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# New Trends Approved in Management of Dyslipidaemia

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**Abstract**

Hypercholesterolemia increases the risk of atherosclerotic cardiovascular disease and is incompletely reversed by statin therapy alone in many patients. Familial hypercholesterolemia (FH) is a common genetic cause of premature cardiovascular disease (CVD). So, most of efforts and directions focused on new therapies as PCSK9 gene was identified in the past decade as a potential therapeutic target for the management of patients with hypercholesterolemia which monoclonal antibodies, Lomitapide, Mipomersen and other therapies hoping to reduce risk of hypercholesterolemia. The novel therapies are aiming for better lipid-lowering effects, fewer side effects and improved clinical outcomes.

**Keywords:** Total cholesterol; HDL-cholesterol; Cell membranes; Certain hormones; Heart disease; Lipid metabolism

**Abbreviations:** TC: Total cholesterol; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; apoB: Apolipoprotein B; FH: Familial hypercholesterolemia; ADH: Autosomal dominant hypercholesterolemia; PCSK9: Proprotein convertase subtilisin/kexin type 9; LDLR: Receptor of the LDL; ARH or FH2: Autosomal recessive hypercholesterolemia; PH: Polygenic hypercholesterolemia; VLDL: Very low-density lipoprotein; ABCA1: ATP-binding cassette transporter; apo A-1: Apolipoprotein A-I; HeFH: Heterozygous state of familial hypercholesterolemia; HoFH: Homogenous state of familial hypercholesterolemia; apo E: Apolipoprotein E; FDB: Familial defective apolipoproteinB-100; LDLRAP1: Low density lipoprotein receptor adaptor protein-1; Lp a: Lipoproteins (a); TSH: Thyroid-stimulating hormone; BUN: Blood Urea Nitrogen; CYP3A4: Cytochrome P3A4; GI: Gastro-Intestinal; ALT: Alanine aminotransferase; ECG: Electrocardiography; TR: Thyroid Receptors; CETP: Cholesterylester Transfer Protein Inhibitors; ACL: ATP-Citrate Lyase Inhibitor; ASCVD: Atherosclerotic Cardiovascular Disease; CAC: Coronary Artery Calcium; CK: Creatine Kinase; mAbs: Monoclonal antibodies; PAD: Peripheral Artery Disease; MI: Myocardial Infarction.

## Introduction

### Hypercholesterolemia

Elevation of total cholesterol (TC) and/or low-density lipoprotein (LDL)-cholesterol or non-HDL-cholesterol in the blood, is also often referred to as dyslipidemia, to encompass it might be accompanied by a decrease in HDL-cholesterol or an increase in triglycerides the fact that.

Dyslipidemia is classified as serum TC, LDL-cholesterol, triglyceride, apolipoprotein B (apoB), or lipoprotein (a) concentrations above the 90%, or HDL-cholesterol or apolipoprotein A-I concentrations below the 10% for the general population.

### Cholesterol

That comes from animals (particularly egg yolks, meat, poultry, fish, and dairy products). The body needs this substance to build cell membranes, make certain hormones, and produce compounds that aid in fat digestion (Figure 1-3).

Too much cholesterol, however, increases a person's risk of developing heart disease [1].

### Classification of Hypercholesterolemia

Primary: lipid metabolism disturbances including:

Familial hypercholesterolemia (FH), which includes:

*Autosomal dominant hypercholesterolemia (ADH) by:*

a) FH by mutations of receptor of the LDL (LDLR).

b) FH by familial defective apoB 100.

c) FH by mutations of proprotein convertase subtilisin/ kexin type 9 (PCSK9) or FH3.

d) Autosomal recessive hypercholesterolemia (ARH or FH2).

e) Polygenic hypercholesterolemia (PH).

f) Hyperlipoproteinemia (a).

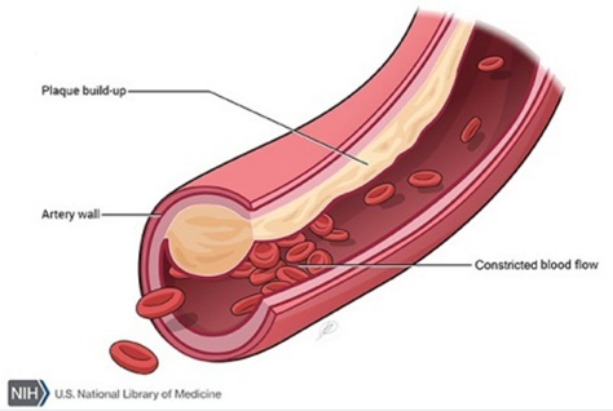


**Figure 1:** Artery plaque [1].

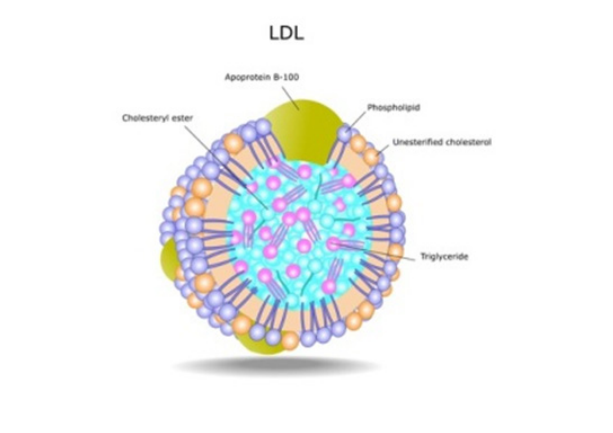


**Figure 2:** Structure of LDL [2].

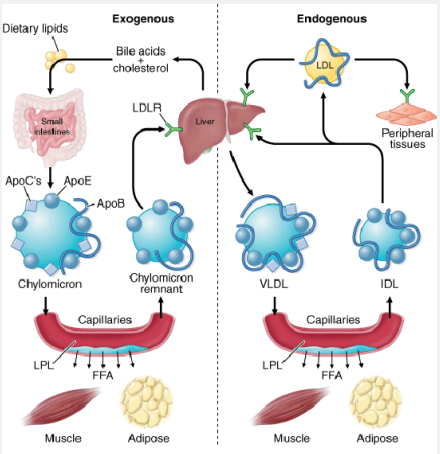


**Figure 3:** Exogenous and endogenous lipid metabolism pathways [2].


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Secondary: basically, as a consequence of environmental factors or other disease causing dyslipidemia:

a) Hypothyroidism, nephrotic syndrome,

b) Cholestasis, asymptomatic acute porphyria,

c) Nervous anorexia, hepatoma,

d) Different drugs: cyclosporine, progestogens, thiazide diuretics [2-4].

