



How to treat hypercholesterolaemia

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Summary

An elevated low density lipoprotein cholesterol is a major cause of atherosclerosis. Reducing the concentration of this lipoprotein stabilises atherosclerotic plaques, and may lead to regression of the atherosclerosis. A moderate reduction of the plasma concentration of this lipoprotein significantly decreases recurrent coronary events. Therapy is a combination of lifestyle modification, nutraceuticals and drug treatment. The most convenient and effective drugs are the HMGCoA reductase inhibitors or 'statins'. They control hyperlipidaemia and help to prevent myocardial infarction, unstable angina, sudden death and stroke.

Key words: antilipidaemic drugs, cholesterol, coronary disease, diet, dietary supplements.

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Introduction

Hypercholesterolaemia is a major risk factor along with smoking, hypertension and diabetes for developing atherosclerosis. Coronary heart disease is almost entirely due to atherosclerosis in the coronary arteries. Atherosclerosis in the carotid arteries also plays a major role in stroke. Rupture of an atheromatous plaque in the coronary arteries is the pathological event underlying the acute coronary syndromes of sudden death, acute myocardial infarction and unstable angina. Plaques that rupture are generally rich in cholesterol and the risk of coronary events is proportional to the serum cholesterol concentration, specifically low density lipoprotein cholesterol.

Lipoproteins

The serum lipids are cholesterol and triglycerides. They are transported in the blood as large molecules known as lipoproteins. In addition to protein (apoproteins), cholesterol, cholesteryl esters and triglycerides, the lipoproteins also carry antioxidants such as vitamin E, dietary polyphenols and co-enzyme Q10. There are five major classes of lipoprotein (Table 1). Intermediate density lipoprotein and low density lipoprotein (LDL) are the most atherogenic, while high density lipoprotein (HDL) is anti-atherogenic.

When triglycerides are elevated, this is usually associated with an elevation of very low density lipoprotein cholesterol (VLDL cholesterol). This lipoprotein has a triglyceride:cholesterol ratio of 2:1. When fasting triglyceride levels are greater than 1.5 mmol/L, the risk of coronary heart disease and stroke increases significantly. Fasting triglyceride levels greater than 1.9 mmol/L, compared to less than 1.5 mmol/L, increase the risk of coronary heart disease and stroke by more than 30%.

When there is an elevated serum cholesterol it is almost always due to an elevation of the LDL cholesterol. Occasionally an elevated cholesterol is due to a high concentration of HDL cholesterol, but these patients are not at increased risk of cardiovascular disease. As LDL cholesterol accounts for 60–70% of the total cholesterol and is atherogenic, it is the target of treatment in patients with hypercholesterolaemia.

Target concentrations

Patients must be assessed for other risk factors, the presence of cardiovascular disease and other causes of raised cholesterol to determine their absolute risk of a coronary event.¹ An appropriate target can then be set for their LDL cholesterol concentration.

A meta-analysis of randomised trials of statins showed that for each 1 mmol/L reduction of LDL cholesterol (which generally equates to a 20% reduction of LDL cholesterol) there is a 20–30% relative risk reduction of coronary heart disease events.² Lowering the LDL a further 30% or so, or an extra 1 mmol/L, reduces coronary heart disease events by a further 20–30%.

The target for an asymptomatic individual who has a low risk of developing coronary heart disease is an LDL cholesterol of

Table 1

Lipoproteins

Chylomicrons	Triglyceride rich	Atherogenic
Very low density lipoprotein		
Intermediate density lipoprotein	Cholesterol rich	Anti-atherogenic
Low density lipoprotein		
High density lipoprotein		

Intermediate and low density lipoprotein contain the highest proportion of cholesterol while chylomicrons contain little cholesterol.

less than 4 mmol/L with triglycerides less than 2 mmol/L, HDL greater than 1 mmol/L and a total cholesterol less than 5.5 mmol/L. For a patient who has already developed coronary heart disease there is the lower target of an LDL cholesterol less than 2.5 mmol/L. Patients with established coronary heart disease and a very high risk of a future cardiovascular event should have a target of less than 2 mmol/L. These targets broadly reflect recommendations by the Australian National Heart Foundation³ and the American Heart Association guidelines.⁴ Reducing LDL cholesterol to below appropriate targets is more important than the method or specific drug used to achieve the reduction.⁵

Diet

Lifestyle factors, particularly a diet rich in saturated fats and low in fibre, play a significant role in the elevation of LDL cholesterol. A key element of the first dietary guidelines to prevent coronary heart disease was to lower foods rich in saturated fat. Subsequent international guidelines have continued to focus on lowering foods rich in saturated fat. Replacing saturated fat with either carbohydrate or foods rich in mono- or polyunsaturated fats and high fibre foods is effective in lowering LDL cholesterol. All of these independently lower LDL cholesterol. Avoid baked foods containing trans fatty acids, such as pies, pastries, cakes and biscuits. An individual patient's response to diet can vary considerably and is usually seen in 4–6 weeks. Some patients are very responsive and can have up to 30% lowering of LDL cholesterol.

