat</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Modest consumption in those who take alcohol may be continued</td>
<td>++</td>
<td>B</td>
</tr>
<tr>
<td>Quit smoking</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content</td>
<td>+/-</td>
<td>C</td>
</tr>
<tr>
<td>Reduce intake of mono- and disaccharides</td>
<td>+/-</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifestyle interventions to reduce TG-rich lipoprotein levels</th>
<th>Magnitude of the effect</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce excessive body weight</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce alcohol intake</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Increase habitual physical activity</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce total amount of dietary carbohydrate</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Use supplements of n-3 polyunsaturated fat</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce intake of mono- and disaccharides</td>
<td>++</td>
<td>B</td>
</tr>
<tr>
<td>Replace saturated fat with mono-or polyunsaturated fat</td>
<td>+</td>
<td>B</td>
</tr>
</tbody>
</table>
### Table 6
Dietary recommendations to lower low-density lipoprotein-cholesterol according to the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias (14)

<table>
<thead>
<tr>
<th></th>
<th>To be preferred</th>
<th>To be used with moderation</th>
<th>To be chosen occasionally in limited amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cereals</td>
<td>Whole grains</td>
<td>Refined bread, rice and pasta, biscuits,corn flakes</td>
<td>Pastries, muffins, pies, croissants</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Raw and cooked vegetables</td>
<td>Potatoes</td>
<td>Vegetables prepared in butter or cream</td>
</tr>
<tr>
<td>Legumes</td>
<td>Lentils, beans, fava beans, peas, chickpeas, soybean</td>
<td>Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice</td>
<td></td>
</tr>
<tr>
<td>Fruit</td>
<td>Fresh or frozen fruit</td>
<td>Non-caloric sweeteners</td>
<td>Sweets and sweeteners</td>
</tr>
<tr>
<td>Sweets and sweeteners</td>
<td>Non-caloric sweeteners</td>
<td>Sucrose, honey, chocolate, candies</td>
<td>Cakes, ice creams, fructose, soft drinks</td>
</tr>
<tr>
<td>Meat and fish</td>
<td>Lean and oily fish, poultry without skin</td>
<td>Lean cuts of beef, lamb, pork or veal, seafood, shellfish</td>
<td>Sausages, salami, bacon, spare ribs, hot dogs, organ meats</td>
</tr>
<tr>
<td>Dairy food and eggs</td>
<td>Skim milk and yogurt</td>
<td>Low fat milk, low fat cheese and other milk products, eggs</td>
<td>Regular cheese, cream, whole milk and yogurt</td>
</tr>
<tr>
<td>Cooking fat and dressings</td>
<td>Vinegar, mustard, fat-free dressings</td>
<td>Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup</td>
<td>Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat</td>
</tr>
<tr>
<td>Nuts/Seeds</td>
<td>All, unsalted (except coconut)</td>
<td>Coconut</td>
<td>Nuts/seeds</td>
</tr>
<tr>
<td>Cooking procedures</td>
<td>Grilling, boiling, steaming</td>
<td>Stir-frying, roasting</td>
<td>Frying</td>
</tr>
</tbody>
</table>

In relation to drug therapy for dyslipidaemia, the ESC/EAS Guidelines affirm that statins are the drugs of first choice up to the highest recommended dose or highest tolerable dose as needed to reach the goal. If it is not reached, addition of a cholesterol absorption inhibitor or a bile acid sequestrant may be considered. In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor may be considered. The management of patients with statin intolerance is discussed below in more detail.