### Classification according to: World Health Organization/ Fredrickson

Dyslipidemia can be classified phenotypically by lipid electrophoresis based on which lipoprotein is raised.

a) Elevated chylomicrons; associated with lipoprotein lipase deficiency, apolipoprotein C-II deficiency.

b) Elevated low-density lipoprotein (LDL); associated with familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism and familial combined hyperlipidemia.

c) Elevated LDL and very low-density lipoprotein (VLDL); associated with familial combined Hyperlipidemia.

d) Elevated intermediate-density lipoprotein; associated with dysbetalipoproteinemia.

e) Elevated VLDL; associated with familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, abdominal obesity, diabetes.

f) Elevated chylomicrons and VLDL; associated with diabetes [5].

### Clinical classification

In a more simple and practical way, dyslipidemia can also be classified as:

a) Isolated hypercholesterolemia: mostly due to LDL-cholesterol elevation.

b) Mixed or combined dyslipidemia: elevations in total or LDL-cholesterol, and in triglycerides.

c) Isolated hypertriglyceridemia: elevation in triglycerides only.

d) Low HDL-cholesterol: either isolated or in association with hypercholesterolemia or hypertriglyceridemia. Causes of low HDL-cholesterol include abdominal obesity with insulin resistance, hypertriglyceridemia, smoking, and genetic diseases such as apoA-I, ABCA1 (ATP-binding cassette transporter), or lecithin-cholesterol acyltransferase deficiency [6].

### Familial Hypercholesterolemia

A group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations and increased risk of premature cardiovascular disease.

There are two types of FH: autosomal dominant and recessive.

a) The most common form of FH: the heterozygous state (HeFH) of ADH, is the most frequent monogenic disorder of human metabolism [7].

b) On the contrary, homozygous ADH (HoFH) affects approximately 1:1,000,000 individuals, although recent data suggest that the prevalence could be quite higher [8].

## Pathophysiology

### Due to decreased clearance of LDL from the plasma

**Defects in the LDLR**

LDLR gene is located in chromosome 19 and codifies a membrane glycoprotein which binds to apoB and apolipoprotein E (apoE) contained in the lipoproteins [9] and play a critical role in regulating the amount of cholesterol in the blood [10].

**Familial defective apolipoproteinB-100 (FDB)**

Allow these particles to attach to specific receptors on the surface of cells, particularly in the liver. The receptors transport low-density lipoproteins into the cell, where they are broken down to release cholesterol. The cholesterol is then used by the cell, stored, or removed from the body [11].

**The PCSK9 gene mutations in chromosome 1**

That helps control blood cholesterol levels by breaking down low-density lipoprotein receptors before they reach the cell surface [12].

**Mutations in low density lipoprotein receptor adaptor protein-1 (LDLRAP1)**

Particularly important in the liver, that is the organ responsible for clearing most excess cholesterol from the body [13].

## Clinical Characteristics

a) High plasma LDL-C levels,

b) Fatty skin deposits called xanthomas over parts of the hands, elbows, knees, ankles and around the cornea of the eye called corneal arcus.

c) Cholesterol deposits in the eye lid called xanthelasmas.

d) Coronary atheroma plaques and premature cardiovascular disease.

*e) HoFH (homogenous state of familial hypercholesterolemia)*

f) True HoFH the LDLR pathway is markedly defective or nonfunctional.

g) The plasma LDL-C levels rise four to eight times above average (>500mg/dL) and the patients suffer from severe cutaneous and tuberous xanthomas.


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h) In the more severe cases, cholesterol can be deposited in the tendons and joints leading to tendinitis and joint pain, requiring surgical removal.

i) In rare cases, patients could present giant ectopic cholesterol xanthomas in the brain, mediastinum, and gluteus muscles [14].

*j) HeFH(heterozygousstateoffamilialhypercholesterolemia)*

k) HeFH show plasma LDL-C levels two to three times above average.

l) Interaction with other genes and the presence of additional risk factors (hypertension, smoking, etc.) (Figure 4).

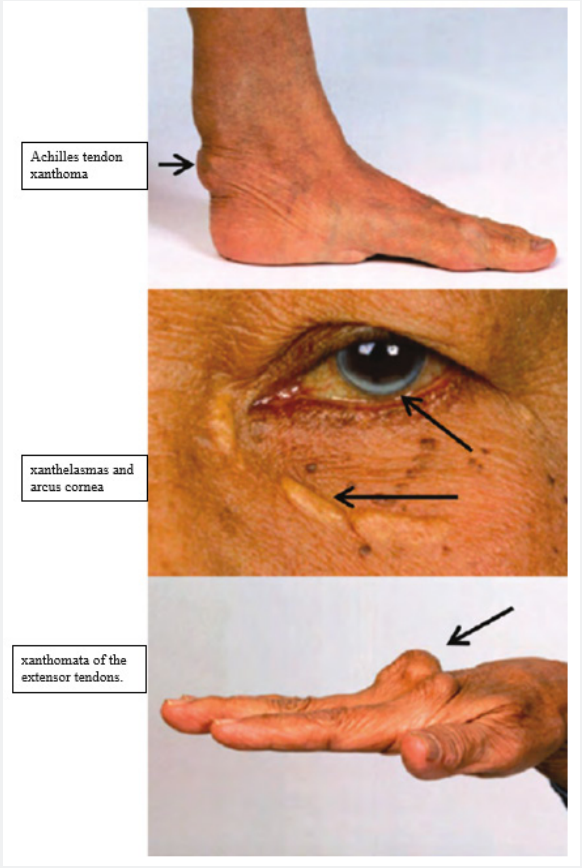


**Figure 4:** Clinical characteristic of hypercholesterolemia [15].

## Definitions

a) Lipoprotein: the particle that transports cholesterol and triglycerides. Lipoproteins are composed of proteins (called apolipoproteins), phospholipids, triglycerides, and cholesterol.

