

Lipid-modifying drugs

Key therapeutic topic

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Key points

- The NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#) makes recommendations on the care and treatment of people at risk of cardiovascular disease (CVD) and people who have had previous CVD. This includes people with chronic kidney disease (CKD), type 1 diabetes and type 2 diabetes.
- When a decision is made to prescribe a statin for primary or secondary prevention of CVD, the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification, recommends using a statin of high intensity and low acquisition cost. The NICE guideline on [familial hypercholesterolaemia](#) gives recommendations for people with this condition.
- People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the NICE technology appraisal guidance on [ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia](#).
- People with primary hypercholesterolaemia or mixed dyslipidaemia should be considered for treatment with the PCSK9 inhibitors alirocumab or evolocumab in line with the NICE technology appraisal guidance on [alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia](#) and [evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia](#).
- The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification, recommends that bile acid sequestrants, nicotinic acid, fibrates and omega-3 fatty acid compounds should not generally be offered (see the guideline for details). It may be

- appropriate to use bile acid sequestrants or fibrates to treat familial hypercholesterolaemia in some circumstances (see the NICE guideline on familial hypercholesterolaemia).
- **Options for local implementation:**
 - Review and, if appropriate, optimise prescribing of lipid-modifying drugs including statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, omega-3 fatty acid compounds and PCSK9 inhibitors to ensure it is in line with NICE guidance.
 - Ensure that decisions relating to prescribing lipid-modifying drugs, especially statins for primary prevention, incorporate principles of [shared decision making](#).

Evidence context

The NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#) (2014) makes recommendations on the care and treatment of people at risk of cardiovascular disease (CVD) and people who have had previous CVD. This includes people with chronic kidney disease (CKD), type 1 diabetes and type 2 diabetes. An update to this guideline is currently being planned. There is a separate NICE guideline on the [identification and management of familial hypercholesterolaemia](#).

The NICE technology appraisal guidance on [ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia](#) was reviewed and updated in February 2016. NICE technology appraisal guidance was published in June 2016 on [alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia](#) and [evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia](#).

NICE has also published a quality standard on [cardiovascular risk assessment and lipid modification](#), which contains a concise set of prioritised statements designed to drive measurable quality improvements within these areas.

Statins

The NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#) recommends that the decision whether to start statin therapy should be made after an informed discussion between the clinician and the person. This discussion should include the risks and benefits of statin treatment, taking into account potential benefits from lifestyle modifications, the person's preferences and factors such as comorbidities, polypharmacy, general frailty and life expectancy. NICE has produced a [patient decision aid](#) to support these discussions in line with the issues highlighted in the medicines optimisation: key therapeutic topic on [shared](#)

decision making.

The NICE guideline on [multimorbidity](#) is helpful when considering stopping statin therapy. This guideline recommends taking into account the possibility of lower overall benefit of continuing treatments that aim to offer prognostic benefit, particularly in people with limited life expectancy or frailty, and discussing whether they wish to continue treatments that may offer them limited overall benefit. An American randomised controlled trial found that discontinuing statin therapy in people with advanced, life-limiting illness may not adversely affect clinical outcomes and may improve some important patient-orientated outcomes, such as quality of life and reducing overall medication burden. This study was discussed in a NICE medicines evidence commentary on [medicines optimisation: discontinuing statin therapy in palliative care](#).

In the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol (LDL-cholesterol; see [appendix A](#) of the guideline for more information). When a decision is made to prescribe a statin, the guideline recommends using a statin of high intensity (more than 40% LDL-cholesterol reduction) and low acquisition cost.

The guideline recommends offering atorvastatin 20 mg daily for primary prevention. Secondary prevention should usually start with atorvastatin 80 mg daily. However, in people with CKD, the initial dose should be 20 mg daily, and in other people, a dose lower than 80 mg daily should be used if there are potential drug interactions with existing therapy, a high risk of adverse effects or the person prefers a lower dose.

NICE recommends measuring total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) and non-HDL-cholesterol in all people who have been started on high-intensity statin treatment as above after 3 months of treatment, aiming for a greater than 40% reduction in non-HDL-cholesterol. If this reduction is not achieved, NICE recommends:

- discussing adherence and the timing of the dose
- optimising adherence to diet and lifestyle measures
- **considering** increasing the dose if the person started on less than atorvastatin 80 mg daily and they are judged to be at higher risk because of comorbidities, risk score or using clinical judgement (see the guideline for dose recommendations in people with CKD).

