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Guidelines

Secondary prevention of cardiovascular disease, including cholesterol targets: summary of updated NICE guidance

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Box start

What you need to know

- Offer 80 mg atorvastatin (unless contraindicated or previously not tolerated) as soon as possible to people with atherothrombotic cardiovascular disease (CVD)
- 2.0 mmol LDL-C (or 2.6 mmol/L non-HDL) is the most cost effective target for patients with established atherothrombotic CVD
- Consider ezetimibe for patients with atherothrombotic CVD, even if their cholesterol level is below the target

Box end

While mortality from acute cardiovascular disease (CVD) has been falling in most developed countries, more people are now living with established CVD, including coronary heart disease, peripheral arterial disease, and stroke or transient ischaemic attack. These individuals remain at high risk of subsequent cardiovascular events and mortality. In the UK, the cost of treating a myocardial infarction is £1310 higher in the first year for someone with established CVD than for a first event.[1] Secondary prevention interventions, such as lowering of low density lipoprotein cholesterol (LDL-C), mitigate this risk and improve outcomes.[2]

Statins, ezetimibe, bempedoic acid, and injectable therapies are approved as lipid lowering therapies in the UK. However, use of these agents is variable,[3] with about one fifth of people with CVD in England receiving no lipid lowering therapy.[4] This is partly because of the absence of nationally agreed LDL-C targets for people with CVD to inform need for therapeutic escalation. Targets between 1.4 mmol/L and 1.8 mmol/L have been advocated by specialist societies and expert consensus, based on data from randomised controlled trials (RCTs).[5 6] Achievement of these targets has been poor, and as of September 2023, in England, only about one third of people with CVD who had a cholesterol test in the last 12 months had either LDL-C below 1.8 mmol/L or non-HDL-C below 2.5 mmol/L.[7]

This article summarises the most recent recommendations from the National Institute for Health and Care Excellence (NICE), first published in 2014, and updated in December 2023, incorporating for the first time LDL-C targets for people with CVD.[8] This guideline is the first to incorporate economic modelling and cost effectiveness in the calculation of cholesterol targets, which could mean that it is more easily implemented.

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italics in square brackets. Evidence certainty is based on GRADE criteria (box 1).

Box start

Box 1 GRADE Working Group grades of evidence

High certainty—we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Box end

Initial treatment

The evidence for these recommendations has not been revisited since the last update[9]; however the wording has been updated to ensure consistency across the guideline.

Randomised controlled trials have shown consistently that reduction of LDL-C by prescribing statins reduces the risk of major cardiovascular events and cardiovascular mortality by approximately one fifth for each 1 mmol/L reduction in LDL-C.[2] For people with established CVD, cost utility analysis in an NHS setting showed that high intensity statins are highly cost effective when compared with no treatment or any other statin regimen.[9]

- Offer atorvastatin 80 mg to people with CVD, whatever their cholesterol level.
  [Based on randomised trial data, high to very low certainty, and economic modelling]
- Offer a lower dose of atorvastatin if any of the following apply:
  - It could react with other drugs
  - There is a high risk of adverse effects
  - The person would prefer to take a lower dose.

  [Based on randomised trial data, high to very low certainty, and the experience and opinion of the guideline committee (GC)]
- Do not delay statin treatment for secondary prevention of CVD but discuss lifestyle changes at the same time if appropriate.
  [Based on the experience and opinion of the GC]
- If a person has acute coronary syndrome do not delay statin treatment. Measure full lipid profile on admission and two to three months after starting treatment.
  [Based on the experience and opinion of the GC]

Lipid targets for people with CVD taking lipid lowering treatments

In people with CVD, LDL-C should be as low as possible to minimise the risk of re-admission to hospital and mortality, based on data from RCTs, genetic studies, and observational cohorts. At a population level, however, this is not cost effective, given that many potent non-statin therapies are expensive.