b) The non-HDL cholesterol: the total cholesterol level minus HDL cholesterol level. It is an approximation of very-low-density lipoprotein (VLDL) plus LDL levels.

c) Myopathy: general term referring to any disease of muscles.

d) Myalgia: muscle ache or weakness without creatine kinase (CK) elevation.

e) Myositis: muscle symptoms with increased CK levels.

f) Rhabdomyolysis: muscle symptoms with marked CK elevation (more than 10 times the upper limit of normal [ULN]) [15].

## Risk factors

a) Multiple major coronary risk factors (especially diabetes).

b) Severe and poorly controlled risk factors (especially continued cigarette smoking).

c) Multiple risk factors of metabolic syndrome:

i. Abdominal obesity (waist circumference in men more than 40 inches [102cm] or in women more than 35inches [88cm]).

ii. Triglycerides 150mg/dL or more.


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iii. Low HDL cholesterol (less than 40mg/dL in men or less than 50mg/dL in women).

iv. Blood pressure 135/85mm Hg or higher.

v. Fasting glucose 110mg/dL or more.

d) Acute coronary syndrome [16].

e) Age: risk may increase as you get older. Men aged 45 years or older and women aged 55 years or older.

f) Gender: After menopause, a woman's LDL cholesterol level ("bad" cholesterol) goes up, as does her risk for heart disease.

g) Family History: risk of high cholesterol may increase if a father or brother was affected by early heart disease (before age 55) or a mother or sister was affected by early heart disease (before age 65).

h) Diet: The trans fats, saturated fat, sugar, and (to a lesser extent) cholesterol in the food you eat raise total and LDL cholesterol levels.

i) Physical Activity: Increased physical activity helps to lower LDL cholesterol and raise HDL cholesterol (the "good" cholesterol) levels. It also helps you lose weight [17] (Figure 5).

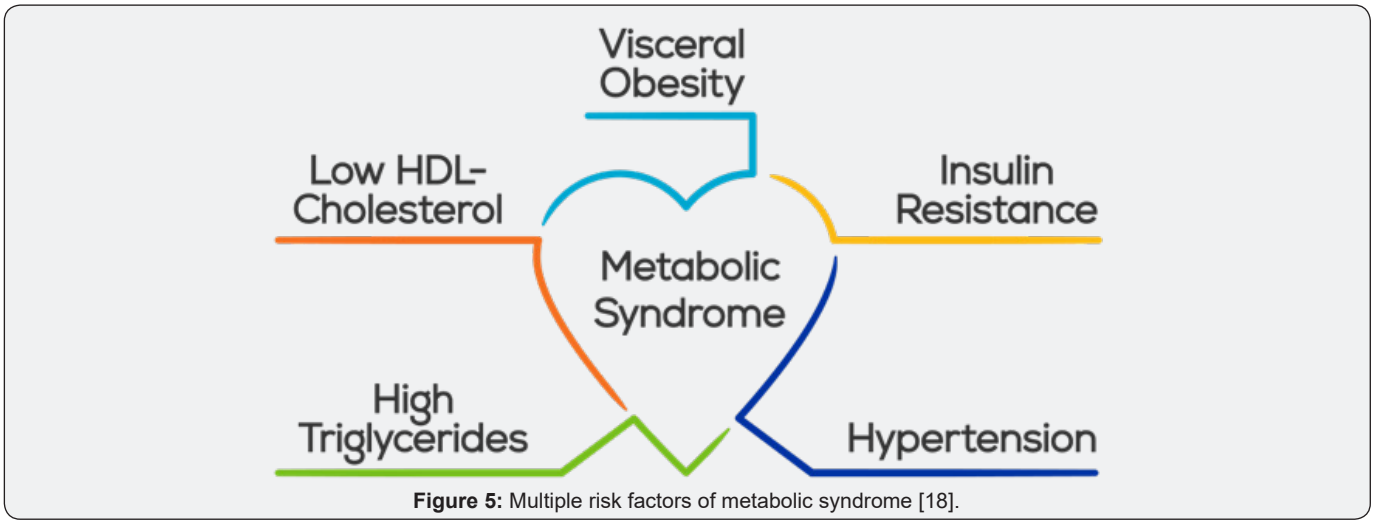


**Figure 5:** Multiple risk factors of metabolic syndrome [18].

## Diseases related to hypercholesteremia

### Coronary heart disease

Cholesterol can build up in the walls of your arteries. Over time, this build-up -- called plaque -- causes hardening of the arteries or atherosclerosis. This causes arteries to become narrowed, which slows the blood flow to the heart muscle. Reduced blood flow can result in angina (chest pain) or in a heart attack if a blood vessel gets blocked completely.

### Stroke

Atherosclerosis causes arteries that lead to the brain to become narrowed and even blocked. If a vessel carrying blood to the brain is blocked completely, you could have a stroke.

### Peripheral vascular disease

In this condition, fatty deposits build up along artery walls and affect blood circulation. This occurs mainly in arteries that lead to the legs and feet.

