National Institute for Health and Care Excellence

Guideline review protocol

# CVD risk assessment and lipid modification

## Clinical protocol for escalation of lipid modification therapy for secondary prevention of CVD

*Review protocol*

*02/2023*

*Developed by NICE*

**Disclaimer**

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

# Contents

# 1 Appendices

# Appendix A: Review protocol

## Review protocol for escalation of lipid modification therapy for secondary prevention of cardiovascular disease (CVD)

| ID | Field | Content |
|---|---|---|
| 1. | Review title | Escalation of lipid modification therapy for secondary prevention of CVD |
| 2. | Review question | In adults with CVD requiring escalation of therapy beyond statins, what is the effectiveness of lipid-lowering therapy? |
| 3. | Objective | **To provide evidence on lipid lowering, CVD event risk reduction achieved, and adverse events experienced during escalation of lipid modification therapy to support the identification of a target for secondary prevention of CVD.**<br>**This review will not be considering sequencing of treatment options listed in the interventions.** |
| 4. | Searches | Key papers:<br>• IMPROVE-IT<br>• FOURIER<br>• ODYSSEY OUTCOMES<br>• ORION-10 and -11<br>• Cochrane review on Ezetimibe<br>• Cochrane review on PCSK9 monoclonals<br><br>The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• Epistemonikos |

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| | | Searches will be restricted by:<br>• English language studies<br>• Human studies<br><br>Other searches:<br>• Reference searching<br>• Citation searching<br>• Inclusion lists of systematic reviews<br><br>The full search strategies will be published in the final review.<br>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). |
| 5. | Condition or domain being studied | Cardiovascular disease |
| 6. | Population | **Inclusion:**<br>• Adults (aged 18 years and older) with CVD.<br>  ○ Studies that include ≥80% participants with CVD (or presenting subgroup data for those with CVD) will be preferentially included.<br>  ○ If insufficient data are available from CVD populations, studies including mixed populations with and without CVD (50-79% CVD) will be considered for inclusion. This will be decided separately for each comparison.<br>CVD is defined as including people with/requiring the following:<br>• Ischaemic stroke<br>• Transient ischaemic attack<br>• Myocardial infarction<br>• Coronary heart disease (for example unstable and stable angina)<br>• Peripheral artery disease<br>• Coronary or non-coronary arterial revascularisation procedures<br><br>**Exclusion:**<br>• Children aged under 18 years of age. |

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| | | • People who are intolerant of or have contraindications to statins.<br>• People with familial hypercholesterolaemia.<br>• People receiving renal replacement therapy.<br>• People with familial clotting disorders that increase cardiovascular risk.<br>• People with other monogenic disorders that increase cardiovascular risk.<br>• People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes.<br><br>**Indirect populations:**<br>Studies with indirect populations must have ≥80% participants matching the protocol to be included, for example:<br>• Studies including those with and without familial hypercholesterolaemia (FH) must have ≥80% without FH (or report subgroup data for the group without FH).<br>• Studies including those with and without renal replacement therapy must have ≥80% without or report subgroup data for this group. |
| 7. | Interventions | • Ezetimibe (+ high or medium intensity statin*)<br>• Inclisiran (+ high or medium intensity statin*)<br>• Alirocumab or evolocumab (+ high or medium intensity statin*) - assuming a class effect for PCSK9 monoclonal antibodies<br>• Combinations of the above interventions (for example, inclisiran + ezetimibe + high or medium intensity statin; or alirocumab/evolocumab + ezetimibe + high or medium intensity statin*)<br><br>Mode of delivery:<br>• Statin – oral<br>• Ezetimibe – oral<br>• Inclisiran – sub-cutaneous injection<br>• Alirocumab or evolocumab – sub-cutaneous injection<br>Pooling of interventions:<br>• Trials investigating ezetimibe, inclisiran or PCSK9 monoclonal antibodies will be pooled into these intervention groups regardless of what other lipid-lowering agents these are combined with as background treatment, if the additional agents are balanced between the intervention and control groups. |

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| | | ***Statin treatment**<br>Studies will be included if ≥50% of participants are receiving high or medium intensity statin therapy as background or randomised treatment (or report subgroup data for the group taking high or medium intensity statins).<br>• Studies with only 50-79% of participants receiving high- or medium-intensity statin therapy will be downgraded for intervention indirectness.<br>Note: high intensity statins are atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins are atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg. |
| 8. | Comparators | • Interventions compared with each other<br>• Placebo / no treatment<br>• High or medium intensity statin |
| 9. | Types of study to be included | Inclusion:<br>• RCTs<br>• Published systematic reviews, network meta-analyses (NMAs) and individual participant data (IPD) meta-analyses of RCT data.<br><br>Exclusion:<br>• Cross-over RCTs<br>• Non-randomised studies<br>• Conference abstracts |
| 10. | Other exclusion criteria | • Trials with aims other than CVD prevention or lipid lowering (e.g., for preventing chemotherapy toxicity).<br>• Non-English language studies.<br>• Follow-up < 3 months.<br>• Trials comparing adding an intervention to statin therapy with doubling the statin dose.<br>• Trials using statin agents or intervention doses not licenced or used in the UK (e.g., pitavastatin, lovastatin, simvastatin 80 mg). |
| 11. | Context | This will inform an update of the recommendation to aim for >40% reduction in non-HDL-C. |
| 12. | Primary outcomes (critical outcomes) | All outcomes are considered equally important for decision making and therefore have all been rated as critical:<br>• LDL-C (change from baseline: absolute change and % change) |