Traditional cuisines which are associated with low LDL cholesterol and low rates of heart disease are Mediterranean-type diets, as found in Greece, Italy and Spain, and cuisine low in total fat such as in Japan. It is also clear that a high intake of fish, particularly fish rich in marine omega-3 fatty acids, is associated with a low risk of heart attack and stroke.

After a myocardial infarction, a Mediterranean-type diet compared to a usual low fat diet is associated with a 50% relative reduction in mortality. This is independent of any change in serum cholesterol (see box).⁶

Weight loss

Weight loss can favourably influence lipids irrespective of how it is achieved. For every kilogram decrease in body weight, LDL cholesterol decreases by 0.02 mmol/L, triglycerides decrease by 0.015 mmol/L and HDL cholesterol increases by 0.14 mmol/L.⁷ Unfortunately, significant weight loss is difficult to achieve and maintain, but losing 5–10 kg is achievable and can make a difference to the risk profile.

Exercise

Most exercise studies have indicated that regular aerobic exercise improves the lipid profile independent of diet and drugs. Regular exercise decreases LDL cholesterol by 10% and

increases HDL cholesterol by 5%.⁸ There is a dose response between the amount of exercise and lipoprotein changes. Moderate aerobic exercise is defined usually as moderate effort of half an hour of intentional exercise most days of the week.

Nutraceuticals

The nutraceuticals that can help to lower LDL cholesterol are plant sterols/stanols and soluble fibre. In Australia, the foods which can be enriched with plant sterols are margarine, milk and yoghurt. A dose of 2–4 g of plant sterols is needed, which equates to at least four teaspoons of plant-enriched margarine per day. A 200 g tub of enriched yoghurt only provides the equivalent of one teaspoon so is not that helpful for achieving targets.

On average plant sterols reduce LDL cholesterol by 10%, but this may vary from 0 to 30%. They have an additive effect to drug therapy.

A tablespoon or two of soluble fibre, such as psyllium, lowers LDL cholesterol by approximately 5%. Garlic and policosanol have been found to have negligible effects in most recent studies. Omega-3 fatty acids from fish oil are effective in lowering triglycerides, but have no effect in lowering LDL cholesterol at usual therapeutic doses. Very high doses of fish oil may in fact increase LDL cholesterol.

Drug therapy

If diet and nutraceuticals do not adequately reduce the LDL cholesterol and the patient remains at high risk of a cardiovascular event, drug therapy is indicated. HMGCoA reductase inhibitors, 'statins', are the first drugs to use. They are extremely efficacious and more than 90% of patients can tolerate them with negligible or no adverse effects. All statins have non-lipid lowering properties such as antiplatelet effects. However, most, if not all, the cardiovascular benefit can be accounted for by the improved lipoprotein profile, mainly by lowering LDL cholesterol.

Mediterranean diet after myocardial infarction⁶

The healthy Mediterranean-type diet initially referred to the food traditionally eaten by the people of Naples. It was vegetarian-like, high in nuts and olive oil, vegetables and pasta which was cooked *al dente*. Fruit was eaten frequently along with some cheese, wine and nuts. The Mediterranean diet later extended to include the traditional diets of Crete and Spain.

The Lyon Diet Heart Study involved just over 600 individuals who had survived a myocardial infarction. After 3.5 years the trial was stopped early as there was a clear benefit for patients on the Mediterranean-type diet compared to a low fat diet. The benefit was independent of drug therapy and serum cholesterol.

Efficacy of statins

Statins differ in efficacy, with the earlier statins lowering LDL to a similar extent to bile resins such as cholestyramine and nicotinic acid. The newer statins, atorvastatin and rosuvastatin, are considerably more efficacious in lowering LDL cholesterol, but there is little evidence as yet that this further improves long-term clinical outcomes. High dose simvastatin and controlled-release fluvastatin are of intermediate efficacy. The highest doses of the most efficacious statins can achieve a 2 mmol/L reduction (which is up to a 60% lowering of LDL from baseline). A number of recent trials have compared moderate to vigorous LDL lowering, and there is the expected predictable greater benefit of cardiovascular disease prevention.

Most of the effect of the statins occurs at less than the maximum dose. If the patient's target cholesterol is not reached, adding another drug may therefore have more effect than increasing the statin dose.