### Diabetes

Diabetes can upset the balance between HDL and LDL cholesterol levels. People with diabetes tend to have LDL particles that stick to arteries and damage blood vessel walls more easily. Glucose (a type of sugar) attaches to lipoproteins (a cholesterol-protein package that enables cholesterol to travel through blood). Sugar coated LDL remains in the bloodstream longer and may lead to the formation of plaque. People with diabetes tend to have low HDL and high triglyceride (another kind of blood fat) levels. Both of these boost the risk of heart and artery disease.

### High blood pressure

When the arteries become hardened and narrowed with cholesterol plaque and calcium, the heart has to strain much harder to pump blood through them. As a result, blood pressure becomes abnormally high. High blood pressure is also linked to heart disease [17].

## Prevention

### Primary prevention

Except for familial causes of hypercholesterolemia, the disease is completely preventable and largely related to the adoption of a healthier the lifestyle.

### Screening

Lowering of low-density lipoprotein (LDL)-cholesterol leads to reduction of cardiovascular events in moderate-to-high-risk patients [18].


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a. *Screening in adults ages >20 years* has been advocated; however, the evidence base in adults ages 21 to 39 years is not clear [19]. Previous guidance has recommended obtaining:

i. Fasting lipid profile for all adults ages ≥20 years; this can be repeated every 5 years.

ii. Non-fasting lipid profile, especially for total, non-high-density lipoprotein (HDL)-, and HDL-cholesterol, is also recommended.

iii. Screening for related cardiovascular risk factors such as hypertension, diabetes mellitus, family history of premature cardiovascular disease and smoking. There is no upper age limit at which screening for hypercholesterolemia should be terminated [20].

b. *For patients <20 years*, the presence of atherosclerotic risk factors such as hypertension, diabetes, tobacco abuse, obesity, and premature cardiovascular disease or significant hypercholesterolemia (total cholesterol >240mg/dL) in the immediate family should prompt the physician to consider screening [21].

### Secondary prevention

a) Dietary reduction in total and saturated fat, weight loss in overweight patients, aerobic exercise, and addition of plant stanols/sterols to the diet leads to a decrease in low-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol.

b) In the US, evolocumab is approved for use in the reduction of risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.

c) Patients should be assessed for the presence of additional cardiovascular risk factors, such as smoking and diabetes, and appropriate management of these risk factors initiated [22-24].

## Diagnosis

### History

a) Focusing on symptoms of coronary artery disease, cerebrovascular disease, and peripheral arterial disease, such as chest pain, shortness of breath, weakness, dysphasia, or claudication.

b) Family history for early onset of coronary heart disease and dyslipidemia in first-degree relatives.

c) Level of exercise and diet at this stage.

### Examination

a) Signs of hypercholesterolemia, such as eyelid xanthelasmas, arcus corneae and xanthomata.

b) Tendinous xanthomas at the Achilles, elbow and knee tendons and over metacarpophalangeal joints are characteristics of heterozygous and homozygous forms of familial hypercholesterolemia.

c) Palmar or cutaneous xanthomas may be present in the homozygous form of familial hypercholesterolemia.

d) Eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet may be present in severe elevations of triglycerides.

e) Palmar and tuberous xanthomas are seen in patients with dysbetalipoproteinemia.

f) There may also be evidence of vascular disease, such as elevated neck veins or bibasal crepitations on lung auscultation (heart failure), hemiplegia (stroke), or diminished pulses (peripheral arterial disease) [17].

### Investigation

a) Lipids are measured in the fasting state: including total cholesterol, triglycerides, high-density lipoprotein (HDL), and estimated low-density lipoprotein (LDL) [25,26].

b) Non-HDL-cholesterol: is a marker of cholesterol carried by pro-atherogenic lipopoproteins: very low-density lipoprotein and remnants, intermediate-density lipoproteins, LDL, and lipoproteins (a) [27].

c) LDL can be accurately estimated in non-fasting states if triglyceride levels are <400 mg/dl.

d) Extremely high lipid levels may give a lactescent (milky) appearance to blood plasma.

e) Routine thyroid-stimulating hormone rules out most cases of hypothyroidism.

f) These may include creatinine levels, fasting blood glucose and glycated hemoglobin, urinalysis, ECG, echocardiogram, cardiac stress testing, cardiac computed tomography to measure coronary calcium scores or luminal obstruction, cardiac catheterization, and vascular studies such as Doppler exam or ankle-brachial indices [17].

### Diagnostic tests

**1st test: lipid profile**

a) Consists of TC, triglycerides, and LDL-, HDL-, and non-HDLcholesterol.

b) TC, non-HDL, and HDL can be measured in the non-fasting state [27].

c) TC values vary by 10% and triglycerides by up to 25% day to day, even in the absence of disease [28].

d) Plasma or serum can be used, with plasma cholesterol being approximately 3% higher than the serum value [29].


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Acute illnesses can influence the lipid profile:

a) Triglycerides increase and cholesterol levels decrease in inflammatory states. In particular.

b) Lipid profiles change significantly 24 hours after an acute myocardial infarction, and measurement should either be performed acutely or postponed until after recovery [30].

**Result**

a) Total cholesterol (TC) >200mg/dl.

b) LDL-cholesterol >100mg/dL.

c) Non-HDLcholesterol >130mg/dL.

d) HDL-cholesterol <40mg/ dL for men and <50mg/dL for women.

e) Triglycerides >344mg/dl.

### Serum thyroid-stimulating hormone (TSH)

a) TSH may be low in secondary hypothyroidism.

### Result

a) Elevated in primary hypothyroidism [17,31] (Table 1).

