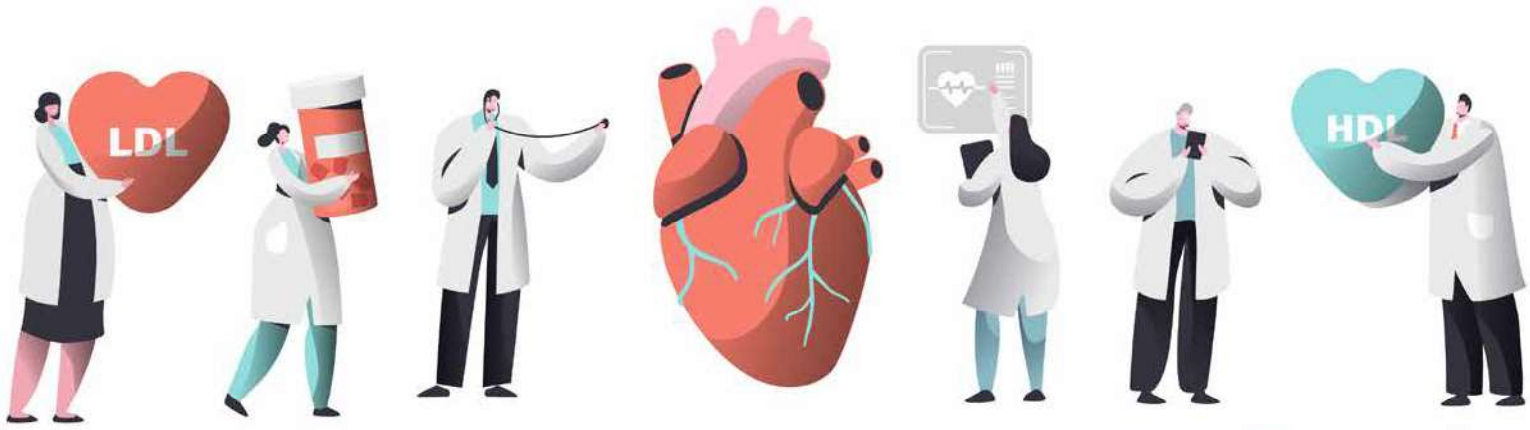

Managing Cholesterol in the Community Setting

Written by Margaret Bermingham, BSc(Pharm), PhD, MPSI, Lecturer in Clinical Pharmacy Practice, School of Pharmacy, University College Cork

Background

Cholesterol is essential in the body for synthesis of steroids, production of plasma membranes, energy expenditure, and bile acid formation. Cholesterol may be synthesised in the body or absorbed from the diet in gastrointestinal tract. Lipids such as cholesterol and triglycerides are insoluble in water, therefore the are transported in the blood in lipoproteins such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL).[1]

A clear link between plasma cholesterol levels, in particular total cholesterol and LDL-cholesterol, and cardiovascular ill-health and mortality has been established. For every 1mmol/L reduction in plasma LDL-cholesterol there is a corresponding 10% reduction in all-cause mortality, a 20% reduction in death from cardiovascular disease (CVD) and a 17% reduction in stroke. Reducing cholesterol levels reduces atherosclerosis and related diseases including ischaemic heart disease, heart attack, stroke and peripheral vascular disease.[2]

Causes of hyperlipidaemia

Hyperlipidaemia occurs where plasma cholesterol, triglycerides or both are elevated above normal levels. The causes of hyperlipidaemia may be primary (or familial) or secondary.[1]

Primary hyperlipidaemia

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an inherited genetic defect that may lead to early development of atherosclerosis and ischaemic heart disease. Homozygous FH is very rare, affecting at most 1:160,000 people. Heterozygous FH is more common and is thought to affect approximately 1:250 people. Heterozygous FH should be suspected where initial total cholesterol is greater than 8.5mmol/L, where there is a family history of premature ischaemic heart disease or where tendon xanthoma are present.[3]

Familial Combined Hyperlipidaemia

Familial combined hyperlipidaemia (FCH) occurs in 1:100 to 1:200 of the population. It occurs as an interaction of multiple genes and the individual's environment. In FCH, high LDL-cholesterol and triglyceride levels are seen, and FCH is associated with premature CVD.[3]

Secondary hyperlipidaemia

Secondary hyperlipidaemia occurs due to diet, a medical disorder such as thyroid disorders, or as a side effect of drug therapy and may account for up to 40% of hyperlipidaemias.[1] Secondary hyperlipidaemia may be corrected by treating the underlying condition, withdrawal of the causative drug or change of diet. Some examples of medications that can cause secondary hyperlipidaemia are given in Table 1.