To inform this new recommendation, a cost utility analysis was developed using estimates of the impact of lipid lowering treatments on LDL-C (from an original network meta-analysis of RCTs),[10] combined with estimates of the impact of LDL-C reduction on major cardiovascular events (from a published meta-analysis of statin RCTs).[2] The economic model measured the impact of lipid lowering treatments across a range of baseline LDL-C levels (0.3 to 4.0 mmol/L), on reduced admissions to hospital (stroke, myocardial infarction, and cardiovascular procedures), increases in life expectancy, and improvements in quality of life. Hospitalisation cost savings were offset against the cost of lipid lowering treatments and associated monitoring costs. The lowest LDL-C target that was cost effective at the benchmark pre-specified in NICE's principles of £20 000 per quality adjusted life year gained,[11] was 2.0 mmol/L or an equivalent non-HDL of 2.6 mmol/L.

• For secondary prevention of CVD aim for LDL-C levels of 2.0 mmol per litre or less, or non-HDL cholesterol levels of 2.6 mmol per litre or less.

[Based on randomised trial data, high to very low certainty, and economic modelling]

Escalating treatment for people treated with statins

For people who are above the LDL-C target while already being treated with statin monotherapy, the GC refers healthcare practitioners to NICE's relevant technology appraisals to allow an informed choice to be made on the basis of the treatment specific expected LDL-C lowering that would achieve the LDL-C target, local availability, and patient preference.

This guideline newly recommends healthcare practitioners consider use of ezetimibe for people at or below the target. The low acquisition price (£1.51 for 28 tablets, at one tablet a day[12]) and its effectiveness (an average 7% reduction in major cardiovascular events) makes ezetimibe highly cost effective for use in people with CVD at all cholesterol levels, and supports the principle of lowering LDL-C as much as possible for maximal risk reduction.

• Make decisions about escalating lipid lowering treatment after an informed discussion between the clinician and the person about the risks and benefits of additional lipid lowering treatments.

[Based on the experience and opinion of the GC]

• Take into account potential benefits from lifestyle changes, the person's preferences, the presence of any comorbidities, whether they are on multiple medications, whether they are frail, and their life expectancy (see also NICE's guideline on multimorbidity[13]).

[Based on the experience and opinion of the GC]

• If the person is taking the maximum tolerated dose and intensity of statin but the lipid target for secondary prevention of CVD is not met (see above), consider additional lipid lowering treatments (see the NICE technology appraisals on alirocumab,[14] evolocumab,[15] ezetimibe,[16] and inclisiran[17]).

[Based on randomised trial data, high to very low certainty, and economic modelling]

• Consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is met (see above).

[Based on randomised trial data, high to very low certainty, and economic modelling]

Secondary prevention of cardiovascular disease when statins are contraindicated or not tolerated

People with CVD should take statins when they can be tolerated safely. However, approximately 9% of patients report an intolerance to all forms of statin therapy, commonly muscle ache and myalgia.[18] In this context, this guideline newly recommends ezetimibe as a cost effective alternative first line therapy.

• Offer ezetimibe instead of a statin to people for whom statins are contraindicated or if after documented discussion, it is recognised the person cannot tolerate statins of any intensity

or dose. This applies whatever the person's cholesterol level (see the NICE technology appraisal on ezetimibe[16]).

[Based on economic modelling and the experience and opinion of the GC]

- If the person is taking ezetimibe but the lipid target for secondary prevention is not met, consider alternative or additional lipid lowering treatments (see the NICE technology appraisals on alirocumab,[14] bempedoic acid,[19] evolocumab,[15] and inclisiran[17]).

  [Based on randomised trial data, high to very low certainty, economic modelling, and the experience and opinion of the GC]

Annual medication review

This recommendation has been updated to focus treatment on people at greatest risk. Healthcare practitioners should measure a full lipid profile annually, to allow estimation of LDL-C, as well as evaluation of familial hypercholesterolaemia and quantification of triglycerides that could inform use of additional approved cholesterol lowering therapies, such as icosapent ethyl.

- Offer an annual full lipid profile to inform discussions about secondary prevention of CVD.