**Table 1:** Differential Diagnosis for Hypercholesterolemia.

| Condition | Signs/Symptoms | Tests |
|---|---|---|
| Obstructive liver disease [17] | a) Stigmata of liver disease, such as jaundice and abdominal tenderness, may be present.<br>b) With significant elevations of bilirubin the patient may also complain of pruritus. | a) Elevated alanine aminotransferase, aspartate aminotransferase, gammaglutamyl transferase, alkaline phosphatase and bilirubin.<br>b) Imaging studies such as abdominal ultrasound or computed tomography scan and magnetic resonance imaging may show dilated biliary ducts and possible cause for obstruction. |
| Nephrotic syndrome [17] | a) The hyperlipidemic response is triggered at least in part by the reduction in plasma oncotic pressure, and the severity of the hyperlipidemia is inversely and closely related to the fall in oncotic pressure.<br>b) Spontaneous or drug induced resolution of nephrotic syndrome reverses hyperlipidemia. | a) Marked elevations in plasma levels of cholesterol and less predictably, triglycerides and lipoprotein (a). High-density lipoprotein (HDL)-cholesterol usually normal or reduced.<br>b) Abnormal serum creatinine, BUN, and serum albumin.<br>c) Elevated 24-hour urinary protein. |
| Chronic renal Insufficiency [17] | a) Dyslipidemia normally presents as hypertriglyceridemia (due to diminished clearance). Low HDL-cholesterol levels are also seen in many patients.<br>b) Patients undergoing peritoneal dialysis are more likely to have an atherogenic lipid profile than those undergoing hemodialysis. | a) About half of patients have triglyceride levels >200mg/dL, about one third have total cholesterol levels >240mg/dL, and 10% to 45% have low-density lipoprotein cholesterol levels >130mg/dL.<br>b) Total cholesterol concentration is sometimes normal or low, which may be in part due to malnutrition in this subset of patients.<br>c) Abnormal serum creatinine, BUN, and serum albumin.<br>d) Elevated 24-hour urinary protein.<br>e) Estimated glomerular filtration rate should be calculated. |
| Hypothyroidism [31] | a) There may be lethargy, cold intolerance, constipation, dry hair or skin, goiter, or delayed return of deep tendon reflexes.<br>b) In a study investigating people referred for the evaluation of hyperlipidemia, hypothyroidism was found to be present in 4.2% of patients.<br>c) A significant reduction in the serum cholesterol concentration during thyroid hormone replacement was only seen in those patients with a serum thyroidstimulating hormone (TSH) concentration >10 milliunits/L. | a) Serum TSH is high and serum free thyroxine may be low. |

**Table 2:** Classification of LDL-C, Total cholesterol, Triglycerides and HDL-C.

| | |
|---|---|
| LDL-cholesterol | *Optimal: <70mg/dL.<br>*Desirable: 70 to <100mg/dL<br>*Near or above desirable:100 to 129mg/dL<br>*Borderline high: 130 to 159mg/dL<br>*High: 160 to 189mg/dL.<br>*Very high: ≥190mg/dL. |


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| | |
|---|---|
| Total cholesterol | *Optimal: <170mg/dL<br>*Desirable: <200mg/dL<br>*Borderline high: 200 to 239mg/dL<br>*High: ≥240mg/dL. |
| Triglycerides | *Ideal: <100mg/dL<br>*Desirable: 100 to <150mg/dL<br>*Borderline high: ≥150mg/dL<br>*High: 200 to 499mg/dL<br>*Very high: ≥500mg/dL. |
| HDL-cholesterol | *Low: <40mg/dL. |

### Diagnostic criteria

Classification of low-density lipoprotein (LDL)-cholesterol, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholestero λ [32,33] (Table 2).

### Classification of non-HDL-cholesterol

Non-HDL-cholesterol is considered high depending on the level of cardiovascular disease risk [34] (Table 3).

**Table 3:** Classification of Non-HDL-C.

| |
|---|
| a) In low- to moderate-risk patients, high non-HDL-cholesterol: ≥145mg/dL. |
| b) In high-risk patients, high non-HDL-cholesterol: ≥130mg/dL. |
| c) In very high-risk patients, high non-HDL-cholesterol: ≥100mg/dL. |

## Discussion

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management:

### In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction. Lifestyle therapy is the primary intervention for metabolic syndrome.

### In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDLC levels by ≥50%.

### In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy.

Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70mg/dL (≥1.8mmol/L). In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8mmol/L) on *maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor.*

### In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10- year ASCVD risk.

If the LDL-C level remains ≥100mg/dL (≥2.6mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100mg/dL (≥2.6mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor.

### In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70mg/dL (≥1.8mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

### In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated] and calculated 10-year risk of ASCVD), the presence of risk-enhancing factors, the potential benefits of lifestyle and statin therapies, the potential for adverse effects and drug–drug interactions, consideration of costs of statin therapy, patient preferences and values in shared decision making.

### In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70mg/dL (≥1.8mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy. If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity. If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.


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**In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favour initiation of statin therapy.**

Risk enhancing factors include:

a) Family history of premature ASCVD.

b) Persistently elevated LDL-C levels ≥160mg/dL (≥4.1mmol/L).

c) Metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (rheumatoid arthritis, psoriasis, or chronic HIV).

d) Persistent elevations of triglycerides ≥175mg/dL (≥1.97mmol/L) and if measured in selected individuals apolipoprotein B ≥130mg/dL, high-sensitivity C-reactive protein ≥2.0mg/L, ankle-brachial index <0.9 and lipoprotein (a) ≥50mg/dl or 125nmol/L, especially at higher values of lipoprotein (a).

e) Risk-enhancing factors may favour statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).

**In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70mg/dL- 189mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.**

If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD. A CAC score of 1 to 99 favours statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥75%, statin therapy is indicated unless otherwise deferred by the outcome of clinician-patient risk discussion.

**Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.**

Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70mg/dL (≥1.8mmol/L) on maximal statin therapy [35].