Primary and secondary prevention of cardiovascular disease

The treatment of hyperlipidaemia falls into two categories, primary and secondary prevention. Primary prevention concerns the treatment of hyperlipidaemia in people who

Table 1. Medications that may cause secondary hyperlipidaemia (adapted from Handhle A, Park A. Hyperlipidaemia. Medicine (Baltimore). 49(9):587–91).[1]

Effect of medication	Medications
Increase LDL-cholesterol level	Ciclosporin Sirolimus Anti-epileptic agents SGLT2 inhibitors
Increase triglyceride level	Anabolic steroids Beta-blockers Glucocorticoids Non-nucleoside reverse transcriptase inhibitors Nucleoside reverse transcriptase inhibitors Olanzapine Progestins Protease inhibitors Retinoids Tamoxifen Thiazide diuretics

Table 2. Risk categories for primary and secondary prevention of cardiovascular disease (adapted from the 2019 ESC/EAS guidelines for the management of dyslipidaemias).[3]

Risk category	Risk factors for this category
Very-high-risk	Documented atherosclerotic CVD including heart attack or unstable angina, stable angina, coronary revascularization, stroke and transient ischaemic attack, and peripheral arterial disease. Diabetes with target organ damage, or early onset of T1DM of long duration (>20 years). Severe chronic kidney disease. A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with atherosclerotic CVD or with another major risk factor.
High-risk	Total cholesterol >8 mmol/L, LDL-cholesterol >4.9 mmol/L, or blood pressure ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with diabetes without target organ damage, with diabetes duration ≥10 years. Moderate chronic kidney disease. A calculated SCORE ≥ 5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with diabetes duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

CVD, cardiovascular disease; FH, Familial Hypercholesterolaemia; SCORE, Systematic Coronary Risk Evaluation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

do not have established CVD. These include people with high cholesterol levels who are at high risk of a CVD due to their comorbidities. These comorbidities include type 1 and type 2 diabetes, chronic kidney disease, and very high individual risk factors (e.g. high blood pressure). People with a high risk of a cardiovascular event calculated using a risk chart such as the Systematic Coronary Risk Evaluation (SCORE) (www.heartscore.org) also require primary prevention.[3]

Secondary prevention concerns patients with established CVD such as angina, previous heart attack, coronary revascularization, stroke, transient ischaemic attack or symptomatic peripheral arterial disease.

The 2019 European Society of Cardiology/ European Atherosclerosis Society (ESC/ EAS) guidelines for the management of dyslipidaemias, outline four risk categories and the patient groups in each of these categories (Table 2).[3] Each patient's target LDL-cholesterol level is based on their risk category.

Target LDL-cholesterol

The 2019 ESC/EAS guidelines for the management of dyslipidaemias also describe target plasma LDL-cholesterol levels according to patient risk level.[3] These are outlined in Table 3.

Treatment of hyperlipidaemia – lifestyle

Heart healthy diets help to lower plasma cholesterol. Heart healthy diets are high in sources of soluble fibre such as fruit, vegetables, whole grains (especially oats and barley), and legumes. They include limited quantities of nuts, lean meats, low-fat dairy, and liquid vegetable oils. Heart healthy diets are low in saturated fats, trans fats, sodium, added sugars and refined grains.[4] It is recommended to grill, boil or steam food rather than to prepare it by frying or roasting.[3]

Weight loss and regular exercise do not result in significant LDL-C reductions; however, they are associated with decreased triglyceride levels and have an important role in cardiovascular health. Smoking cessation may contribute to a small increase in HDL-cholesterol levels and is associated with improved cardiovascular health. High alcohol consumption can lead to high triglyceride levels.[3]

Pharmacological interventions

Prior to starting cholesterol-lowering therapy, it is recommended to check baseline total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels.[5] Thyroid function should be assessed, and hypothyroidism treated before prescribing cholesterol lowering therapy. Liver function should be assessed, and statin therapy should not be started if liver transaminases are ≥3-times the upper limit of normal.[5]

In patients with a history of unexplained muscle pain, creatine kinase (CK) levels should be checked. If CK levels are abnormal, they should be checked again within 7 days. Where CK remains ≥5-times the upper limit of normal, a statin should not be prescribed.[5]

Lifestyle issues such as healthy eating, smoking cessation, alcohol consumption, weight reduction, and physical activity, should be discussed as appropriate.[5] The Making Every Contact Count brief intervention approach may be useful here.[6]

Statins

Statins are associated with a reduction in LDL-cholesterol level of 30-60%, a reduction in triglyceride level of 20-40%, and an increase in HDL-cholesterol level of approximately 5%. Clinical trials consistently demonstrate the role of statins in reducing cholesterol and in lowering cardiovascular death and ill-health.[2]

Five statins are marketed in Ireland, atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. The LDL-cholesterol lowering effect of rosuvastatin and atorvastatin is greater than that of the other agents. Rosuvastatin and atorvastatin also have a longer half-life than the other agents, meaning that they can be taken at any time of the day. Shorter acting agents should be taken at night.

