NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Cardiovascular disease: risk assessment and reduction, including lipid modification

Draft for consultation, September 2023

This guideline update introduces a new target for lipid levels for secondary prevention of cardiovascular disease (CVD) and guidance on lipid-lowering treatments other than statins alone to achieve that target.

It will update recommendation 1.4.30 in NICE guideline CG181 (last updated May 2023) for secondary prevention only. The existing recommendation will still apply for primary prevention.

The recommendations for people with chronic kidney disease are not being updated.

The consultation draft includes the new recommendations and some existing recommendations for context.

The numbering and layout of recommendations in this draft will change when they are incorporated into the existing guideline. There may be further structural changes to section 1.4.

Who is it for?

- Healthcare professionals
- People who are at risk of CVD or who have CVD

What does the consultation document include?

- the new recommendations
- proposed NICE indicator

- rationale and impact section that explains why the committee made the new recommendations and how they might affect practice.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence review, the scope, details of the committee and any declarations of interest.

New and updated recommendations

We have reviewed the evidence on escalation of lipid-lowering treatment for people with CVD.

You are invited to comment on:

- The new and updated recommendations. These are marked as **[December 2023]**.
- The recommendation that we propose to delete from the 2014 guideline. The reasons for this are given in table 1.
- The recommendations shaded in yellow and ending **[May 2023, amended December 2023]**, where we have had to make changes because of introducing the new recommendations. The reasons for the changes are given in table 2.

We have not reviewed the evidence for the recommendations shaded in grey (marked **[May 2023]**), and cannot accept comments on them.

See update information for a full explanation of what is being updated.

Full details of the evidence and the committee's discussion on the December 2023 recommendations are in evidence review D: escalation of lipid modification therapy for secondary prevention of CVD. Evidence for the May 2023 recommendations is in evidence review C: risk assessment and reduction, including lipid modification.

Proposed NICE indicator

In October 2022, NICE consulted on a draft indicator that was potentially suitable for local and national general practice measurement frameworks, including those underpinned with financial incentives. The indicator looked to establish a target

figure for non-HDL cholesterol for secondary prevention of CVD. In general, stakeholders supported using an absolute target to guide treatment decisions and support quality improvement. However, there was disagreement as to what the target figure should be.

The revised proposed indicator aligns to the new recommendation 1.6.1. We welcome stakeholder comments on this proposed indicator.

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Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.6 Lipid-lowering treatment for secondary prevention of cardiovascular disease

Lipid target for people taking lipid-lowering treatments

1.6.1 For secondary prevention of CVD aim for non-HDL cholesterol levels of 2.6 mmol/litre or less, or where non-HDL is not recorded, LDL cholesterol levels of 2.0 mmol/litre or less. **[December 2023]**

Statins for people with and without type 1 or 2 diabetes

Initial treatment

1.6.2 Offer atorvastatin 80 mg to people with CVD, whatever their cholesterol level. Use a lower dose of atorvastatin if any of the following apply:

- potential drug interactions
- high risk of adverse effects
- patient preference. **[May 2023, amended December 2023]**

In May 2023, this was an off-label use of atorvastatin. See NICE's information on prescribing medicines.

1.6.3 Do not delay statin treatment for secondary prevention of CVD but consider lifestyle changes at the same time if appropriate. **[May 2023]**

1.6.4 If a person has acute coronary syndrome do not delay statin treatment. Take a lipid sample on admission to hospital and about 3 months after starting treatment. **[May 2023]**

Optimising treatment for people on statins

1.6.5 If the lipid target for secondary prevention of CVD (see recommendation 1.6.1) is not achieved:

- discuss adherence and timing of statin dose
- optimise adherence to diet and lifestyle measures
- consider increasing the statin dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk profile or using clinical judgement. **[May 2023, amended December 2023]**

1.6.6 If someone reports adverse effects when taking a high-intensity statin try the following strategies with them:

- stopping the statin and trying again when the symptoms have resolved
- changing to a different statin in the same intensity group (rosuvastatin if already receiving atorvastatin)
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group. **[2014, amended December 2023]**

1.6.7 If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated intensity and dose of statin. **[2014, amended December 2023]**