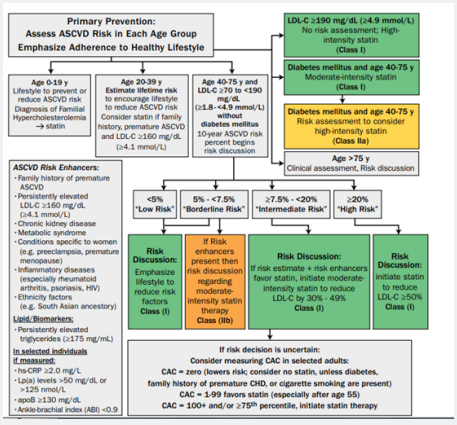


**Figure 6:** Primary prevention.

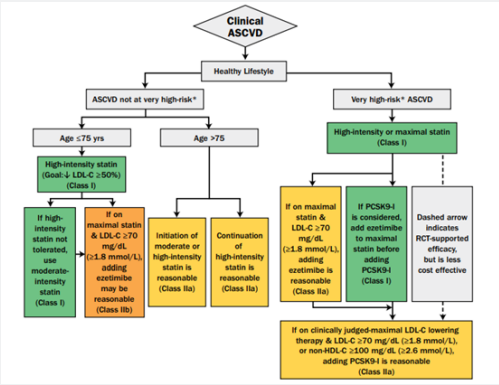


**Figure 7:** Secondary prevention.


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## Treatment targets

a) Reduce atherosclerotic CV risk in adults.

b) The importance of LDL-C lowering to prevent CVD is strongly emphasized.

Smoking: No exposure to tobacco in any form.

Diet: Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.

Physical activity: 2.5-5h moderately vigorous physical activity per week or 30-60min most days.

Body weight: BMI 20-25kg/m2, waist circumference <94cm (men) and <80cm (women).

Blood pressure: <140/90mmHg.

Lipids LDL-C is the primary target:

a) Very high-risk: LDL-C <1.8mmol/L (70mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135mg/dL).

b) High-risk: LDL-C < 2.6mmol/L (100mg/dL) or a reduction of at least 50% if the baseline b is between 2.6 and 5.2mmol/L (100 and 200mg/dL).

c) Low to moderate risk: LDL-C <3mmol/L (115mg/dL).

d) 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.

e) HDL-C: no target, but >1mmol/L (40mg/dL) in men and >1.2mmol/L (48mg/dL) in women indicates lower risk.

f) TG: no target but <1.7mmol/L (150mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

g) Diabetes: HbA1c <7% (<53mmol/mol) [35] (Figure 6 & 7).

## Treatment

a) Primary prevention over life span [35].

b) Secondary ASCVD Prevention [35].

c) Pharmacological treatment

d) Lipid-Lowering Drugs

## Statin

### Mechanism of action

Statins reduce synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity. The reduction in intracellular cholesterol concentration induces low-density lipoprotein receptor (LDLR) expression on the hepatocyte cell surface, which results in increased LDL-C catabolism and a decreased LDL-C synthesis and other apo B-containing lipoproteins including TG-rich particles [36].

### Side effects

a) Myopathy.

b) Elevated liver enzymes (rarely hepatotoxicity).

c) Muscle cell damage and death (rhabdomyolysis) result in the release of creatine phosphokinase (CK) and myoglobin among other intracellular molecules, while the accumulation of myoglobin in the kidneys can lead to renal failure and death [37-42] (Table 4).

**Table 4:** High, Moderate and Low Intensity of Statin [35].

| | High-Intensity | Moderate Intensity | Low Intensity |
|---|---|---|---|
| LDL-C lowering | ≥50% | 30%-49% | <30% |
| Statins | * Atorvastatin 40-80 mg. | * Atorvastatin 10-20mg. | |
| | * Rosuvastatin 20-40 mg. | * Rosuvastatin 5-10mg. | * Simvastatin 10mg. |
| | | * Simvastatin 20-40mg. | |
| | | * Pravastatin 40-80mg. | |
| | | * Lovastatin 40-80mg. | |
| | | * Fluvastatin XL 80mg. | * Pravastatin 10-20mg. |
| | | * Flyvastatin 40mg. | * Lovastatin 20mg. |
| | | (BID). | * Fluvastatin 20-40mg. |
| | | * Pitavastatin 1-4mg. | |

## Non-Statin Therapy

### New trends approved in treatment of hypercholesterolemia

The potential role of certain additional options, including microsomal transfer protein inhibitors, liver-selective thyroid hormone mimetics, and oligonucleotides that supress ApoB [43,15] (Table 5).

## Lomitapide

### Mechanism of action

Inhibiting the microsomal triglyceride transfer protein in the liver, that is necessary for TG absorption by the chylomicrons in the intestine and phospholipids by VLDL in the hepatocytes [44].


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**Table 5:** Non-Statin Therapies of Hypercholesterolemia.

| Drug | MOA[36] | Effect[35] |
|---|---|---|
| Ezetimibe (Cholesterol Absorption Inhibitors) | * The first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients.<br>* Blocks cholesterol absorption across the intestinal border.<br>* Ezetimibe is the most commonly used non-statin agent. | * Lowers cholesterol.<br>* It lowers LDL-C levels by 13% to 20%. |
| | a) Has a low incidence of side effect. | |
| Bile acid sequestrants (Cholestyramine, colestipol and colsevelam) | * Bile acids are synthesized in the liver from cholesterol.<br>* Increased LDL catabolism.<br>* Reduced cholesterol absorption. | * Reduce cholesterol.<br>* Increase VLDL.<br>* Reduce LDL-C levels by 15% to 30% depending on the dose.<br>N.B:<br>* Not absorbed and do not cause systemic side effects, but they are associated with gastrointestinal complaints (e.g., constipation).<br>* Cause severe hypertriglyceridemia when fasting triglycerides are ≥300mg/dl (≥3.4 mmol/L). |
| | a) In the management of FH, bile acid sequestrants may be recommended either as monotherapy in younger patients, pregnant women or women who want to become pregnant and patients requiring modest LDL reduction.<br>b) Combination therapy with statins in patients with very high LDL levels. | |
| Nicotinic acid (Vitamin B3) | * Has broad lipid-modulating action.<br>* Reduce LDL and VLDL synthesis. | * Raising HDL-C by 25%.<br>* Reducing LDL-C by 15 -18%.<br>* Reducing TG by 20-40% at the 2 g/day dose.<br>* Lowering Lp(a) levels by up to 30% at this dose. |
| | a) Nicotinic acid has also been shown to reduce insulin sensitivity and impair glucose control in T2DM patients.<br>b) Increased risk of myopathy when combined with statins. | |
| Fibrates (Gemfibrozil, fenofibrate and clofibrate) | * Increased VLDL clearance.<br>* Reduce LDL synthesis. | * Reduce TG.<br>* Reduce cholesterol.<br>* Reduce LDL, VLDL.<br>* Increase HDL. |
| | a) The addition of fibrates to statins has been associated with higher incidence of myopathy, rhabdomyolysis and liver dysfunction.<br>b) Gemfibrozil should not be co-prescribed with statins. | |
| Fish Oil | * Less atherogenic lipid profile in FH patients [38,39].<br>* Cardio-protective.<br>* Reducing arterial stiffness and improving blood pressure [40,41].<br>* Recent meta-analysis reported a weakness of fish oils to achieve significant positive outcomes [42]. | |