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| | | • Non-HDL-C (change from baseline: absolute change and % change)<br>• Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) (time-to-event)<br>  ○ Other definitions will be included, and indirectness will be discussed on a case-by-case basis<br>• Quality of life, any validated measure (continuous)<br><br>Treatment-related adverse effects (dichotomous):<br>• Myopathy/rhabdomyolysis<br>• New-onset diabetes<br>• Increased liver transaminases (>3-times upper-limit of normal)<br>• Cancer<br>• Gall-bladder related disease<br>• Injection site reactions<br>• Nausea<br>• Influenza<br><br>**Time points for data extraction:**<br>• Lipid level outcomes: 3-12 months (use the latest reported in this range).<br>• CV events and quality of life: 1 year and ≥2 years (use the latest reported). For studies that do not report at these time points, events reported at ≥6 but <12 months will be extracted but downgraded for indirectness.<br>• Adverse event outcomes: use the latest reported. |
| 13. | Data extraction (selection and coding) | EndNote will be used for reference management, citations and bibliographies.<br><br>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated for sifting.<br><br>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br><br>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). |

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| | | 10% of all evidence reviews are quality assured by a senior reviewer. This includes checking:<br>• papers were included/excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. |
| 14. | Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>• Randomised controlled trials: Cochrane RoB (2.0) |
| 15. | Strategy for data synthesis | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.<br>For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported in addition to risk ratios. Only one measure will be considered for decision making. This will be agreed with the committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence.<br>For continuous outcomes, if the same outcome is reported on different numerical scales these will be pooled where possible. If the studies use the same outcome measured in different units, this will be converted one to another using a simple multiplier. Otherwise, the standardised mean difference will be calculated if different scales are used for the same outcome across studies.<br>Heterogeneity between the studies in effect measures will be assessed using the $I^2$ statistic and visually inspected. An $I^2$ value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. |

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| | | GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.<br><br>Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome.<br><br>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/<br><br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.<br><br>WinBUGS will be used for network meta-analysis, which will be considered for the outcome of percentage change in LDL-C if possible, given the data identified. This will be discussed with the committee to determine whether it is appropriate and of added benefit to conduct a network meta-analysis given the available data once the pairwise analysis has been completed. | |
| 16. | Analysis of sub-groups | Sensitivity analyses will be carried out for the following subgroups if data are available (regardless of heterogeneity):<br>• baseline LDL-C: as reported by trials<br>• baseline non-HDL-C: as reported by trials<br>• statin intensity during trial period (medium; high; or mixed)<br><br>Subgroups that will be investigated if heterogeneity is present:<br>• Use of concomitant lipid-lowering therapies versus no background lipid-lowering therapies. | |
| 17. | Type and method of review | ☒ | Intervention |
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |

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| 18. | Language | English | | |
| 19. | Country | England | | |
| 20. | Anticipated or actual start date | December 2022 | | |
| 21. | Anticipated completion date | September 2023 | | |
| 22. | Stage of review at time of this submission | Review stage | Started | Completed |
| | | Preliminary searches | ☑ | ☑ |
| | | Piloting of the study selection process | ☑ | ☑ |
| | | Formal screening of search results against eligibility criteria | ☑ | ☐ |
| | | Data extraction | ☐ | ☐ |
| | | Risk of bias (quality) assessment | ☐ | ☐ |
| | | Data analysis | ☐ | ☐ |
| 23. | Named contact | Guideline Development Team NGC<br>E-mail: cvdescalationtherapy@nice.org.uk<br>Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) | | |
| 24. | Review team members | From NICE:<br>Serena Carville<br>Eleanor Samarasekera<br>Melina Vasileiou<br>Kate Lovibond<br>Alfredo Mariani<br>David Wonderling | | |

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| | | Lina Gulhane | |
| 25. | Funding sources/sponsor | Development of this systematic review is being funded by NICE. | |
| 26. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. | |
| 27. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10368 | |
| 28. | Other registration details | NA | |
| 29. | Reference/URL for published protocol | | |
| 30. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. | |
| 31. | Keywords | CVD; cardiovascular disease; secondary prevention; statin; ezetimibe; PCSK9; alirocumab; evolocumab; inclisiran; LDL-C; non HDL-C; target. | |
| 32. | Details of existing review of same topic by same authors | NA | |
| 33. | Current review status | ☒ | Ongoing |
| | | ☐ | Completed but not published |

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| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 34. | Additional information | NA | |
| 35. | Details of final publication | www.nice.org.uk | |