1.6.8 Advise the person that any statin at any dose reduces CVD risk. **[2014, amended December 2023]**

Escalating treatment for people on statins

1.6.9 Offer ezetimibe in addition to the maximum tolerated intensity and dose of statin if the lipid target for secondary prevention of CVD is not achieved (see recommendation 1.6.1). **[December 2023]**

1.6.10 If the lipid target for secondary prevention of CVD is not achieved (see recommendation 1.6.1), consider alirocumab, evolocumab and inclisiran (see the NICE technology appraisals on inclisiran, evolocumab and alirocumab). **[December 2023]**

1.6.11 Consider ezetimibe in addition to the maximum tolerated intensity and dose of statin even if the lipid target for secondary prevention of CVD is achieved (see recommendation 1.6.1). **[December 2023]**

Statins are contraindicated or not tolerated

1.6.12 Offer ezetimibe instead of a statin to people for whom statins are contraindicated or, if after documented discussion of the strategies outlined in recommendation 1.6.6, it is recognised that the person cannot tolerate statins of any intensity or dose. This applies whatever the person's cholesterol level. **[December 2023]**

1.6.13 If the lipid target for secondary prevention is not achieved (see recommendation 1.6.1), consider alirocumab, bempedoic acid, evolocumab and inclisiran (see the NICE technology appraisals on inclisiran, bempedoic acid, evolocumab and alirocumab). **[December 2023]**

Monitoring response to treatment

1.6.14 Measure liver transaminase, total cholesterol, HDL cholesterol and triglyceride levels and calculate non-HDL cholesterol and LDL cholesterol about 3 months after starting or changing lipid-lowering treatment. **[May 2023, amended December 2023]**

1.6.15 Provide annual medication reviews for people on lipid-lowering treatment.

- Use these reviews to discuss and encourage medicines adherence and lifestyle changes and address CVD risk factors.
- Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion. **[May 2023, amended December 2023]**

To support quality improvement in managing cholesterol levels for people with cardiovascular disease, the following NICE indicator is being proposed as suitable for inclusion in local and national general practice measurement frameworks, including those underpinned with financial incentives:

IND2022-133: The percentage of patients with CVD in whom the last recorded non-HDL cholesterol level (measured in the preceding 12 months) is 2.6 mmol/litre or less, or last recorded LDL cholesterol level (measured in the preceding 12 months) is 2.0 mmol/litre or less, if non-HDL cholesterol is not recorded.

See the full details of the proposed NICE indicator.

For a short explanation of why the committee made the December 2023 recommendations and how they might affect practice, see the rationale and impact section on lipid target, and lipid-lowering treatments other than statins alone.

Full details of the evidence and the committee's discussion are in evidence review D: escalation of lipid modification therapy for secondary prevention of CVD.

Terms used in this guideline

High-intensity statin

The following doses for statins are high intensity, based on the percentage reduction in low-density lipoprotein (LDL) cholesterol they can produce:

- atorvastatin: 20 mg to 80 mg
- rosuvastatin: 10 mg to 40 mg

Rationale and impact

This section briefly explain why the committee made the December 2023 recommendations and how they might affect practice.

Lipid target, and lipid-lowering treatments other than statins alone

Recommendations 1.6.1 and 1.6.9 to 1.6.13

Why the committee made the December 2023 recommendations

Lipid target, and escalating treatment for people on statins alone

The committee agreed lipid levels should be reduced as much as possible in people with CVD. However, people respond differently to statins and other lipid-lowering treatments and it is not cost-effective to offer the full range of treatments to everyone with CVD.

The clinical evidence of individually analysed studies consisted of 34 randomised control trials (RCTs). Clinically significant reductions in LDL and non-HDL cholesterol levels were seen for all 4 lipid-lowering treatments compared to placebo.

Modest reductions in major cardiovascular events such as myocardial infarction, stroke and related deaths were also seen for all 4 medicines. The committee agreed that these were likely to be underestimates because some of the trials involved short follow-up periods, of 1 year or less. There was no clinically important increased risk of adverse events. Injection site reactions were more frequent with PCSK9i and inclisiran than with placebo but these were mild and not persistent.

An economic model was developed using estimates of the impact of lipid-lowering treatments on cholesterol reduction (from a network meta-analysis of the 34 RCTs), combined with estimates of the impact of cholesterol reduction on major cardiovascular events (from a published meta analysis of statin RCTs). The economic model calculated, for all possible baseline cholesterol levels, the reduced admissions to hospital for stroke, myocardial infarction and cardiovascular procedures, and the associated life expectancy increases, quality of life improvements and treatment cost savings, as a result of taking lipid-lowering treatments. This was offset against the cost of lipid-lowering treatments and associated monitoring costs.

