CLINICAL REVIEW

Hypercholesterolaemia and its management

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SOURCES AND SELECTION CRITERIA

We selected references if they included a recent meta-analysis or provided a useful, objective, and comprehensive account including extensive recent references. We chose them from a search of PubMed, personal reference lists, and three textbooks[26-28]

Hypercholesterolaemia is one of the major causes of atherosclerosis. Although there are many causes, hypercholesterolaemia is the permissive factor that allows other risk factors to operate.[1] The incidence of coronary heart disease is usually low where population plasma cholesterol concentrations are low.[2] In Britain coronary heart disease is a major cause of mortality, and a recent Department of Health survey suggested that the average plasma cholesterol concentration in the United Kingdom was 5.9 mmol/l, much higher than the 4 mmol/l seen in rural China and Japan, where heart disease is uncommon.[3] Many studies before and after the introduction of statins have indicated that reducing the prevalence of hypercholesterolaemia is an important means of decreasing coronary risk.

What is hypercholesterolaemia?

Cholesterol plays an important role as the precursor for steroid hormones and bile acids and it is essential for the structural integrity of cell membranes. It is transported in the body in lipoproteins. Figure 1 shows the role of cholesterol in lipoprotein metabolism.

Conventionally the upper limit for laboratory reference ranges is based on the 95th or 90th centile for a healthy population. This does not apply to plasma cholesterol, however, as several studies show that the epidemiological relation between plasma cholesterol and risk of coronary heart disease extends to the lower end of the cholesterol distribution. Although the relation becomes progressively steeper, there is no obvious threshold below which it ceases to exist.[5] Therefore, it is more rational to base a desirable or healthy concentration of plasma cholesterol on the value at which coronary risk is considered unacceptably high. Most patients developing coronary heart disease have plasma cholesterol concentrations that are likely to be between the 30th and 90th centile for their population of origin.[6] A population is considered to be unhealthy when its average plasma cholesterol concentration exceeds 5 mmol/l (equivalent to low density lipoprotein (LDL) cholesterol of 3 mmol/l).[7]

The Joint British Societies (JBS2) guidelines on prevention of cardiovascular disease recommend that the optimal levels of plasma cholesterol should be ≤4 mmol/l (LDL cholesterol ≤2 mmol/l) in patients with pre-existing atherosclerotic disease or diabetes or in those who have a combination of other risk factors that produce a risk of cardiovascular disease (coronary heart disease and stroke) of 20% or more over the next 10 years.[8] These risk factors include male sex, increased age, cigarette smoking, high blood pressure, impaired fasting glucose concentration, low concentrations of high density lipoprotein (HDL) cholesterol, raised triglycerides, Indian subcontinent ancestry, and low socioeconomic class.

Who gets hyperlipidaemia?

Hypercholesterolaemia usually results from nutritional factors such as obesity and a diet high in saturated fats combined with an underlying polygenic predisposition. There is overproduction of LDL,[9] and

Box 1 Causes of hyperlipidaemia

Some causes of secondary hyperlipidaemia
- Nephrotic syndrome
- Obstructive jaundice
- Hypothyroidism
- Cushing's syndrome
- Anorexia nervosa
- Thiazide diuretics
- Ciclosporin

Some causes of mixed hyperlipidaemia*
- Type 2 diabetes mellitus
- Obesity, particularly if accompanied by features of the metabolic syndrome
- Alcohol excess
- Monoclonal gammopathy
- Renal dialysis
- Glucocorticoids
- β blockers
- Retinoic acid derivatives

*Increase in plasma cholesterol and triglycerides

its genetic component is unlikely to be monogenic, unless it is extreme. Hypercholesterolaemia can also have an entirely genetic cause. A common example of this is monogenic familial hypercholesterolaemia, an autosomal dominant disorder in which the LDL cholesterol is raised from birth (table 1).[10] It is characterised by a dominant pattern of inheritance of premature coronary disease and/or tendon xanthomata.[11]

Raised plasma triglyceride concentration in association with hypercholesterolaemia is common (table 2) and poses an additional risk of coronary heart disease.[12] Usually such patients have an increase in both low density lipoprotein (VLDL) cholesterol and LDL cholesterol and a decrease in HDL cholesterol. This condition is called combined hyperlipidaemia or, if there is a strong familial tendency, familial combined hyperlipidaemia. Usually the disorder is polygenic with a strong overlap with glucose intolerance, diabetes, and the metabolic syndrome and may precede the onset of diabetes.[13]

Occasionally patients with hypercholesterolaemia have a plasma triglyceride concentration of >10 mmol/l owing to an increase in both chylomicrons and VLDL. The plasma has a milky appearance and eruptive xanthomata, and other features such as acute pancreatitis may occur. Such patients should be referred to lipid clinics for treatment.