**Table 6:** Effect of Lomitapide on LDL and LP(a) [46].

| | | |
|---|---|---|
| LDL reduced | By 50% at 26week of treatment. | * Its effect on LDL maintained from 26 to 78 weeks of treatment. |
| Lipoprotein(a) reduced | By 15% at 26week of treatment. | * Lp(a) levels return back to baseline at week 78. |

a) Co-administration of Lomitapide with cytochrome P3A4 (CYP3A4) inhibitors should be avoided [44].

b) Increased hepatic fat content and elevation of transaminases, which resolved after dose reduction [45].

c) Gastro-Intestinal (GI) adverse events [45,46] which may be resolved by slow dose titration, low-fat diet, and avoidance of mealtimes [44,46,47] (Table 6).

## Mipomersen

### Mechanism of action

Antisense oligonucleotide that binds ApoB mRNA and subsequently down regulates the expression of ApoB by the ribosomes and the production of VLDL [44,48].

Notes:

a) Administered as a 200mg subcutaneous once-weekly injection [49].

b) Lowering lipid in pediatric [50].

c) The most common adverse effect:

d) Injection-site reactions.

e) Flu-like symptoms.

f) Elevated ALT (<3 × URL) [51,52].

g) Increased intrahepatic TG content [53, 54] (Table 7).


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**Table 7:** Effect of Mipomersen in Lipid.

| | |
|---|---|
| LDL level reduced by | * 21% in patients with HoFH. |
| | * 28% in HeFH.[55] |
| The maximum tolerated standard lipid-lowering treatment in HoFH patients: | * LDL reduced by 25%. |
| | * ApoB reduced by 27%. |
| | * Lp(a) reduced by 31%[53] |

## Thyroid Mimetics

### Mechanism of action

Thyroid hormones act on two main types of receptors, thyroid receptors α and β (TRα and TRβ) [55,56]. Endogenous thyroid hormones having Lipid-Lowering effects through TRβ; but not be utilized due to TRα-induced cardiac, muscle and bone thyrotoxic side effects [57,56].

Selective TRβ agonists could offer an additional approach in HF treatment by induction hepatic bile acid production and up-regulation the expression of the HDL receptor, the receptor type B-Class I (SR-B1), leading to increased transport of cholesterol into HDL particles [57]. These agents can interfere with cholesterol metabolism, without the unwanted TRα-related side effects [55].

Selective TRβ agonists (GC-1 (sobetirome) and KB2115 (eprotirome)) decrease serum cholesterol levels by increasing cholesterol utilization for synthesis of bile acids and inducing their subsequent fecal excretion in an LDLR-independent manner [57].

Notes: Due to the reported side effects, the future role of thyroid mimetics will depend on their safety profile and some of these agents may potentially find a role in HoFH treatment [56] (Table 8).

**Table 8:** Characteristics of Thyromimetics Eprotirome and Sobetirome.

| Drug | Lipid effect | Side effect |
|---|---|---|
| Eprotirome (KB2115) | * Dose-dependent LDL lowering effect.<br>* 22% LDL reduction [59]. | * induced cartilage damage [59].<br>* induced liver injury |
| Sobetirome (GC-1) | * Remarkable LDL reduction. | Mild suppression of the hypothalamic-pituitary axis. [57] |
| | * decreased TG and Lp(a) levels. | |

## Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) Inhibitors

### Mechanism of action

PCSK9 is a serine protease produced by hepatocytes [48] blocks the LDLR recycling by mediating clathrinmediated endocytosis and subsequently inducing the lysosomatic degradation of LDLR [58,59] and this leads to LDL accumulation in the circulation [60] and eventually promotes atherogenesis, with high PCSK9 levels correlating to the degree of coronary artery calcification [61].

The strategies that target the binding include:

a) Monoclonal antibodies (mAbs) that bind to PCSK9 in the plasma, thereby preventing it from binding to LDL-R.

b) Modified binding proteins such as adnectins, and small-molecule inhibitors. Notably, development of a small-molecule inhibitor of PCSK9 [62].

a) Effect:

LDL reduction: up to a 55% as monotherapy, and 75% combined with a statin [63-68] (Figure 8) & (Table 9 & 10).

**Table 9:** Monoclonal antibodies PSCK9 Inhibitors.

| *Alirocumab* | *Evolocumab* |
|---|---|
| a) Administrated subcutaneously every 2 weeks [65,66].<br>b) Showed significant and persistent reductions in LDL, non-HDL cholesterol, and Lp(a) levels [67,68,69]. | c) Administrated subcutaneously every 4 weeks [65,66].<br>a) Treatment for both HeFH and HoFH.<br>b) Used in statin-intolerant patients and for significantly lowering LDL.<br>d) Improves ApoA1, ApoB, Lp(a), non-HDL cholesterol, and triglycerides [67]. |
| Side Effects:<br>e) Mild injectionsite reactions [15].<br>f) Upper respiratory tract infections, back pain and influenza [71].<br>g) Very rarely leucocytoclastic vasculitis [15]. | |

Two additional PCSK9 inhibitors:

a) Bococizumab
b) LY3015014 [72].