The model took 2 alternative approaches. In both approaches, the sequence of escalation of treatment from a statin was first statin plus ezetimibe and then statin plus inclisiran plus ezetimibe. PCSK9 inhibitors were not included in the main analyses because they are much more expensive but only slightly more effective than inclisiran. In the first approach the lipid levels at which it was cost effective to

escalate treatment were estimated separately for ezetimibe and for adding inclisiran to ezetimibe. The second approach looked at a single lipid level at which it was cost effective to escalate treatment.

The first approach showed it was cost effective to treat with a statin plus ezetimibe at any lipid level. The addition of inclisiran was cost effective for people with LDL cholesterol levels of more than 3.1 mmol/litre after treatment with a statin plus ezetimibe.

The second approach demonstrated that escalation of treatment was cost effective for people on statins with LDL cholesterol levels of more than 2.2 mmol/litre. There was a little more uncertainty about the cost effectiveness of escalating treatment for people with LDL cholesterol levels between 2.0 and 2.2. The committee decided to favour 2.0, to allow more people to be treated.

A separate analysis indicated that escalation of treatment was cost effective for non-HDL cholesterol of more than 2.9 mmol/litre. The evidence linking non-HDL cholesterol to major cardiovascular events was much weaker than for LDL cholesterol and therefore the LDL model was favoured as the more evidence-based approach. Based on the proportion of people that would be escalated, a non-HDL cholesterol target of 2.6 mmol/litre was considered equivalent to 2.0 mmol/litre LDL cholesterol. This target is slightly higher than other national and international targets because, unlike other targets, it is explicitly based on the cost effectiveness of treatment escalation. However, the committee thought it was sufficiently similar to mean it was likely to be implemented. Even though the economic analyses based on LDL treatment effects were more robust, the committee thought that an LDL cholesterol target should not take precedence over a non-HDL cholesterol target. A non-HDL target is generally preferable because it does not require a fasting blood test.

The committee agreed it was better to recommend statins alone as the initial treatment and then ezetimibe if LDL cholesterol levels were more than 2.0 mmol/litre, rather than offering statins plus ezetimibe from the outset and then another lipid-lowering treatment if LDL cholesterol levels were more than 3.1 mmol/litre. Although the second approach would mean everyone getting ezetimibe, not just those with

LDL levels of more than 2.0 mmol/litre, it would also mean people with LDL levels between 2.0 and 3.1 mmol/litre not getting other lipid lowering treatments, and so favours people less in need of treatment. Given that the evidence from the first approach showed that ezetimibe was cost effective regardless of the person's lipid levels, the committee agreed that it could be considered for people with lipid levels below the agreed targets where additional risk lowering is desirable. They noted that the trade-off between reducing risk and increasing medication should be taken into account. Furthermore, the committee agreed that recommending ezetimibe to people at lower levels of cholesterol might cause confusion among those who believe their cholesterol to be adequately under control with a statin alone and adherence may be lower for people on 2 pills rather than 1.

The committee noted that a lipid target based on a percentage reduction in non-HDL cholesterol was not practical as current electronic clinical systems are not set up to generate this data. The lack of a baseline figure against which to measure any percentage reduction is a particular problem in secondary prevention as people may start lipid-lowering treatment after an acute event and their lipid level at that time may not be recorded.

Statins are contraindicated or not tolerated

The committee did not review the evidence for the clinical effectiveness of lipid-lowering treatments in people who are statin intolerant or for whom statins are contraindicated but based their recommendations on the NICE technology appraisals on inclisiran, bempedoic acid, evolocumab and alirocumab.

The committee emphasised that statin therapy is known to be the most effective method of reducing the risk of CVD events and that this should be the mainstay of treatment. They highlighted the importance of following recommendation 1.6.6 on strategies of what to do if someone reports adverse effects when taking a high-intensity statin before deciding someone is statin intolerant.