Box 2 Calculating LDL cholesterol and non-HDL cholesterol concentrations*

- Low density lipoprotein cholesterol = total serum cholesterol − (HDL cholesterol + (serum triglycerides/2.2))
- Non-HDL cholesterol = total cholesterol − HDL cholesterol

*All values in mmol/l

Remnant removal disease (type III hyperlipoproteinaemia) leads to combined hyperlipidaemia.[14] Although rare, it carries a high risk of both coronary heart disease and peripheral vascular disease early in life. Typically striate palmar and tuberoeruptive xanthomata occur.[15] Chylomicron remnants accumulate in the circulation owing to homozygosity for the apo E2 isoform of apolipoprotein E, the ligand important for their hepatic clearance. It has variable penetrance, suggesting that some other cause such as obesity or insulin resistance is necessary for its expression.

Table 2 and box 1 outline the diagnostic classification of hypercholesterolaemia. Before primary hypercholesterolaemia is diagnosed underlying secondary causes should be excluded.

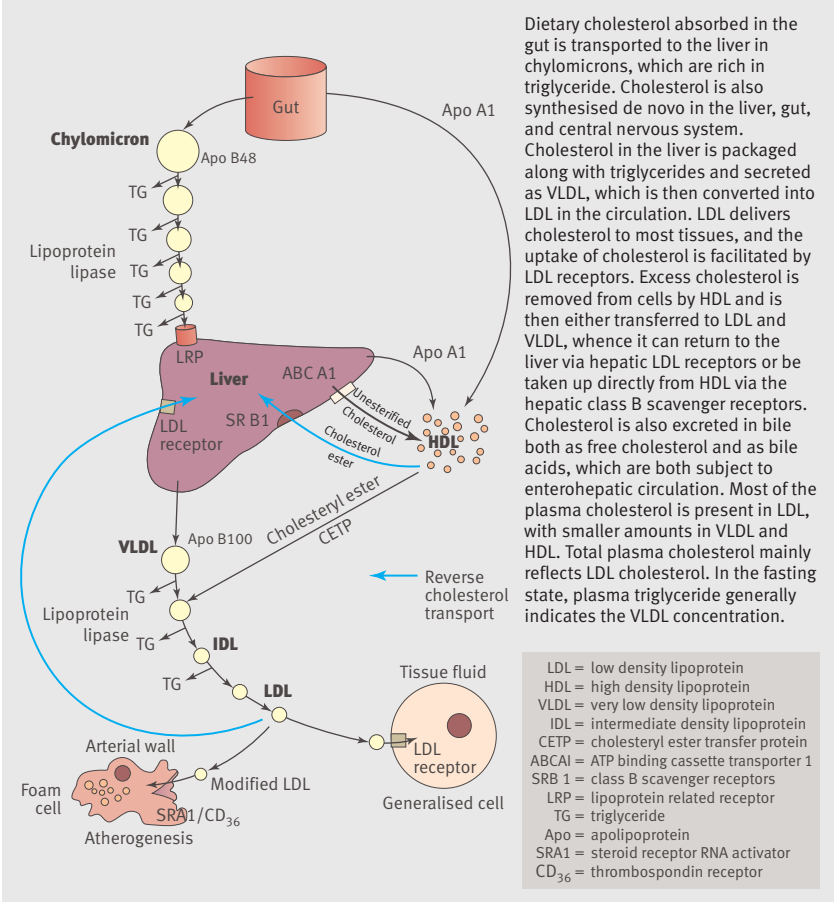

Fig 1 | The role of cholesterol in the metabolism of lipoprotein. Adapted from Charlton-Menys[4]

