Lipid-modifying drugs

Key therapeutic topic
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Options for local implementation

- When a decision is made to prescribe a statin for primary or secondary prevention of cardiovascular disease, 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 hypercholesterolemia (which is being updated; publication expected April 2017) 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, nicotinic acid or fibrates to treat familial hypercholesterolaemia in some circumstances (see the NICE guideline on familial hypercholesterolemia).
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.

Evidence context

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.

People with familial hypercholesterolaemia are outside the scope of the guideline. There is a separate NICE guideline on the identification and management of familial hypercholesterolemia (which is being updated; publication expected April 2017). Recommendations on treating familial hypercholesterolaemia in adults are summarised in this key therapeutics topic: see the guideline for recommendations on treating the condition in children and young people.

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 about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. NICE has produced a patient decision aid to help a person thinking about statins for primary prevention of CVD weigh up the possible advantages and disadvantages of the different options.
For the purpose of the guideline, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol (LDL-C; see appendix A of the guideline for more information). High-intensity statins (more than 40% LDL-C reduction) are:

- atorvastatin 20–80 mg daily
- rosuvastatin 10–40 mg daily
- simvastatin 80 mg daily.

When a decision is made to prescribe a statin, the guideline recommends using a statin of high intensity and low acquisition cost.

Before offering statin treatment for primary prevention of CVD, NICE recommends discussing the benefits of lifestyle modification with the person and, if possible, optimising the management of all other modifiable CVD risk factors. The guideline recommends offering atorvastatin 20 mg daily for primary prevention to people who have a 10% or greater 10-year risk of developing CVD (estimated using the QRISK2 assessment tool), including those with type 2 diabetes and CKD. Among people with type 1 diabetes, primary prevention with statins may be considered in all adults and should be offered to adults who are older than 40 years, or who have had diabetes for more than 10 years, or who have established nephropathy, or who have other CVD risk factors. In adults with type 1 diabetes, treatment should be started with atorvastatin 20 mg daily.

NICE recommends that secondary prevention of CVD 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-C) and non-HDL-C 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-C. 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 statin 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 hypercholesterolemia (which is being updated; publication expected April 2017) 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-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

**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 possible high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily. In the May 2010 edition of Drug Safety Update, the 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.

The full guideline notes that the clinical outcomes of the only study that compared atorvastatin with rosuvastatin for prevention of CVD (SATURN, Nicholls et al. 2011) were inconclusive. It states 'Given the considerably higher cost of using rosuvastatin, it would need to be considerably more effective than atorvastatin for there to be a possibility that its use could be cost-effective. In the absence of trial evidence of greater effectiveness the guideline development group are therefore unable to recommend the use of rosuvastatin'.

**Ezetimibe**

The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification recommends that 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. This technology appraisal guidance makes explicit reference to the NICE guidelines on cardiovascular disease: risk assessment and reduction, including lipid modification and familial hypercholesterolaemia (which is being updated; publication expected April 2017).
The technology appraisal guidance recommends ezetimibe monotherapy as an option for treating heterozygous-familial or non-familial hypercholesterolaemia in adults in 2 broad situations:

- As an 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 in people who have started statin treatment but whose serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration or because dose titration is limited by intolerance to the initial statin therapy (defined as above) and consideration is being given to changing from initial statin therapy to an alternative statin.

Appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. Therefore, in the second of the situations above, in people with non-familial hypercholesterolaemia, adding ezetimibe to atorvastatin (the initial statin therapy recommended in the guideline) is an option if (and only if) a greater than 40% reduction in non-HDL-C is not achieved:

- despite optimising adherence and timing of the dose of atorvastatin and optimising adherence to diet and lifestyle measures, and

- increasing the dose of atorvastatin (if started at less than 80 mg daily) is not effective or not tolerated or the person has to decrease the dose because of tolerability problems (intolerance to statins is discussed below), and

- changing to a different statin is being considered.

The NICE guideline on familial hypercholesterolaemia gives recommendations on appropriate control of cholesterol concentrations in people with familial hypercholesterolaemia. 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 the homozygous form of this condition should be undertaken within a specialist centre.

The large, multicentre, randomised controlled trial (RCT) IMPROVE-IT (Cannon et al. 2015) was discussed in a NICE medicines evidence commentary on acute coronary syndrome: ezetimibe added to simvastatin (IMPROVE-IT study). IMPROVE-IT found that adding ezetimibe to simvastatin 40 mg after acute coronary syndrome produced a greater reduction in risk of
cardiovascular events than simvastatin 40–80 mg alone. However, the effect of the combination on this risk is that which would be predicted from the degree of lowering of LDL-C seen with a high-intensity statin such as atorvastatin 20–80 mg daily. The study provides no reason to depart from recommendations in the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.

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-C concentrations are persistently above the thresholds specified (see table 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 LDL-C concentrations above which alirocumab or evolocumab are recommended as options

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<tr>
<th></th>
<th>Without CVD</th>
<th>With CVD</th>
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<tr>
<td></td>
<td></td>
<td>High risk&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Primary non-familial hypercholesterolaemia or mixed dyslipidaemia</td>
<td>Not recommended</td>
<td>Only if LDL-C persistently &gt;4.0 mmol/L</td>
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<tr>
<td>Primary heterozygous-familial hypercholesterolaemia</td>
<td>Only if LDL-C persistently &gt;5.0 mmol/L</td>
<td>Only if LDL-C persistently &gt;3.5 mmol/L</td>
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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.