Adverse effects of statins

If adverse effects occur, more than 90% appear within the first three months. Adverse effects tend to be dose related and are similar between statins. If a patient has adverse effects from one statin, the dose can be lowered, given in divided doses or every second day. Alternatively, the patient can be switched to another statin or a controlled-release formulation.

The common adverse effects are musculoskeletal aches. Occasionally there is an associated increase in creatine kinase and rarely (less than 1/1000) a true myositis can occur. There is increased risk of myositis in those with renal failure, diabetes and in the elderly. If the creatine kinase is greater than 300 IU/mL, consider stopping the statin and repeat the test one week later.

A rise in the liver transaminases can occur so liver function tests are recommended before and during treatment. True hepatitis is extremely rare. Measure liver function every six months and if the transaminases are greater than twice the upper limit, stop the statin and repeat the liver function test in 3–4 weeks. Depending on the results, restart at the same dose, for example, if the patient's transaminase levels were only just above the cut-off point and then normalised after stopping the statin. Otherwise, restart the patient on half the dose and retest their liver function in 3–4 weeks. Many patients have a mild transient elevation of liver enzymes which is of no consequence. Persistent elevation of liver enzymes that are in the moderate range (up to 2–3 times above the upper limit of normal) may relate to the presence of fatty liver disease rather than drug therapy.

Long-term follow-up of patients in trials has not shown an increase in the risk of cancer from long-term exposure to statins.

Other drugs

In approximately 75% of the patients who cannot tolerate even half the usual dose of statins, ezetimibe can be effective.

Ezetimibe inhibits the absorption of dietary cholesterol. The dose of ezetimibe is 10 mg per day and there is no value in going higher. Ezetimibe lowers LDL by approximately 15%. Some individuals develop aches and pains on the usual dose of ezetimibe (10 mg/day). Reducing the dose to 10 mg once per week still produces some lowering of LDL cholesterol but without the adverse effects. Ezetimibe can further reduce LDL cholesterol in patients on maximum doses of statins. Adding ezetimibe 10 mg per day can often lead to a synergistic lowering of LDL cholesterol by an extra 20–25%. Patients who are very sensitive to statin adverse effects can be stabilised on ezetimibe, then given a mini dose of a statin, such as rosuvastatin 2.5 mg every second or third day, with significant benefit. However, there is no current evidence that ezetimibe reduces the risk of heart attack or stroke, either alone or in combination with statins.

After statins and ezetimibe, other drugs to consider are bile resins (for example cholestyramine), fenofibrate and nicotinic acid (niacin, vitamin B₃). More than 50% of patients cannot tolerate more than 4 g of cholestyramine per day, and it is best mixed with juice. One sachet per day is expected to lower the LDL cholesterol by around 10% and it has an additive effect with statin therapy. Fenofibrate 145 g per day lowers LDL cholesterol by around 10%, but its major role is to lower triglycerides. Nicotinic acid at a dose of 3 g per day lowers LDL cholesterol by about 20%, but more than 75% of patients cannot tolerate even half this dose due to severe flushing. Gemfibrozil has no effect on lowering LDL cholesterol.

Treatment of hypertriglyceridaemia

First-line treatment for elevated triglycerides (VLDL cholesterol) consists of a diet rich in mono- and polyunsaturated fat and low glycaemic index carbohydrate food, caloric restriction (leading to weight reduction) and exercise. The next step is consideration of marine omega-3 fatty acids (fish oil) and fibrates.

Conclusion

Elevated LDL cholesterol is a major risk factor for coronary heart disease and is the major target of therapy to prevent coronary events. In patients with clinical coronary heart disease, lowering the LDL cholesterol to less than 2.5 mmol/L lowers the relative risk of developing coronary events by approximately 25%, and lowering it to below 2 mmol/L reduces the relative risk by 50%. Therapy involves diet, regular exercise, nutraceuticals and drug treatment along with attention to other risk factors. Statins are the first choice of drug therapy.

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Further reading

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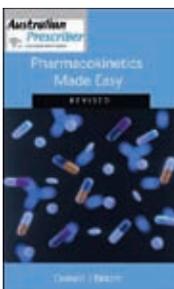
Associate Professor Colquhoun has received honoraria for talks for Merck Sharp & Dohme, Pfizer, AstraZeneca, Solvay and Bristol-Myers Squibb.

Self-test questions

The following statements are either true or false (answers on page 139)

- Most of the effect of a statin on low density lipoprotein cholesterol occurs below the maximum recommended dose.
- Fish oil can significantly reduce concentrations of low density lipoprotein cholesterol.

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