In high-risk patients with isolated hypertriglyceridaemia (>2.3 mmol/L, 200 mg/dL), drug treatment should also be planned. Statin treatment may also be the first drug choice for reducing CVD risk in these individuals. If despite statin treatment these high-risk patients still have TG >2.3 mmol/L (200 mg/dL), fenofibrate may be considered in addition to the statin. The addition of n-3 fatty acids may decrease TG further. The n-3 fatty acids are safe and well tolerated. In this context, an important reminder is the extra risk of
myopathy associated with the combination of fibrates, especially gemfibrozil, with statins.
The ESC/EAS guidelines on dyslipidaemia offer specific advice in different clinical scenarios such as genetic disorders of lipoprotein metabolism, detection and treatment of patients with heterozygous familial hypercholesterolaemia, management of dyslipidaemia in women, treatment of dyslipidaemia in older adults, in diabetes-related dyslipidaemia, in metabolic syndrome, heart failure or valvular disease, autoimmune diseases, patients with moderate to severe chronic kidney disease, transplant patients, patients with peripheral arterial disease (including carotid artery disease), in primary and secondary prevention of stroke, in human immunodeficiency virus patients, and in patients with mental disorders. This information may be of much interest for healthcare providers dealing with patients included in these categories, but we cannot deal with them in this Module due to space constraints and the overall goals of the ESPEN LLL Programme.

**ACC/AHA Guidelines (13)**
These Guidelines have only considered RCTs as a valid source of evidence. In contrast, ESC/EAS and NICE guidelines also consider other sources of information to help translate evidence into clinical practice.
The ACC/AHA Guidelines establish 4 categories of candidates for treatment of dyslipidaemia:
1) Patients with clinical atherosclerotic cardiovascular disease (ASCVD)
2) Subjects with LDL-C ≥190 mg/d, and Age ≥21 years
3) Primary prevention – Patients with Diabetes, Age 40-75 years, LDL-C 70-189 mg/dL
4) Primary prevention – Patients without Diabetes†: Age 40-75 years, LDL-C 70-189 mg/dL, ≥7.5% 10-year ASCVD risk.
High-intensity statin therapy is recommended for the first two categories. The intensity of use of the different statins is shown in Table 7.

**Table 7**
Classification of statins according to intensity of LDL-C decrease. Statins and doses listed in italics are approved for use but have not been studied in randomized controlled trials. Adapted from 2013 ACC/AHA Blood Cholesterol Guideline.

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lowers LDL-C by ≥ 50%)</td>
<td>(Lowers LDL-C by 30-50%)</td>
<td>(Lowers LDL-C by &lt; 30%)</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 2-4 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID</td>
<td></td>
</tr>
</tbody>
</table>

For patients with diabetes, it is necessary to calculate 10-yr risk of atherosclerotic CVD with the ASCVD tool. If risk is <7.5%, or age is >75 years the patients will receive moderate intensity statin therapy, but if risk is >7.5%, then high-intensity statin therapy is indicated.
For patients without diabetes with LDL-C and age 40-75 years, that is, primary prevention, the 10-yr risk of atherosclerotic CVD is estimated with the ASCVD tool. If risk is...
is >7.5%, physicians should offer moderate-to high-intensity statin therapy after a thorough discussion with the patient concerning the potential for ASCVD risk reduction benefits, potential for adverse effects, drug-drug interactions, and patient preferences. Optimal lifestyle has always to be emphasized.

The ACC/AHA Guidelines do not recommend a specific target for treatment. The rationale for this position is that there is not enough evidence from randomized clinical trials (RCT) to support titration of drug therapy to specific LDL-C and/or non-HDL-C goals. Current RCT data do not indicate clearly what the target should be. The decrease of cardiovascular events that happens with the reduction of LDL-C is a continuum that does not allow setting a particular cut off level of LDL-C that must be achieved. On the other hand, there is strong evidence that appropriate intensity of statin therapy may reduce ASCVD risk in the patients most likely to benefit from it.

In the same vein the ACC/AHA guidelines do not recommend primary prescription of non-statin therapies, because they do not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy. Furthermore, the rate of additional adverse effects from multidrug therapy used to achieve a specific goal is unknown as is the net benefit from a treat-to-target approach.

If there is no target for treatment, it does not make sense measuring lipid profiles to check if this target has been achieved with the treatment. However, these guidelines do recommend checking a lipid panel after 4 to 12 weeks of treatment. The goal of measuring LDL-C levels and their percentage reduction is to assess response to therapy and adherence. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the healthcare provider can reinforce medication adherence, emphasize adherence to intensive lifestyle changes and exclude secondary causes of hyperlipidaemia.