TABLE 3. Target LDL-cholesterol level according to cardiovascular risk profile (adapted from the 2019 ESC/EAS guidelines for the management of dyslipidaemias).[3]

Patient type	Target LDL-cholesterol level
Very-high-risk	A reduction in LDL-cholesterol of at least 50% from baseline Target LDL-cholesterol <1.4mmol/L Secondary prevention where second vascular event occurs within 2 years and patient is on maximum statin therapy Target LDL-cholesterol <1.0mmol/L
High CVD risk	A reduction in LDL-cholesterol of at least 50% from baseline Target LDL-cholesterol <1.8mmol/L
Moderate-risk	Target LDL-cholesterol <2.6mmol/L
Low-risk	Target LDL-cholesterol <3.0mmol/L

In Ireland, the HSE Medicines Management Programme recommends atorvastatin as the preferred statin for the treatment of hypercholesterolaemia and prevention of CV events. The usual starting dose of atorvastatin is 10mg once daily. The dose may be adjusted at intervals of four weeks or more, in order to achieve target LDL-cholesterol level.[5] In secondary prevention, a high-intensity statin, such as atorvastatin 80mg daily, should be initiated immediately after diagnosis.[1]

Ezetimibe

Ezetimibe reduces the intestinal absorption of dietary and biliary cholesterol, thereby reducing the amount of cholesterol reaching the liver. Ezetimibe is usually used as a second line therapy and is licenced for use alone or in combination with a statin. The usual dose is 10mg daily.

Ezetimibe reduces LDL-cholesterol by up to 22%. Combining ezetimibe and a statin can decrease LDL-cholesterol by a further 15 – 20%.[3] Combination formulations of ezetimibe include Atozet® (with atorvastatin), Inegy® (with simvastatin), and Suvezen® (with rosuvastatin). Adverse effects include moderate elevations of liver enzymes, muscle pain, and abdominal pain.

PCSK9 inhibitors

PCSK9 inhibitors evolocumab (Repatha®) and alirocumab (Praluent®) are monoclonal antibodies and are administered by subcutaneous injection. The PCSK9 inhibitors have demonstrated an LDL-cholesterol lowering effect of up to 60% when used alone and up to 70% when prescribed with a statin. They can lower triglycerides by over 25%.[3] The PCSK9 inhibitors are also associated with a reduction in risk of heart attack and stroke.

Both agents are indicated for use in adults aged ≥18 years[7,8] and Repatha® is indicated in patients aged ≥12 years with homozygous FH. The usual dose of Repatha is 140mg every two week or 420mg once a month.[8] The usual starting dose for alirocumab is 75 mg once every 2 weeks. Patients requiring larger LDL-C reduction may be started on 150 mg once every 2 weeks, or 300 mg once a month.[7]

Both evolocumab and alirocumab can be used in combination with a statin or in combination with a statin and another lipid-lowering drug. They may also be used alone or with non-statin lipid-lowering therapies in patients where a statin is not tolerated or is contraindicated. In Ireland, both Repatha® and Praluent® are reimbursable on the High Tech Medicines scheme.[9]

Inclisiran

Inclisiran (Leqvio®) is a first-in-class small-interfering RNA (siRNA) agent for lipid-lowering. It acts by "silencing" the gene that encodes PCSK9, enabling the liver to increase its uptake of plasma LDL-cholesterol. Inclisiren is associated with a 50% reduction in LDL-cholesterol and is indicated in adults with primary hypercholesterolaemia or mixed dyslipidaemia.[10]

Inclisiran can be prescribed in combination with a statin or can be prescribed with other lipid-lowering therapies in patients who do not reach target LDL-cholesterol level with the maximum tolerated dose of a statin. It can also be prescribed alone or in combination with other lipid-lowering therapies in patients where a statin is not tolerated or is contraindicated. The usual dose of inclisiran is 284 mg administered as a single subcutaneous injection at baseline, again at three months and every six months thereafter. The reimbursement of Leqvio® is currently under review by the National Centre for Pharmacoeconomics (November 2021).[11]

Other agents used in the treatment of dyslipidaemia include bile acid salts such as colestyramine and colesevelam; and fibrates such as gemfibrozil and fenofibrate.

Monitoring

The HSE Medicines Management Programme outlines the key monitoring requirements for patients receiving lipid-lowering therapies.[5] Patients receiving lipid-lowering therapies should be reviewed after three months of treatment and then at least annually.

At review dose response, lifestyle modifications and tolerability of medication should be discussed. If necessary, the choice of cholesterol lowering medication, medication dose and drug-drug interactions should also be discussed.

In patients receiving statin therapy, check liver function three months after initiating treatment and again at 12 months. It is not necessary to check again unless clinically indicated. Patients should be monitored for serious adverse effects of statins such as severe myalgia, myositis or persistently elevated liver enzymes. Medication adherence should be discussed and the possibility of non-adherence considered where target LDL-cholesterol levels are not reached.[3,5]

References available on request