How to investigate the patient with hypercholesterolaemia

Before treatment is started for hypercholesterolaemia a detailed history, clinical examination, and baseline laboratory tests are needed to discover causes of secondary hypercholesterolaemia, manifestations of primary lipoprotein disorders, and any complications related to atherosclerosis. A family and occupational history—including a history of smoking, alcohol intake, and dietary preferences—will help to indicate the extent to which these factors contribute to hypercholesterolaemia and/or to risk of cardiovascular disease and to gauge the patient's ability to change lifestyle. The physical examination should include blood pressure, body weight, height, waist circumference, and a search for xanthomata. A family history is essential to facilitate cascade testing in primary hypercholesterolaemia.[16]

Laboratory assessment in hypercholesterolaemia

When screening for hypercholesterolaemia it is advisable to take blood samples after a fast of at least 10 hours to avoid the postprandial contribution to plasma triglycerides. If plasma triglycerides do not exceed 4.5 mmol/l, the LDL cholesterol concentration can be calculated by the Friedewald formula (box 2). If low density lipoprotein cholesterol cannot be measured owing to hypertriglyceridaemia, then non-HDL cholesterol can be used as a target for statin treatment. Biological and laboratory variations in plasma cholesterol concentrations mean that tests should be done

Box 3 Starting statin treatment without formal estimation of cardiovascular risk

Statin treatment should be considered in the following people without formal estimation of cardiovascular risk[8 17]:

- Those with atherosclerotic cardiovascular disease including coronary heart disease, stroke, transient cerebral ischaemia, peripheral arterial disease
- Those with type 1 and type 2 diabetes mellitus who are aged ≥40 years (or younger if additional cardiovascular risk factors are present)
- Those with renal dysfunction including diabetic nephropathy
- Those with familial hypercholesterolaemia, familial combined hyperlipidaemia, or other genetic dyslipidaemias
- Ratio of total cholesterol:HDL cholesterol ≥6.0

more than once before treatment is started. Laboratory reports should also provide HDL cholesterol values and the total cholesterol:HDL ratio to help assess risk of cardiovascular disease, but LDL cholesterol should be used as the target for treatment where possible. The targets for non-HDL cholesterol are 0.75 mmol/l higher than for LDL cholesterol.

In assessing risk of cardiovascular disease it is also essential to measure fasting glucose concentration. Before lipid lowering treatment is started, liver function tests, creatine kinase activity, serum creatinine, and dipstick urine protein should be measured. In some patients specialised assays may be needed to identify the cause of hypercholesterolaemia.

When should treatment for hypercholesterolaemia be introduced?

The introduction of cholesterol lowering drugs should always be based on an assessment of risk of cardiovascular disease. In patients without diabetes, the pre-existing risk can be estimated using the JBS2 charts[8] or the JBS2 cardiovascular risk assessor computer program (www.heartuk.org.uk/new/pages/prof/jbs_cv_riskassessor.html) (figure 2).

Cholesterol lowering drugs are intended for use in people between the age of 40 and 70 years. The assessment tables are likely to underestimate risk in people with adverse family history, impaired fasting glucose, or impaired glucose tolerance; people from the Indian subcontinent; people with hypertriglyceridaemia or renal dysfunction; and in the presence of multiple comorbidities. The computer program makes adjustments for these. The footnote to the tables recommends multiplying the cardiovascular risk by 1.3-1.5 when one or more of these factors are present. In certain groups of patients—for example, those with inherited dyslipidaemia—treatment through diet and with appropriate drugs should be started without calculating cardiovascular risk (box 3).[8 17] The charts and computer program are designed to assist clinical judgment not to replace it. They should be used along with the clinical approach described above.

Table 1 | Diagnostic criteria for heterozygous familial hypercholesterolaemia, taken from the Simon Broome familial hypercholesterolemia register (www.primarycare.ox.ac.uk/research/vascular/research/simon_broome)

Criterion	Description
A	Total cholesterol concentration >7.5 mmol/l (adults) or >6.7 mmol/l (children aged <16 years); *or* low density lipoprotein cholesterol concentration >4.9 mmol/l in adults or >4.0 mmol/l in children
B	Tendinous xanthomata in the patient or a first degree relative
C	DNA based evidence of an LDLR mutation, familial defective apo B100, or a PCSK9 mutation
D	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative
E	Family history of raised total cholesterol concentration >7.5 mmol/l in a first or second degree relative

A + B or A + C, constitutes a definite diagnosis of heterozygous familial hypercholesterolaemia.
A + D or A + E constitutes possible heterozygous familial hypercholesterolaemia.

What are the targets for cholesterol lowering?

