



# Surveillance report 2018 – Cardiovascular disease: risk assessment and reduction, including lipid modification (2014) NICE guideline CG181

Surveillance report

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## Surveillance decision

We will plan an update of the guideline on [cardiovascular disease](#). The update will focus on identifying and assessing cardiovascular disease (CVD) risk, and lipid modification therapy for the primary and secondary prevention of CVD.

During surveillance editorial or factual corrections were identified. Details are included in [appendix A](#): summary of evidence from surveillance.

## *Reason for the decision*

### Assessing the evidence

We found 214 studies through surveillance of this guideline.

Evidence that could affect recommendations was identified. We judged the impact of the new evidence on the following sections of the guideline with consideration of feedback from topic experts, including those who helped to develop the guideline:

### *Identifying and assessing cardiovascular disease risk*

NICE guideline CG181 recommends (1.1.8) using the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. The collective new evidence and topic expert feedback indicates that the inclusion of additional clinical variables in QRISK3 has a greater potential value to identify those at most risk of heart disease and stroke.

The new evidence suggests that QRISK3 performs well for people with type 1 diabetes and chronic kidney disease, and may help some people with these conditions to make an informed choice on whether to take statins. There is therefore a potential impact on recommendations 1.1.9 and 1.1.11, which advise against using risk tools for people with type 1 diabetes and chronic kidney disease, respectively. This may also have a consequential impact on recommendations 1.3.23, 1.3.24, and 1.3.27 for the treatment of people with these conditions.

There is also a potential need to amend recommendations 1.1.8 and 1.1.10 to advise the use of QRISK3 in place of QRISK2 because QRISK2 is due to be superseded by QRISK3 in 2018.

New evidence supporting the use of lifetime risk calculation to more accurately assess patients for lifestyle changes and eventually lipid lowering drugs was not specific to the UK population. However, the surveillance literature search strategy did not extend to all observational studies.

Additional stakeholder feedback indicating the need to review this area raises a potential impact on recommendation 1.1.4 to consider lifetime risk as an alternative to 10-year risk. This may also have consequential impacts on recommendation 1.1.26 for communicating risk and on recommendations 1.3.18 and 1.3.26 for primary prevention of CVD.

**Decision:** This area of the guideline should be updated.

### ***Lifestyle modifications for the primary and secondary prevention of CVD***

Topic expert advice highlighted that NHS Choices is not considered to be an authoritative source, and references to it in recommendations 1.2.1–1.2.4, 1.2.11 and 1.2.13 should be removed. There is a potential impact to review the wording of these recommendations, which was originally derived from NHS Choices.

**Decision:** This area of the guideline should be updated.

### ***Lipid modification therapy for the primary and secondary prevention of CVD***

NICE guideline CG181 advises that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. In developing the guideline, the committee were unable to judge if rosuvastatin 10 mg, 20 mg or 40 mg would be more effective than atorvastatin 80 mg in reducing CVD events. Given the considerably higher cost of using rosuvastatin at that time, it would have needed 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 committee were therefore unable to recommend the use of rosuvastatin.

However, the new evidence from an individual patient data (IPD) meta-analysis and a large RCT supporting rosuvastatin at doses of 10–40 mg, which constitute high intensity doses, has a potential impact on recommendation 1.3.18 due to the imminent expiry of the rosuvastatin patent and the drug's future availability in a generic form. There is a potential need to update the health economic model to review cost effectiveness in the light of changing acquisition costs.

Topic expert feedback indicating the need to review recommendation 1.3.28, for using high-intensity statins to achieve a percentage reduction rather than an absolute lipid target level, is supported by new IPD meta-analysis evidence. This indicates large inter-individual variation in lipid level reductions achieved from statins, and that the lower the LDL-C level attained by statins, the greater the clinical benefit accrued. There is a potential impact on this recommendation.

New evidence and topic expert feedback also indicates that statins, particularly rosuvastatin, are effective in reducing the risk of myocardial infarction and hospitalisation due to heart failure, but not death due to heart failure, in people with existing heart failure. There is a potential impact to consider specific recommendations in this context.

New evidence and expert feedback also indicates that patients with statin intolerance are now recognised as a group at increased CVD risk, and that there is a need to set out a clearer definition of statin intolerance. In developing the guideline, the committee decided that statin intolerance should be defined clinically as the inability to tolerate 3 different statins. The evidence reviews for NICE guideline CG181 did not find clear benefit for other drugs so the guideline committee were not able to recommend alternatives to statins. Instead the recommended approach was to seek specialist advice about other possible treatment options.