The economic modelling included a scenario where people who are intolerant to statins or for whom statins were contraindicated followed a distinct treatment pathway but were treated to the same lipid target as those on statins. The committee discussed whether the lipid target should be different because of the different

treatment options and associated costs. However, it was noted that this may introduce inequality regarding access to lipid-lowering treatment. Also, the target at which escalation of lipid-lowering treatment is cost effective did not change when the statin intolerant population was included in the economic model, largely because the prevalence of statin intolerance is low, and could be lower than the 9.1% assumed in the model. Therefore, the committee agreed that the target for people who cannot take statins should be the same as for those who can take statins.

They made a recommendation to offer ezetimibe to people who cannot take statins (in line with TA694) and, if this does not result in the person achieving the lipid target in this guideline, to offer additional lipid-lowering treatments (in line with other technology appraisals).

How the December 2023 recommendations might affect practice

It is expected that recommending a specific lipid target for secondary prevention of CVD will lead to an increased use of lipid-lowering treatments. The committee was aware that NHS England had recently introduced a target as part of the Quality and Outcomes Framework (QOF). The target recommended in this guideline is similar to the 2023/2024 QOF.

Increased uptake of statins, ezetimibe and other lipid-lowering treatments would result in higher medication and monitoring costs to the NHS. It would also contribute to increased workload burden in primary care GP practices and pharmacies and in laboratories processing monitoring tests. The committee agreed this increase was necessary for downstream improvements in population health and the extra cost of lipid-lowering treatment would be partly offset by savings due to a reduction in CVD events (including admissions for stroke or heart disease and cardiovascular procedures).

Return to recommendations

Context

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for almost 18 million deaths each year (over 30% of all global deaths).

Over 70 million prescriptions for statins are dispensed in England each year, costing the NHS around £100 million. The total healthcare cost of CVD in England is estimated to be £7.4 billion.

Despite the weight of conclusive research and consistent national and international guidelines, many people at significant risk of CVD do not receive lipid-lowering treatments, or they receive inadequate treatment. Anxieties about the safety of statins may mean healthcare professionals are reticent about offering them, and people are reluctant to start or continue statin treatment. Depending on statin intensity, 30% to 50% of people stop taking statins within 6 years.

Over the past 5 years, more evidence has become available on the benefits and adverse effects of statins.

Ways to estimate and explain CVD risk have also improved, and healthcare professionals now have more varied and accurate approaches available for individualised risk assessment. This can empower patients and professionals to discuss interventions to reduce short- and long-term CVD risk.

Increasing awareness of elevated lipids (including cholesterol) as a risk factor for CVD, so that appropriate intervention can be provided, is critical to the delivery of the NHS Long Term Plan. By 2029, the ambition in England is for at least 45% of people aged 40 to 74 who are at significant risk of developing CVD to be on appropriate lipid-lowering treatment. Local achievement of this ambition can be monitored using the CVDPREVENT audit.

Proposed NICE indicator

IND2022-133: The percentage of patients with CVD in whom the last recorded non-HDL cholesterol level (measured in the preceding 12 months) is 2.6 mmol/litre or less, or last recorded LDL cholesterol level (measured in the preceding 12 months) is 2.0 mmol/litre or less, if non-HDL cholesterol is not recorded.

Indicator type

General practice indicator.

Rationale

This indicator aims to support improvements in secondary prevention of cardiovascular disease by managing cholesterol levels. Where non-HDL cholesterol is more than 2.6 mmol/litre (2.0 mmol/litre for LDL cholesterol), treatment should be escalated in line with NICE guidance.

Specification

Numerator: the number in the denominator whose last recorded non-HDL cholesterol level (measured in the preceding 12 months) is 2.6 mmol/litre or less, or last recorded LDL cholesterol level is 2.0 mmol/litre or less, if non-HDL cholesterol is not recorded.

Denominator: the number of patients with CVD. Existing QOF registers could be used for coronary heart disease (CHD001), stroke or transient ischaemic attack (STIA001 excluding haemorrhagic stroke) and symptomatic peripheral arterial disease (PAD001).

Definition: For the purposes of this indicator, CVD is defined as angina, previous myocardial infarction, revascularisations, ischaemic stroke or transient ischaemic attack or symptomatic peripheral arterial disease.

Exclusions: Patients with a diagnosis of familial hypercholesterolaemia or diagnosed with CVD in the last 3 months of the reporting period.

Personalised care adjustments or exception reporting should be considered to account for situations where the patient declines a cholesterol test, does not attend or if cholesterol management is not appropriate for the individual.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on cardiovascular conditions.