Many people will currently be taking a low-intensity or medium-intensity statin (such as simvastatin 40 mg daily). NICE recommends that healthcare professionals should discuss the likely

benefits and potential risks of changing to a high-intensity statin with such people when they have a medication review, and agree with the person whether a change is needed.

The NICE guideline on the [identification and management of familial hypercholesterolaemia](#) recommends statins as the initial treatment. In adults, the dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-cholesterol concentration of greater than 50% from baseline (that is, LDL-cholesterol concentration before treatment). See the guideline for recommendations on treating the condition in children and young people.

Rosuvastatin and high-dose simvastatin

The only high-intensity statin specifically named in the NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#) is atorvastatin 20–80 mg daily. Other high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily.

In the [May 2010 edition of Drug Safety Update](#), the Medicines and Healthcare products Regulatory Agency (MHRA) advised that there is an increased risk of myopathy associated with simvastatin 80 mg daily, and that this dose should be considered only in people with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risk.

Rosuvastatin was not recommended in the guideline because, at the time of publication, it was considerably more expensive than atorvastatin, with no evidence of greater effectiveness ([full guideline](#)). Since then, the price of rosuvastatin has reduced. The [surveillance review](#) carried out in 2018 notes a potential need to update the guideline for various reasons, including the availability of rosuvastatin in a generic form.

Ezetimibe

The NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#) and the NICE technology appraisal guidance on [ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia](#) cross refer to each other.

NICE recommends ezetimibe as an option for treating primary heterozygous-familial or non-familial hypercholesterolaemia in adults:

- As monotherapy, as a possible alternative to a statin in people in whom statins are

- contraindicated or not tolerated; intolerance is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- In addition to initial statin therapy for people who have started statin treatment but in whom:
 - serum total or LDL-cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and
 - changing to a different statin is being considered.

Use of ezetimibe in people with homozygous familial hypercholesterolaemia was outside the scope of the NICE technology appraisal guidance. The NICE guideline on familial hypercholesterolaemia recommends that prescribing of drug therapy for adults with homozygous familial hypercholesterolaemia should be undertaken within a specialist centre.

Alirocumab and evolocumab

Alirocumab and evolocumab are lipid-modifying monoclonal antibodies (PCSK9 inhibitors) administered by subcutaneous injection. They are recommended for use in specified circumstances (more narrowly defined than their marketing authorisations) in NICE technology appraisal guidance on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia and evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. The technology appraisals recommend them as options for these conditions, **only if**:

- LDL-cholesterol concentrations are persistently above the thresholds specified (see table 1 below) despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).
- The dosage of evolocumab is 140 mg every 2 weeks (it is also licensed at a dosage of 420 mg once monthly; doses are clinically equivalent).
- The companies provide them with the discounts agreed in the patient access schemes.

Table 1 LDL-cholesterol concentrations above which alirocumab or evolocumab are recommended as options

	Without CVD	With CVD	
		High risk ^a	Very high risk ^b
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended	Only if LDL-cholesterol persistently >4.0 mmol/L	Only if LDL-cholesterol persistently >3.5 mmol/L
Primary heterozygous-familial hypercholesterolaemia	Only if LDL-cholesterol persistently >5.0 mmol/L	Only if LDL-cholesterol persistently >3.5 mmol/L	
^a High risk means a history of any of the following: acute coronary syndrome, coronary or other arterial revascularisation, chronic heart disease, ischaemic stroke, peripheral arterial disease. ^b Very high risk means recurrent CV events or CV events in more than 1 vascular bed (polyvascular disease).			
Abbreviations: CV, cardiovascular; CVD, cardiovascular disease, LDL-cholesterol, low-density lipoprotein cholesterol.			

Evolocumab is also [licensed](#) for treating **homozygous** familial hypercholesterolaemia in adults and young people aged 12 years and over. This indication was outside the [scope](#) of the NICE technology appraisal.

Cardiovascular outcomes trials of alirocumab (ODYSSEY OUTCOMES, [Schwartz et al. 2018](#)) and evolocumab (FOURIER, [Sabatine et al. 2017](#)) have been published since the technology appraisals.