  [Based on the experience and opinion of the GC]

Implementation

The high resource costs of some lipid lowering therapies, including acquisition and healthcare staff time, may create a barrier to implementation, but are likely to be offset by costs related to cardiovascular events prevented. The economic model for this guideline showed that many people can achieve the target with modestly priced oral medicines, such as statins alone or when combined with ezetimibe.

The slightly lower LDL-C target in existing guidelines, 1.8 mmol/L, seems close to the 2.0 mmol/L newly presented in this guideline; however, the economic model suggests that the additional cost to achieve a target of 1.8 mmol/L for everyone with CVD was considerable. We anticipate the Qualities and Outcome Framework indicator CHOL002[20 21] will be realigned to the guideline target in the 2024/25 GP contract, which will incentivise implementation in primary care. This guideline does not preclude aiming for a lower LDL-C target on an individual basis, with wider use of ezetimibe with statin therapy.

Healthcare practitioners might find it difficult to provide further escalation to patients taking maximal statin and ezetimibe therapy who have LDL-C between 2.0 and 2.6 mmol/L. No national funding mandate exists for advanced therapies, such as inclisiran or PCSK9 inhibitors, for use in patients in this range. Therefore, the escalation option of ezetimibe or inclisiran should be chosen carefully to reduce the occurrence of this scenario.

Although the strongest trial evidence was reported for LDL-C and a recommendation was made to carry out a full lipid profile annually, LDL-C testing varies across the country, and therefore, a corresponding non-HDL-C value was also recommended.

Box start

Future research

The guideline committee amended and endorsed existing research questions, although these were not specific to secondary prevention:

- What is the effectiveness of age alone and other routinely available risk factors compared with the formal structured multifactorial risk assessment to identify people at high risk of developing CVD?
- What is the effectiveness of statin treatment in older people?
- What is the effectiveness of statins and/or other lipid lowering treatment in people with type 1 diabetes?

Box end

Box start

Guidelines into practice

- What is the target cholesterol level you use for treating people with CVD?
- In which patients with CVD do you offer lipid lowering therapy other than a statin?

Box end

Box start

Further information on the guidance

The guideline referred to in this article was produced by the National Institute for Health and Care Excellence (NICE). The views expressed in this article are those of the authors and not necessarily those of NICE.

This guidance was developed in accordance with NICE guideline methodology (www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf). A guideline committee (GC) was established, which incorporated healthcare and allied healthcare professionals (one consultant cardiologist, one consultant physician in ageing and health, one advanced nurse practitioner, one clinical senior lecturer in primary care, one consultant nephrologist, one associate professor and honorary consultant physician, one professor of cardiovascular medicine and honorary consultant cardiologist, one professor of cardiology and consultant cardiologist, one associate professor and honorary consultant in metabolic medicine, one advanced clinical pharmacist for cardiovascular services, one advanced nurse practitioner, one senior clinical lecturer in primary care and mental health, one consultant stroke physician, one consultant physician in diabetes, endocrinology and lipid metabolism, one professor of genetic epidemiology and honorary consultant, clinical pharmacology and general (internal) medicine, one nurse educator and associate lecturer, one chair of geriatric and stroke medicine and honorary consultant stroke physician), and two lay members.

The guideline is available at www.nice.org.uk/guidance/ng238.

The GC identified relevant review questions and collected and appraised clinical and cost effectiveness evidence. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes or themes rather than the quality of the study. The GC agreed recommendations for clinical practice based on the available evidence or, when evidence was not found, based on their experience and opinion using informal consensus methods.