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-C, 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.

The summaries of product characteristics for both alirocumab and evolocumab state that their effects on cardiovascular morbidity and mortality have not yet been determined. In ODYSSEY LONG TERM (Robinson et al. 2015), an RCT of alirocumab in 2341 people at high risk for cardiovascular events who had LDL-C levels of 1.8 mmol/L or more and were receiving treatment with statins at the maximum tolerated dose (with or without other lipid-lowering therapy), a post-hoc analysis of data at 78 weeks suggested a reduction in the risk of major cardiovascular events. However, this must be interpreted cautiously. A cardiovascular outcomes trial of alirocumab in people with a history of acute coronary syndrome in the past year, ODYSSEY OUTCOMES, is ongoing and is expected to complete in early 2018. A cardiovascular outcomes trial of evolocumab in people with CVD at high risk of recurrence, FOURIER, has been completed, but not yet published.

**Intolerance to statins**

The NICE technology appraisal guidance on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia states 'The committee heard from the clinical expert that although up to approximately 23% of people with primary hypercholesterolemia were currently reported to be intolerant to statins, the true rate was likely to be between 0.5% to 3.0% of the population because there were no clear diagnostic criteria for statin intolerance.' 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 GAUSS-3 study which compared evolocumab with ezetimibe in people with muscle symptoms confirmed by statin re-challenge (Nissen et al. 2016) illustrated the difficulties of identifying people
with true statin intolerance. This 2-stage RCT recruited 511 adults with uncontrolled LDL-C and a history of intolerance to 2 or more statins. In a double-blind crossover phase only 43% of participants experienced muscle-related adverse effects with atorvastatin 20 mg but not with placebo. More than a quarter (27%) of participants experienced them with placebo but not atorvastatin. This study suggests that careful selection is necessary to identify those people who are truly intolerant of statins and in whom treatment with non-statin alternatives is most appropriate.

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.

**Bile acid sequestrants, fibrates and nicotinic acid**

The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification recommends that bile acid sequestrants (anion exchange resins) and nicotinic acid (niacin) should not be offered for primary or secondary prevention of CVD, alone or in combination with a statin, including in people with CKD or type 1 or type 2 diabetes. The guideline recommends that fibrates should not be routinely offered for monotherapy for primary or secondary prevention of CVD including in people with CKD or type 1 or type 2 diabetes, and should not be recommended in combination with a statin in these indications.

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, a fibrate or nicotinic acid to reduce their LDL-C concentration. The decision to offer treatment with a bile acid sequestrant, a fibrate or nicotinic acid in addition to initial statin therapy should be taken by a specialist with expertise in familial hypercholesterolaemia. Healthcare professionals should exercise caution when adding a fibrate or nicotinic acid to a statin because of

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the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together.

**Omega-3 fatty acid compounds**

The NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification recommends that people with or at high risk of CVD should be advised to consume at least 2 portions of fish per week, including a portion of oily fish. However, it advises that omega-3 fatty acid compounds should not be offered for primary or secondary prevention of CVD, alone or in combination with a statin, including in people with CKD or type 1 or type 2 diabetes. 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.

**Prescribing data**

The following medicines optimisation key therapeutic topic (MO KTT) prescribing comparator is available to support this topic[^1]:

- **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.

The development of further prescribing comparators to support this key therapeutic topic is being explored by the NHS England Medicines Optimisation Intelligence Group[^2].

Prescription Cost Analysis data of prescriptions dispensed in the community in England shows national statin and ezetimibe prescribing. In terms of costs, rosvuastatin 10–40 mg daily is between £220.87 and £359.58 per patient per year more costly than atorvastatin 20–80 mg daily at equivalent LDL-C-lowering doses. Adding ezetimibe 10 mg daily to a statin would cost an additional £342.03 per year ([Drug Tariff](https://www.nice.org.uk/terms-and-conditions#notice-of-rights) December 2016).
Other lipid modifying drugs: % items

- Data for the 3-month period July to September 2016 show a 5.9 fold variation in prescribing rates at Clinical Commissioning Group (CCG) level, from 1.05% to 6.20%.

- Between the 3-month period October to December 2013 and the 3-month period July to September 2016 there was a 20.2% decrease in the comparator value for England (total prescribing) from 2.66% to 2.12%.

- Over the same period there was a 33.0% decrease in the variation between CCGs, as measured by the inter-decile range, an absolute decrease of 0.77%. The inter-decile range is the difference between the highest and lowest values after the highest and lowest 10% of values have been removed.

[1] The comparators and associated data presented here are based on the previous key therapeutic topics publication (February 2016). Data provided by NHS Digital (October 2016; source: Information Services Portal, Business Services Authority). For details of any update to the comparators refer to the NHS Digital website and the Information Services Portal, Business Services Authority.


Update information

January 2017: This topic was retained for the 2017 update of medicines optimisation: key therapeutic topics. The evidence context has been updated in the light of new guidance and important new evidence, including PCSK9 inhibitors.

About this key therapeutic topic

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

For information about the process used to develop the key therapeutic topics, see the integrated process statement.

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