In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Among the potential drugs, we can mention niacin, bile acid sequestrants, cholesterol-absorption inhibitors, fibrates, and omega-3 fatty acids. In patients at very high-risk, with persistently high LDL-C despite treatment with the maximal tolerated statin dose, in combination with ezetimibe or other drugs, or in patients with statin intolerance, a PCSK9 inhibitor, or mipomersen and lomitapide may be considered.

In 2016 ACC/AHA published a consensus decision pathway on the role of non-statin therapies for lowering LDL-cholesterol in the management of the risk of atherosclerotic cardiovascular disease. For each risk category this consensus recommends how to follow up patients, how to give more value to rechecking lipid profiles, and how best to add other drugs to statins to improve the treatment response (27). In certain sense, it seems that the ACC/AHA is approaching the LDL-C hypothesis ("The Lower the Better") more favoured by ESC/EAS, away from the statin pleiotropic effects, which would be independent of the values of LDL-C achieved.

Combinations of drugs require the checking of different laboratory parameters before or during their administration for early discovery of (for example) elevation of glucose, haemoglobin A1c, uric acid, hepatic enzymes, creatinine or creatine kinase (13, 14). For example, when ezetimibe is coadministered with a statin, it is advisable to monitor transaminase levels, and discontinue ezetimibe if persistent ALT elevations ≥3 times ULN occur.

Biliary acid sequestrants (BAS) should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe hypertriglyceridemia, hypercholesterolaemia, and chronic pancreatitis could occur.
elevation of triglyceride levels might occur. A fasting lipid panel should be obtained before BAS are initiated, 3 months after initiation, and every 6 to 12 months thereafter. It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL.

Niacin should not be used if hepatic transaminase elevations are higher than 2 to 3 times ULN, there are persistent severe cutaneous symptoms, persistent hyperglycaemia, or if acute gout, unexplained abdominal pain, other gastrointestinal symptoms, new-onset atrial fibrillation, or weight loss occur.

Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are $\geq 500$ mg/dL, are judged to outweigh the potential risk for adverse effects. Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR $< 30$ mL/min per 1.73 m$^2$, is present. If eGFR is between 30 and 59 mL/min per 1.73 m$^2$, the dose of fenofibrate should not exceed 54 mg/day. If, during follow-up, the eGFR decreases persistently to $\leq 30$ mL/min per 1.73 m$^2$, fenofibrate should be discontinued. It is important to emphasize that gemfibrozil should not be initiated in patients on statin therapy because of an increased risk of muscle symptoms and rhabdomyolysis.

After the publication of these guidelines, there have been comparisons of ACC/AHA and ESC/EAS Guideline Recommendations in Primary Prevention of Cardiovascular Disease. A research team calculated the 10-year risk for hard atherosclerotic CVD (ASCVD) following the ACC/AHA guideline, and the 10-year risk of CVD mortality following the ESC/EAS guideline, and they determined eligibility for primary prevention of CVD. This study included 7279 individuals free of CVD, aged 45 to 75 years, examined between 1997 and 2008 for the Rotterdam Study, a prospective population-based cohort. The ACC/AHA guidelines would recommend statin initiation in 58.9% of the participant, while the ESC/EAS guidelines would in 33.0% (overlapping by 95.8% with ACC/AHA). Recommendations from both guidelines and trial evidence overlapped for 1546 participants (21.2%). The conclusion, based on this European population study, was that ACC/AHA and ESC/EAS prevention guidelines often did not align at the individual level. However, for one-fifth of the general population, guidelines on both sides of the Atlantic recommend statin initiation, with trial data supporting the efficacy of this approach (28).