The targets to which plasma cholesterol should be lowered have changed over the years, but the near linear relation between the log of the risk and cholesterol reduction described by the Cholesterol Trialists Collaboration[18] forms part of the evidence for setting targets. The JBS2 guidelines[8] advocate an optimal total cholesterol target of <4.0 mmol/l (or a 25% reduction) or an LDL cholesterol concentration of <2.0 mmol/l (or a 30% reduction) for both primary and secondary prevention and for people with diabetes mellitus.

The 2008 guidelines from the National Institute for Health and Clinical Excellence (NICE) on lipid modification[19] agree with the JBS2 guidelines on secondary prevention targets but do not advise any targets for primary prevention. They recommend that when the decision to prescribe a statin for primary prevention has been made patients should be given 40 mg of simvastatin without further monitoring of serum lipids, unless clinical judgment or patient preference indicate a review of drug treatment or lipid profile. The JBS2 and NICE guidelines both advise an "audit" concentration of total cholesterol of 5 mmol/l or an LDL cholesterol concentration of <3 mmol/l as the minimum standard of care for high risk individuals.

Clinicians should be aware that cholesterol lowering treatment can reduce the cholesterol content of an atheromatous plaque, which may be too small for angioplasty or bypass surgery but which can rupture, enabling clot formation, arterial occlusion, and the acute clinical syndromes associated with atherosclerosis.[20]

What treatments are available to lower plasma cholesterol?

The strength of the evidence that cardiovascular risk can be decreased by treatment with statins[18] means that the most appropriate approach to treating people at the highest risk combines lifestyle advice with use of statins.

Lifestyle measures

Lifestyle measures such as stopping smoking, decreasing excess alcohol consumption, increasing physical activity, losing weight, and following a low fat saturated

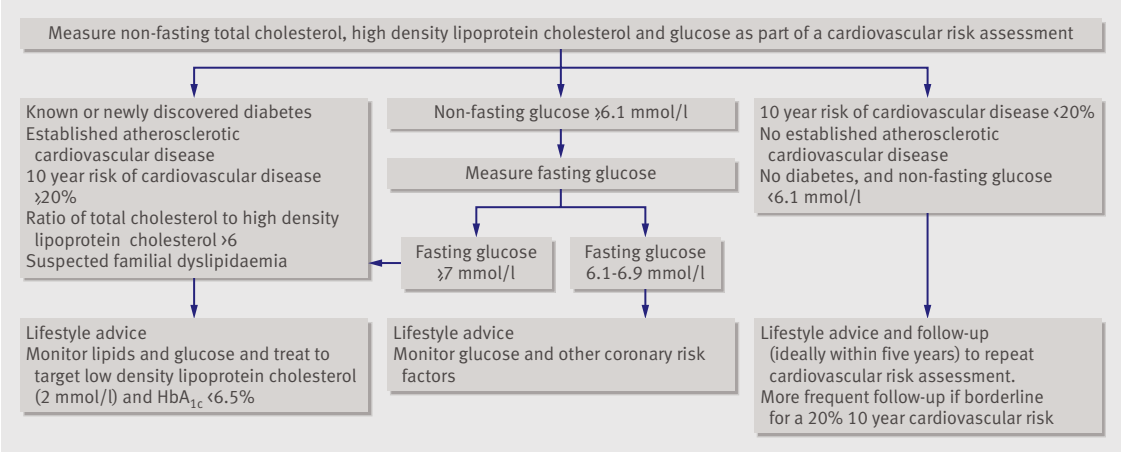

Fig 2 | **Summary of the Joint British Societies' guidelines on preventing cardiovascular disease in clinical practice[8]**

diet will all decrease the risk of cardiovascular disease. However, dietary advice given by health professionals often produces inadequate lowering of cholesterol, typically by about 3%, although reductions of 10% or more have been seen in studies carried out in controlled conditions on a metabolic ward.[21]

Plant sterols

A recent systematic review suggests that margarines and drinks containing plant sterols or stanols rather than saturated fat can decrease plasma cholesterol by up to 10%.[22]

Statins

Several large trials of primary and secondary prevention of coronary heart disease using statins have established their efficacy. A meta-analysis of 14 statin trials using data from 90 056 participants showed that for each 1 mmol/l lowering of plasma LDL cholesterol coronary and stroke events fell by about 21% and this was accompanied by a decrease in all cause mortality.[18]