The scope and the draft of the guideline went through a rigorous reviewing process, during which stakeholder organisations were invited to comment; the GC took all comments into consideration when producing the final version of the guideline.
NICE will conduct regular reviews after publication of the guidance, to determine whether the evidence base has progressed significantly enough to alter the current guideline recommendations and require an update.
A resource impact report and tool can be found here:
www.nice.org.uk/guidance/ng238/resources.
Box end

Box start
How patients were involved in the creation of this article
Committee members involved in this guideline update included lay members, Satwinder Kaur and Colin Wilkinson, who contributed to the formulation of the recommendations summarised here.
Box end

The members of the Guideline Committee were: Nigel Beckett, Beverley Bostock (until May 2023), Chris Clark, Hugh Gallagher, Mark Glover (until February 2023), Satwinder Kaur, Paul Leeson, Joseph Mills (chair), Riyaz Patel (topic adviser), David Preiss, Ruth Price, Sharon Seber (from October 2023), Eduard Shantsila, Wayne Sunman, Colin Wilkinson; Co-opted members: Parijat De, Aroon Hingorani, Judith Magowan, Chakravarthi Rajkumar.

Members of the NICE development technical team were: Serena Carville (guideline lead until May 2023), Lina Gulhane (senior information manager), Kusal Lokuge (health economist, from July 2023) Alfredo Mariani (senior health economist), Patrick Muller (technical adviser), Joanna Perkin (content Editor), Eleanor Samarasekera (lead technical analyst), Sharon Swain (guideline lead from May 2023), Amelia Unsworth (project manager), Melina Vasileiou (technical analyst, until July 2023), and David Wonderling (senior health economics adviser).

Members of the NICE commissioning and quality assurance team were: Phil Alderson, Catrina Charlton, Andy Hutchinson, Syed Mohiuddin, Kay Nolan, Rachel Woodcraft.

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Clinical Practice Research Datalink staff involved with data analysis: Michael Lonergen, Jessie Oyinlola, Rachael Williams, Ellie Yelland.

Contributorship and guarantor: EJS and Melina Vasileiou reviewed and assessed the trial evidence. AM and DW conducted the health economic modelling. CW, RSP, and JM interpreted the evidence and generated the recommendations with other committee members. All authors contributed to the initial draft of this article, helped revise the manuscript, and approved the final version for publication and agree to be accountable for the accuracy and integrity of the work. DW is responsible for the overall content as guarantor.

Lina Gulhane conducted the literature searches. Beatrice Downing and Nicky Welton conducted the network meta-analysis. Michael Lonergen and Jessie Oyinlola conducted the analysis of event rates and mortality. Patrick Muller and Vanessa Kam conducted the analysis of cholesterol data. Lynn Kincaid, Shaun Rowark, Rachael Williams, and Ellie Yelland

supported the data analysis and data access. Lindsay Claxton, Kusal Lokuge, and Miaoqing Yang supported the health economic modelling.

The NICE technical teams were led by Catrina Charlton, Serena Carville, Kay Nolan, Sharon Swain. Amelia Unsworth was project manager. Joanna Perkin edited the recommendations. Formal quality assurance was provided by: Phil Alderson, Andy Hutchinson, Syed Mohiuddin, and Rachel Woodcraft.

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Mark Glover was a member of the committee until his very sad and untimely death in February 2023. The chair and other members of the committee pay tribute to Mark's work on the CVD suite of guideline updates and remember him as a valued colleague and friend.

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<jrn>1 Zhou J, Wu R, Williams C, et al. Prediction models for individual-level healthcare Costs associated with cardiovascular events in the UK. *Pharmacoeconomics* 2023;41:547-59. PubMed doi:10.1007/s40273-022-01219-6</jrn>

<jrn>2 Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81. PubMed doi:10.1016/S0140-6736(10)61350-5</jrn>

<jrn>3 Connelly D, Cohen D, McCartney M. Fewer than 5,000 people prescribed anticholesterol drug inclisiran in primary care as of July 2023. *Pharm J* 2023;2023. https://pharmaceutical-journal.com/article/news/fewer-than-5000-people-prescribed-anticholesterol-drug-inclisiran-in-primary-care-as-of-july-2023.</jrn>

<eref>4 CVDPrevent audit. CVDP009CHOL: Percentage of patients aged 18 and over with GP recorded CVD (narrow definition), who are currently treated with lipid lowering therapy. https://www.cvdprevent.nhs.uk/data-explorer?period=10&area=1&indicator=34.</eref>