For details of the guideline committee see the committee member list.

Update information

May 2023

We have reviewed the evidence on risk assessment tools for primary prevention of CVD, cardioprotective diets and statin treatment for primary and secondary prevention of CVD.

December 2023

We have reviewed the evidence on escalation of lipid-lowering treatment for people with CVD.

Recommendations that have been deleted, or changed without an evidence review

We propose to delete 1 recommendation from the 2014 guideline. Table 1 sets out this recommendation. An explanation for the proposed deletion is given.

For the recommendations shaded in yellow and ending **[May 2023, amended December 2023]**, we have had to make changes because of introducing the new recommendations. The reasons for the changes are given in table 2.

See also the previous NICE guideline and supporting documents.

Table 1: Recommendations that have been deleted

Recommendation in 2014 guideline	Comment
1.4.48 Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with CVD who are intolerant to 3 different statins. Seek advice by telephone, virtual clinic or referral.	In current clinical practice these groups would be managed in primary care. The management of genetic dyslipidaemias is outside of the scope of the guideline. Guidance is now given on people are intolerant to statin in the guideline.

Table 2 Amended recommendation wording (change to intent) without an evidence review

Recommendation in May 2023 guideline	Recommendation in December 2023 guideline	Reason for change
1.4.23 Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if any of the following apply: • potential drug interactions • high risk of adverse effects • patient preference. In May 2023, this was an off-label use of atorvastatin. See NICE's information on prescribing medicines.	1.6.2 Offer atorvastatin 80 mg to people with CVD, whatever their cholesterol level. Use a lower dose of atorvastatin if any of the following apply: • potential drug interactions • high risk of adverse effects • patient preference. In December 2023, this was an off-label use of atorvastatin. See NICE's information on prescribing medicines.	This recommendation has been amended to make it clear that it applies whatever the person's cholesterol level.
1.4.29 Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment.	1.6.14 Measure liver transaminase, total cholesterol, HDL cholesterol and triglyceride levels and calculate non-HDL cholesterol and LDL cholesterol about 3 months after starting or changing lipid-lowering treatment.	This recommendation has been amended to explain that non-HDL cholesterol and LDL cholesterol levels are calculated using total cholesterol, HDL cholesterol and triglyceride levels. The requirement to measure triglyceride levels has been added. Liver transaminase has been added to be consistent with recommendation
1.4.31 If a greater than 40% reduction in non-HDL cholesterol is not achieved:	1.6.5 If the lipid target for secondary prevention of CVD is not achieved (see recommendation 1.6.1):	Amended to apply to new lipid target for secondary prevention. Also amended to clarify that this recommendation is about optimising statin treatment.

• discuss adherence and timing of dose • optimise adherence to diet and lifestyle measures • consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.	• discuss adherence and timing of statin dose • optimise adherence to diet and lifestyle measures • consider increasing the statin dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk profile or using clinical judgement.	
1.4.32 Provide annual medication reviews for people taking statins. • Use these reviews to discuss medicines adherence and lifestyle changes and address CVD risk factors. • Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion.	1.6.15 Provide annual medication reviews for people on lipid-lowering treatment. • Use these reviews to discuss and encourage medicines adherence and lifestyle changes and address CVD risk factors. • Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion.	Amended to apply to people on any lipid-lowering treatment, not just statins.
1.4.46 If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose.	1.6.7 If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated intensity and dose of statin.	Amended to make it clear that the dose and intensity of statin needs to be taken into account.
1.4.47 Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking a high-intensity statin discuss the following possible strategies with them: • stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin • changing to a different statin in the same intensity group	1.6.6 If someone reports adverse effects when taking a high-intensity statin discuss try the following strategies with them: • stopping the statin and trying again when the symptoms have resolved • changing to a different statin in the same intensity group	Split this recommendation into 2 recommendations and amended to be more person-focused. Remove reference to checking if symptoms related to the statin as need to think more widely about what might be causing the adverse effect.

(rosuvastatin if already receiving atorvastatin) • reducing the dose within the same intensity group • changing the statin to a lower intensity group.	(rosuvastatin if already receiving atorvastatin) • reducing the dose within the same intensity group • changing the statin to a lower intensity group. 1.6.8 Advise the person that any statin at any dose reduces CVD risk.	

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