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**Table 10:** Monoclonal antibodies PSCK9 Inhibitors.

| ACC (2016-updated in 2017) | ESC/EAS (2017-updated in 2018) |
|---|---|
| Indications:<br>a) Either a PCSK9 inhibitor or ezetimibe as a second line agent as an addition to maximum tolerated statin for patients with clinical ASCVD with comorbidities and baseline LDL _1.8mmol/l (70mg/dL).<br>b) Should be preferred when >25% further reduction in LDL is required after discussing all parameters with the patient.<br><br>Specific criteria:<br>1. ASCVD without comorbidities and LDL ≥2.6mmol/L (100mg/dL) while on maximum tolerated statin and ezetimibe and a reduction of LDL <50% from baseline.<br>2. ASCVD with comorbidities and LDL ≥1.8mmol/l (70mg/dL), or non-HDL ≥2.6mmol/L (100mg/dL) in diabetic patients, while on maximum tolerated statin and ezetimibe and a reduction of LDL <50% from baseline.<br>3. ASCVD with baseline LDL ≥4.9mmol/L (190mg/dL) and post-treatment LDL ≥1.8mmol/l (70mg/dL) while on maximum tolerated statin and a reduction of LDL <50%, as an alternative to ezetimibe or bile acid sequestrant.<br>4. Without ASCVD and LDL ≥4.9mmol/L (190mg/dL) and post-treatment LDL ≥2.6mmol/l (100mg/dL) while on maximum tolerated statin and a reduction of LDL <50%, as an alternative to ezetimibe or bile acid sequestrant.<br>1. Before LDL apheresis in HoFH patients, except LDLR negative patients. | Indications:<br>a) Adults with HeFH, non-familial hypercholesterolemia, or mixed dyslipidemia with diet, maximum tolerated statin (or when statin-intolerant/contraindicated), or other medications, not achieving LDL goals.<br>b) Adults and ≥12 y.o. with HoFH on other medications.<br>c) Symptomatic PAD.<br>d) Recurrent or recent MI.<br>e) Multivessel disease.<br><br>Specific criteria:<br>1. Severe ASCVD and LDL >2.6mmol/L (100mg/dL).<br>2. ASCVD and LDL >3.6mmol/L (140mg/dL).<br>3. Diabetes with target organ disease or major risk factors (no ASCVD) and LDL >3.6mmol/L (140mg/dL).<br>4. HeFH without ASCVD and LDL >4.5–5mmol/L (175–200mg/dL) (according to risk).<br>5. HoFH (after maximum treatment, including LDL apheresis)—all patients except from those with negative-negative LDLR mutations.<br>6. Statin intolerant patients on ezetimibe and any of the above criteria |

**Table 11:** Types of CETP.

| Drug | Effect |
|---|---|
| Anacetrapib | * Interferes with lipid exchange.<br>* Reduces LDL by increasing ApoB100-LDL binding to LDLR.<br>* Removing ApoB from the circulation [75]. |
| Torcetrapib | * Increase HDL by 72.1%.<br>* Lower LDL by 24.9% [76]. |

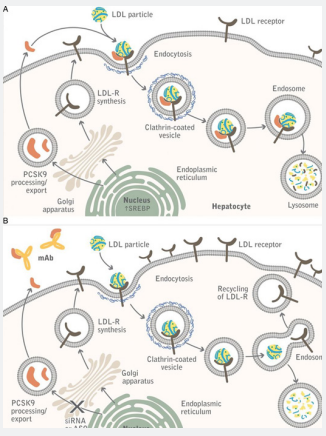


**Figure 8:** PSCK9 mode of action [64].


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### Cholesterylester Transfer Protein (CETP) Inhibitors

#### Mechanism of action

CETP induces the transport of cholesteryl esters and TG from HDL molecules to atherogenic molecules, such as the ApoB-containing lipoproteins [15,69-73] (Table 11).

Notes:

a) Dalcetrapib in patients with recent acute coronary syndrome events showed poor efficacy when added to standard of care treatment, failing to reduce CVD recurrence [74].

b) Evacetrapib was also abandoned due to lack of improved CVD outcomes [75].

c) TA-8995 has good results on lipid metabolism [75,74,76].

### ATP-Citrate Lyase (ACL) Inhibitor

#### Mechanism of action:

The ACL inhibitor ETC-1002 (bempedoic acid) has been found to lower cholesterol biosynthesis by depriving cells of the necessary substrates [77,56].

Reduce C-reactive protein levels, better CVD outcomes may be possible through its implication in pro-inflammation processes [78].

### Plaque Regression Treatment (rHDL) in FH:

#### Mechanism of action

Intravenous infusion of reconstituted HDL or an HDL-mimetic particle (CER-001) has shown encouraging results in reversing coronary atherosclerotic damage [15,79].

Acts potentially by promoting reverse cholesterol transport and increasing the concentration of ApoA-I [15,74].

#### Surgical Therapy in FH

a) Ileal bypass and liver transplantation could be options in patients at increased CVD risk who fail to reach the treatment targets or tolerate conventional treatment options [15,80-82].

b) Portacaval shunt can reduce the absorption of cholesterol and enhance bile acid excretion [83].

#### Gene-Targeted Therapy in FH

Genetic therapy may offer a promising approach for the treatment of FH in the near future [71,84].

## Conclusion

Due to the FH-related high CVD morbidity and mortality, early prevention and effective management of these patients is essential through organized primary care and/or Lipid Specialist care centers. Current research further focuses on new monoclonal antibodies/genetic targeting approaches which may offer novel options in order to significantly lower LDL and prevent/reduce ASCVD in FH.

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