<jrn>5 Visseren FLJ, Mach F, Smulders YM, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227-337. PubMed doi:10.1093/eurheartj/ehab484</jrn>

<jrn>6 Lloyd-Jones DM, Morris PB, Ballantyne CM, et al; Writing Committee. 2022 ACC Expert Consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2022;80:1366-418. PubMed doi:10.1016/j.jacc.2022.07.006</jrn>

<eref>7 CVDPrevent audit. CVDP007CHOL: Percentage of patients aged 18 and over, with GP recorded CVD (narrow definition), in whom the most recent blood cholesterol level (measured in the preceding 12 months) is non-HDL cholesterol less than 2.5mmol/l or LDL-

cholesterol less than 1.8mmol/l. https://www.cvdprevent.nhs.uk/data-explorer?period=10&area=1&indicator=30.</eref>
<bok>8 National Institute of Health and Care Excellence (NICE). *Cardiovascular disease: risk assessment and reduction, including lipid modification.* NICE, 2023, NICE guideline NG238.</bok>
<eref>9 National Institute of Health and Care Excellence (NICE). Evidence review for statins: efficacy and adverse effects. NICE, London 2023. https://www.nice.org.uk/guidance/ng238/evidence/c-statins-efficacy-and-adverse-effects-pdf-13253901663</eref>
<eref>10 National Institute of Health and Care Excellence (NICE). Network meta-analysis of changes in LDL cholesterol and non-HDL cholesterol as a result of escalation of lipid-lowering treatment for secondary prevention of CVD. NICE, London 2023. https://www.nice.org.uk/guidance/ng238/evidence/network-metaanalysis-of-changes-in-ldl-cholesterol-and-nonhdl-cholesterol-as-a-result-of-escalation-of-lipidlowering-treatment-for-secondary-prevention-of-cvd-pdf-13254044222</eref>
<eref>11 National Institute of Health and Care Excellence (NICE). The principles that guide the development of NICE guidance and standards. https://www.nice.org.uk/about/who-we-are/our-principles</eref>
<eref>12 NHS Drug tariff. https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff</eref>
<bok>13 National Institute of Health and Care Excellence (NICE). *Multimorbidity: clinical assessment and management.* NICE, 2016, NICE guideline NG56.</bok>
<bok>14 National Institute for Health and Care Excellence. *Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. NICE technological appraisal TA393.* NICE, 2016.</bok>
<bok>15 National Institute for Health and Care Excellence. *Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. NICE technological appraisal TA394.* NICE, 2016.</bok>
<bok>16 National Institute for Health and Care Excellence. *Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. NICE technological appraisal TA385.* NICE, 2016.</bok>
<bok>17 National Institute for Health and Care Excellence. *Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia. NICE technological appraisal TA733.* NICE, 2021.</bok>
<jrn>18 Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. *Eur Heart J* 2022;43:3213-23. PubMed doi:10.1093/eurheartj/ehac015</jrn>
<bok>19 National Institute for Health and Care Excellence. *Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia. NICE technological appraisal TA694.* NICE, 2021.</bok>
<eref>20 National Institute of Health and Care Excellence (NICE). NICE Quality and Outcomes Framework indicator. The percentage of patients with CVD in whom the last recorded LDL cholesterol level (measured in the preceding 12 months) is 2.0 mmol per litre or less, or last recorded non-HDL cholesterol level (measured in the preceding 12 months) is 2.6 mmol per litre or less, if LDL cholesterol is not recorded. 2023. https://www.nice.org.uk/standards-and-indicators/qofindicators/the-percentage-of-patients-with-cvd-in-whom-the-last-recorded-ldl-cholesterol-level-is-2-0-mmol-per-litre-or-less-or-last-recorded-non-hdl-cholesterol-level-is-2-6-mmol-per-litre-or-less-if-ldl-cholesterol-is-not-recorded</eref>

<eref>21 NHS England. Quality and outcomes framework guidance for 2023/24. https://www.england.nhs.uk/long-read/quality-and-outcomes-framework-guidance-for-2023-24/</eref>