Other authors, based on data from a cohort of 44889 individuals aged 40-75 recruited in 2003-09 in the Copenhagen General Population Study, concluded that the ACC/AHA guidelines were superior to the ESC/EAS guidelines for primary prevention of ASCVD, that is, for accurately assigning statin therapy to those who would benefit most (29). For clinical practitioners it is important to identify the common ground of the different guidelines, highlighting similarities rather than differences (30). It is also of interest to follow updates on approved lipid-lowering drugs to offer the best therapeutic advice to individuals with cardiovascular risk (31).

**NICE (15)**

Although we have studied the American and European Guidelines in some detail, it is still interesting to have a look at the British Guidelines. The National Institute of Clinical Excellence issued its guideline CG 181, “Cardiovascular disease: risk assessment and reduction, including lipid modification”, in 2014, with later updates in the following years. They recognize first the decrease in death rates from CVD in the UK since the late 1970s, but also the recognition that more progress can be made taking into consideration that CVD is preventable in many cases. Furthermore, some risk factors have increased (obesity and type 2 diabetes mellitus). The guidelines distinguish between non-modifiable
and modifiable risk factors, such as smoking, high blood levels of non-high density lipoprotein cholesterol, lack of physical activity, unhealthy diet, alcohol intake above recommended levels, overweight and obesity. They should be addressed properly. These guidelines call for assessment of CVD risk every 5 years in everyone between the ages of 40 and 74, who has not already been diagnosed with CVD, diabetes, or chronic kidney disease. Total cholesterol is an important predictor of CVD events. But the NICE guidelines give priority to the measurement of non-high density lipoprotein (HDL-C) cholesterol, the difference between total and HDL cholesterol, because they see it as a more accurate predictor of CVD events. Therefore, in these guidelines non-HDL-C has replaced low density lipoprotein (LDL) cholesterol as the primary target for reducing cardiovascular risk with lipid-modifying treatment. In contrast with other guidelines, the NICE guidelines endorse a raised triglyceride level as a risk factor for CVD that is independent of total cholesterol.

A person’s 10 year CVD risk should be assessed using the QRISK®3 assessment tool (apart from people already known to be at high risk, for example, people with type 1 diabetes aged over 40 and/or with nephropathy, certain people with chronic kidney disease, people with familial hypercholesterolaemia, and people aged 85 years or older). Most people will be able to reduce whatever risk they have by changes in lifestyle, optimizing treatment of relevant comorbidities, and by drug treatment, if appropriate. Lifestyle measures that can reduce CVD risk include:

1) Smoking cessation. 2) Weight loss if overweight or obese. 3) Eating a healthy diet. 4) Keeping alcohol consumption within the recommended limits. 5) Being physically active. Statin treatment should be offered for the primary prevention of CVD to people with an estimated 10 year CVD risk of 10% or more if lifestyle interventions have not proved effective.

Atorvastatin 20 mg a day is then the recommended statin if the person decides to take drug treatment after an informed discussion about benefits and harms, always taking into consideration co-morbidities, life expectancy and avoidance of contraindications.

For secondary prevention of CVD, high-intensity statin treatment should be advised in people with existing CVD. Atorvastatin 80 mg is recommended. A lower dose may be offered if potential drug interactions, risk of adverse effects exist, or for patient preference. A lipid sample should be taken at baseline and again after 3 months of starting treatment. Statin treatment should not be delayed while modifiable risk factors are being managed.

An annual non-fasting blood test for non-HDL cholesterol can be planned. The aim is a reduction of ≥40% in non-HDL cholesterol. If this is not achieved: 1) discuss adherence and timing of dose; 2) optimise adherence to diet and lifestyle measures; 3) consider increasing the dose if started on atorvastatin < 80 mg.

It is also important to keep in mind that primary and secondary prevention of CVD also involves: 1) Addressing other modifiable CVD risk factors through lifestyle intervention. 2) Identifying and managing secondary causes of dyslipidaemia (for example hypothyroidism). 3) Arranging follow up to monitor for adverse effects and to review drug treatment.

### 4.4 Monitoring Lipids and Enzymes in Patients on Lipid-lowering Therapy

The ESC/EAS Guidelines include recommendations for the follow-up of patients with dyslipidaemia and with complications of their treatment (14):
4.4.1 Testing Lipids

How often should lipids be tested?
• Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where concomitant drug treatment is suggested such as ACS and very high-risk patients.