The FOURIER study was a large randomised controlled trial of evolocumab in people with clinically evident atherosclerotic CVD plus other factors that placed them at higher cardiovascular risk, such as having diabetes, being a current smoker or being aged over 65 years at randomisation. The study was discussed in the NICE medicines evidence commentary on [hyperlipidaemia: clinical outcome data for evolocumab](#). Participants, who were receiving maximal tolerated lipid-lowering therapy, were randomised to receive evolocumab or placebo. The study found that evolocumab reduced the risk of the composite cardiovascular outcome (death from cardiovascular causes, myocardial infarction [MI], stroke, hospitalisation for unstable angina, or coronary revascularisation). No statistically significant benefit was seen on the risk of death from cardiovascular causes but the

median follow-up was only 2.2 years. This limits the conclusions that can be drawn on any possible long-term adverse effects of evolocumab or of controlling cholesterol to very low levels.

The ODYSSEY OUTCOMES study recruited people who had been admitted to hospital with acute coronary syndrome in the previous 12 months and who were receiving stable treatment with atorvastatin or rosuvastatin. Compared with placebo, alirocumab reduced the risk of the primary composite endpoint, which was similar to that in the FOURIER study: death from coronary heart disease, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalisation. But, also similar to the FOURIER study, no statistically significant benefit was seen on the risk of death from cardiovascular causes. Median follow-up was 2.8 years, so conclusions on any possible long-term adverse effects of alirocumab or of controlling cholesterol to very low levels are again limited.

Intolerance to statins

A large observational study, which was discussed in a NICE medicines evidence commentary on [statins: many people who stop treatment due to side effects may be able to restart treatment](#), suggested that many people who have discontinued statins because of an adverse event, especially muscle pain, may be able to restart the same or a different statin. The NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#) provides recommendations about monitoring for adverse effects of statins and managing intolerance to statins. It advises that, if a person is not able to tolerate a high-intensity statin, the aim should be to treat with the maximum tolerated dose. NICE recommends telling the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins, the following strategies should be discussed with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group.

A NICE medicines evidence commentary on [statin therapy: could liver function monitoring be reduced](#), discussed an observational study of a local policy that allowed GPs to select a single enzyme (ALT) test to check liver function in people on statins (rather than full liver function tests [LFTs]) and the introduction of locally developed guidance on frequency of testing in line with the NICE guideline. The study found that this reduced the frequency of LFT requests in this group and the associated costs.

Bile acid sequestrants, fibrates and nicotinic acid

Bile acid sequestrants (anion exchange resins), fibrates and nicotinic acid (niacin) are not recommended, alone or in combination with a statin, for preventing CVD in the NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#).

The NICE guideline on [familial hypercholesterolaemia](#) recommends that adults with the condition who have intolerance or contraindications to statins or ezetimibe should be offered referral to a specialist with expertise in this condition for consideration for treatment with a bile acid sequestrant or a fibrate to reduce their LDL-cholesterol concentration.

Omega-3 fatty acid compounds

Omega-3 fatty acid compounds, alone or in combination with a statin, are not recommended for preventing CVD, in the NICE guideline on [cardiovascular disease: risk assessment and reduction, including lipid modification](#). Moreover, the guideline recommends that healthcare professionals should tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD.

The NICE guideline on [familial hypercholesterolaemia](#) also states that people with this condition should not routinely be recommended to take omega-3 fatty acid supplements. In addition, the NICE guideline on [myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease](#) recommends that healthcare professionals should not offer or advise people who have had an MI to use omega-3 fatty acid capsules or omega-3 fatty acid supplemented foods to prevent another MI.

Practice examples and shared learning

There is a NICE shared learning case study relating to lipid-modifying drugs, showing how NICE guidance and standards have been put into practice by an NHS organisation:

- [New opportunities for the treatment of hyperlipidaemia: initiation of PCSK9 monoclonal antibodies utilising a multi-disciplinary approach](#).

Prescribing data, metrics or supporting resources

At this point, the following metrics have been identified to support this topic.

A medicines optimisation: key therapeutic topic [prescribing comparator](#) is available:

- **Other lipid modifying drugs: % items:** the number of prescription items for bile acid sequestrants, fibrates, nicotinic acid, omega-3 fatty acid compounds and 'other lipid modifying drugs' (BNF 2.12 sub-set) as a percentage of total prescription items for BNF 2.12.

Update information

September 2019: This topic was removed from the retired list and included in the 2019 rapid update of medicines optimisation: key therapeutic topics. Editorial changes have been completed, 2 medicines evidence commentaries have been added, information about outcome studies for PCSK9 inhibitors have been added, and text has been updated to reflect the price change for rosuvastatin.

About this key therapeutic topic

This document summarises the evidence base on this key therapeutic topic that has been identified to support medicines optimisation. **It is not formal NICE guidance.**

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