This linear decrease extends down to current LDL cholesterol targets of 2 mmol/l. Patients in clinical trials whose pretreatment LDL cholesterol concentrations were <3 mmol/l showed the same reduction in relative risk of cardiovascular disease with statin treatment as those with higher LDL cholesterol concentrations.[18]

Statins are generally well tolerated and efficacious. However, efficacy varies: at a maximum dose of 40 mg, pravastatin reduces LDL cholesterol by 29%, and at a maximum dose of 80 mg, simvastatin, atorvastatin, and rosuvastatin reduce LDL cholesterol by 42%, 55%, and 58% respectively.[23] Each doubling of dose with a statin results in a further 5-6% reduction in LDL cholesterol.

Table 2 | **Most commonly encountered causes of primary hypercholesterolaemia**

Diagnosis	Prevalence (%)	Inheritance	Clinical features	Biochemistry
Common hypercholesterolaemia*	70	Polygenic	Usually none (sometimes corneal arcus, xanthelasmata)	Raised cholesterol owing to low density lipoprotein
Heterozygous familial hypercholesterolaemia	0.2	Monogenic	Cholesterol raised from childhood. In adulthood often tendon xanthomata or Achilles tenosynovitis; sometimes corneal arcus and xanthelasmata	Raised cholesterol owing to low density lipoprotein
Familial defective apoplipoprotein B	0.2	Monogenic	Usually none. Occasionally familial hypercholesterolaemia phenotype	Raised cholesterol owing to low density lipoprotein
Combined hyperlipidaemia†	10	Polygenic	Usually none (sometimes corneal arcus, xanthelasmata); overlap with dyslipidaemia of type 2 diabetes and metabolic syndrome	Raised triglycerides and cholesterol owing increased very low density lipoprotein
Type III hyperlipoproteinaemia (dysbetalipoproteinaemia; remnant removal disease)	0.02	Monogenic	Striate palmar xanthomata; tuberoeruptive xanthomata	Raised triglycerides and cholesterol owing to intermediate density lipoprotein and chylomicron remnants. Usually apo E2 homozygosity
Severe hypertriglyceridaemia (>10 mmol/l)	0.1	Polygenic or monogenic	Eruptive xanthomata; acute pancreatitis; milky plasma; lipaemia retinalis	Raised triglycerides owing to fasting chylomicronaemia and increased very low density lipoprotein

Prevalence is approximate and refers to the adult population in the UK (Durrington, see "Additional education resources" box).
*Defined as plasma cholesterol ≥5 mmol/l in middle age.
†Defined as plasma cholesterol ≥5 mmol/l and fasting plasma triglycerides ≥1.7 mmol/l in the absence of diagnostic features of heterozygous familial hypercholesterolaemia (table 1).

ADDITIONAL EDUCATIONAL RESOURCES FOR PATIENTS

- HEART UK, 7 North Road, Maidenhead SL6 1PE (www.heartuk.org.uk; helpline, tel: 0845 450 5988)—Raises awareness about the risks of high cholesterol and about better detection of those at risk; provides information and advice on preventing premature deaths, particularly in those with inherited high cholesterol
- British Heart Foundation, 14 Fitzhardinge Street, London W1H 6DH (www.bhf.org.uk; heart information line, tel: 08450 70 80 70)—Supports heart patients, invests in research, and provides information to help people reduce their risk of dying prematurely from a heart or circulatory related illness
- British Nutrition Foundation (www.nutrition.org.uk)—Provides impartial interpretation and effective dissemination of scientifically based knowledge and advice on the relation between diet, physical activity, and health
- *Cholesterol*—Information leaflet about cholesterol published by the NHS for patients (http://cks.library.nhs.uk/patient_information_leaflet/cholesterol)
- *Cholesterol*— Information leaflet about cholesterol published by Patient UK for patients (www.patient.co.uk/showdoc/23068704/)

About 1-3% of patients complain of side effects such as tiredness, indigestion, or change in bowel habit. Some patients develop increases in liver transaminase or creatine kinase activity. Tests for liver function should be done before and about three months after statins are started. If serum transaminase activity increases to three times the upper limit of normal then treatment should be stopped.