How often should a patient’s lipids be tested after starting lipid-lowering treatment?
• 8 (±4) weeks after starting treatment.
• 8 (±4) weeks after adjustment of treatment until within the target range.

How often should lipids be tested once a patient has reached the target or optimal lipid level?
• Annually (unless there is an adherence problem or other specific reasons for more frequent reviews).

According to ACC/AHA Guidelines adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter. Other safety measures should be performed as clinically indicated. The goal of lipid measurement is not reaching a target range, but to assess adherence, safety and therapeutic response (13).

As a difference from the ACC/AHA and ESC/EAS, a fasting sample is not needed for compliance with the NICE Guidelines (15).

4.4.2 Monitoring Liver and Muscle Enzymes

How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?
• Before treatment.
• Once 8–12 weeks after starting a drug treatment or after dose increase.
• Routine monitoring of ALT thereafter is not recommended during lipid-lowering treatment.

What if liver enzymes become elevated in a person taking lipid-lowering drugs?
If ALT <3x ULN:
• Continue therapy.
• Recheck liver enzymes in 4–6 weeks.

If value rises to ≥3x ULN
• Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
• Cautious reintroduction of therapy may be considered after ALT has returned to normal.
• If ALT remains elevated check for the other reasons.

How often should CK be measured in patients taking lipid-lowering drugs?
Pre-treatment
• Before starting therapy.
• If baseline CK is >4x ULN, do not start drug therapy; recheck.
Monitoring
• Routine monitoring of CK is not necessary.
• Check CK if patient develops myalgia.

Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy.

Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, those on concomitant interfering therapy or multiple medications, those with liver or renal disease, or athletes.

ACC/AHA Guidelines agree with this approach.

During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

What if CK becomes elevated in a person taking lipid-lowering drugs?

Re-evaluate indication for statin treatment.
If ≥4 x ULN:
• If CK >10x ULN: stop treatment, check renal function and monitor CK every 2 weeks.
• If CK <10x ULN: if no symptoms, continue lipid lowering therapy while monitoring CK.
• If CK <10x ULN: if symptoms present, stop statin and monitor normalization of CK, before re-challenge with a lower statin dose.
  • Consider the possibility of transient CK elevation for other reasons such as exertion.
  • Consider myopathy if CK remains elevated. The ACC/AHA Guidelines mention other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).
  • Consider combination therapy or an alternative drug.

If <4 x ULN:
• If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
• If muscle symptoms, monitor symptoms and CK regularly.
• If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
• Consider re-challenge with the same or another statin.
• Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy.

For details on CK elevation and treatment of muscular symptoms during statin treatment see algorithm in supplementary.

Fig. 3 shows the algorithm proposed by ESC/EAS Guidelines for the treatment of muscular symptoms during statin treatment.
5. Summary

The term dyslipidaemia includes a number of abnormalities in plasma lipids, including an increase in total cholesterol, cholesterol transported by low density lipoprotein (cLDL) and triglycerides, and a decrease in cholesterol transported by high density lipoprotein (cHDL). Hyperlipidaemia may be divided into primary, due to genetic factors, and secondary, due to acquired conditions such as diabetes. Elevated plasma lipids can accumulate in certain tissues. In the skin, xanthelasma and several types of xanthoma may develop. High levels of triglycerides may trigger acute pancreatitis. However, atherosclerosis is the most important clinical consequence of dyslipidaemia. The development of the atherosclerotic plaque has been extensively studied and the main steps are briefly described. Clinical guidelines recommend lipid screening for primary prevention of coronary heart disease starting in adults at 20 to 45 years depending on the particular guideline. Plasma lipid concentrations are stratified according to the presence of different cardiovascular risk factors in an individual and could be different among different subjects. Therefore, recommendations on when to start medical therapy depend both on LDL levels and on other risk factors for CHD.
6. References


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