However, a substantial number of patients with dyslipidaemia already have abnormal serum liver function tests owing to non-alcoholic steatohepatitis, with increases in alanine aminotransferase and γ glutamyl transpeptidase being particularly common in patients with hypertriglyceridaemia. This is not a reason to withhold statin treatment. Fluctuations in alanine aminotransferase may create the impression that it has risen as a result of statin treatment. But hepatotoxicity induced by statins is rare, and in patients at high risk of cardiovascular disease statins should not be discontinued because of abnormal liver function tests without firm proof of causality.[24]

Myositis induced by statins is also uncommon,[24] and minor fluctuation in creatine kinase activity and in muscle discomfort should not lead to discontinuation of statins. People who are physically active or are of African origin can have creatine kinase levels as high as 1000 U/l regardless of statin treatment. Untreated hypothyroidism and certain drugs when used with statins can increase the possibility of myositis.[25] Nevertheless, when patients complain of tiredness or muscle pain then liver function tests and measuring creatine kinase activity should be part of the routine investigations. If patients are convinced that the symptoms are linked to statin use, then it is worth trying another statin.

Other pharmacological agents

For patients who are unable to tolerate statins, bile acid sequestrants or alternatives such as nicotinic acid can be used, but these are more likely than statins to cause side effects. Fibrates increase HDL cholesterol and lower plasma triglycerides but have marginal effect in lowering LDL cholesterol. Moreover, several large trials of fibrates have shown that although non-fatal cardiovascular events are decreased, total mortality increases.

TIPS FOR NON-SPECIALISTS

- A desirable or healthy plasma cholesterol concentration is based on the value associated with a coronary risk that is unacceptably high
- Both the JBS 2 guidelines and the NICE guidelines advocate assessment of coronary risk based on the Framingham equation (www.framinghamheartstudy.org/risk/index.html)
- A clinical approach to hypercholesterolaemia will often identify genetic hyperlipidaemias, which are associated with premature coronary heart disease
- Patients with the following conditions should be referred to a specialist lipid clinic:
  - -Suspected genetic hyperlipidaemias
  - -Abnormal pretreatment liver enzymes or creatine kinase activity
  - -Intolerance to or side effects from lipid lowering treatment
  - -Mixed hyperlipidaemia
  - -Resistance to statin treatment
  - -Patients taking complex combinations of drugs with high risk of serious drug interaction with lipid modification treatment
  - -Secondary hyperlipidaemia
  - -Dyslipidaemia related to HIV
  - -Lipodystrophy syndromes
  - -Post-transplant hyperlipidaemia
- The introduction of cholesterol lowering drugs should always be based on assessment of cardiovascular risk

ADDITIONAL EDUCATIONAL RESOURCES FOR HEALTHCARE PROFESSIONALS

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SUMMARY POINTS

The relation between plasma cholesterol concentration and coronary heart disease is curvilinear and without threshold

Hypercholesterolaemia is a leading cause of atherosclerosis

Hypercholesterolaemia can result from eating a diet high in saturated fat, primary disorders of lipid metabolism, and conditions that lead to hypercholesterolaemia

The Joint British Societies (JBS2) charts and guidelines can be used to assess coronary risk, but they may underestimate risk in certain comorbid conditions. Therefore a clinical approach to estimate overall risk is important

Statins represent a relatively safe way to lower cholesterol

Abnormal liver function tests can occur in dyslipidaemia, and statins should not be stopped, especially in high risk patients, without good cause

Combination treatments

In patients who do not achieve target cholesterol levels when they are taking statins, combination treatment can be used. It is usual to combine a statin with ezetimibe, which will lower LDL cholesterol by a further 15%. Nicotinic acid, fibrates, and the fish oil preparation Omacor (Solvay), which have the advantage of lowering plasma triglycerides too, can also be used in combination with statins to lower LDL cholesterol. Currently large randomised controlled trials are looking at whether statins and fibrates combined are more beneficial than statins alone.

Combination treatments are associated with more side effects and must be used with caution. Gemfibrozil, in particular, interferes with the conjugation of statins, increasing the chances of myositis, and it should not be combined with statins. Combinations of statins with fibrates or nicotinic acid should not be used in secondary hyperlipidaemia, elderly people, or those being treated long term with ciclosporin, tacrolimus, macrolide antibiotics, or antifungals. Lipid lowering drugs should be stopped at least three months before a woman plans to conceive because of potential teratogenicity.

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Provenance and peer review: Commissioned; externally peer reviewed.

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