However, with the emergence of new alternative treatments, there is a potential need for NICE guideline CG181 to cross refer to the following technology appraisals, in the event of statin intolerance:

- [Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia \(2016\) NICE technology appraisal guidance 394](#)
- [Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia \(2016\) NICE technology appraisal guidance 393](#)
- [Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia \(2016\) NICE technology appraisal guidance 385](#)

A large ongoing trial, [ODYSSEY Outcomes](#), was also highlighted by topic experts and is likely to publish in 2018. The trial is evaluating efficacy and safety of alirocumab, in patients with well-documented statin intolerance and moderate to very high CVD risk. This will be monitored for publication by NICE.

Topic experts also noted that the NICE technology appraisals on alirocumab and evolocumab are applicable to patients with inadequate control of non-HDL-cholesterol or LDL-cholesterol, who are on maximum tolerated statin therapy. Baseline pre-treatment LDL-Cholesterol and CVD risk determine eligibility. These interventions and risk assessments are within the scope of NICE guideline CG181 and it was advised by topic experts that these should be linked to the guideline recommendations as part of an update.

**Decision:** This area of the guideline should be updated.

All other evidence was deemed consistent with current recommendations.

## Equalities

No equalities issues were identified during the surveillance process.

## Overall decision

After considering all the evidence and views of topic experts, we decided that a partial update is necessary for this guideline.

See [how we made the decision](#) for further information.

## Commentary on selected evidence

With advice from topic experts we selected 1 study for further commentary.

### *Identifying and assessing CVD risk: risk tools for formal risk assessment*

We selected the cohort study by [Hippisley-Cox et al. \(2017\)](#) for a full commentary because it is directly relevant to the existing recommended risk tool, QRISK2, has a potential impact on the guideline and included a large and representative NHS sample.

### What the guideline recommends

NICE's guideline on cardiovascular disease (CVD) recommends using the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. It advises against the use of a risk assessment tool to assess CVD risk in people:

- with type 1 diabetes
- with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m<sup>2</sup> and/or albuminuria
- who are at high risk of developing CVD because of familial hypercholesterolaemia
- who have pre-existing CVD.

The guideline also recommends that people with an estimated 10-year risk of CVD of 10% or more should be prioritised for a full formal risk assessment, and should be offered atorvastatin 20 mg for primary prevention of CVD.

### Methods

The prospective cohort study by Hippisley-Cox (2017) aimed to develop and validate an updated version of the QRISK tool, QRISK3, to enable estimation of 10-year CVD risk for men and women. General practices in England that had been using the EMIS computer system for at least one year were included. Patients were excluded if they:

- were not aged between 25 and 84 years
- had no postcode related Townsend score (indicating absence of deprivation data, homelessness or no permanent residence)

- had pre-existing CVD
- were using prescribed statins at study recruitment.

A total of 981 practices with 7.89 million patients in England were used to develop the risk scores and 328 practices with 2.67 million patients were used to validate the scores. To establish separate 10-year risk equations for men and women, Cox proportional hazards models were used in the derivation cohort. CVD, defined as 'a composite outcome of coronary heart disease, ischaemic stroke, or transient ischaemic attack', was the primary outcome.

Risk factors in the new algorithm included those already in QRISK2 and several additional new ones:

- chronic kidney disease
- a measure of systolic blood pressure variability
- migraine
- corticosteroid use
- systemic lupus erythematosus
- second generation 'atypical' antipsychotic use
- diagnosis of severe mental illness
- diagnosis of HIV/AIDS
- diagnosis or treatment of erectile dysfunction in men.

Three models were developed; model A contained the same variables as the 2017 version of QRISK2. Models B and C included the additional variables that met the inclusion criteria but differed in that model B did not include the standard deviation of serial systolic blood pressure values, whereas model C did.

Patients were classified as being at high risk of CVD if their 10-year risk was 10% or greater, as recommended by NICE's guideline on CVD.



## Results

In total, there were 363,565 incident cases of CVD arising from 50.8 million person years of observation, during a median follow up of 4.4 years.

In terms of variation in time to diagnosis of CVD, the QRISK3 algorithm accounted for 54.8% of the variation in men and 59.6% of the variation in women for model A. Models B and C performed similarly.

In terms of calibration, defined by comparing the mean predicted risks at 10-years with the observed risk by 10th of predicted risk, the results showed that:

- The mean predicted risk was 6.4% in men, with an observed 10-year risk of 7.5% (95% confidence interval [CI] 7.5% to 7.6%).
- The mean predicted risk was 4.7% in women, with an observed 10-year risk of 5.8% (95% CI 5.8% to 5.9%).
- The models appeared to be well calibrated, with the mean predicted risks and the observed risks corresponding closely within each model and in each age group, except in those aged 25–39 where mean observed risks were marginally lower than the predicted risks.

HIV/AIDS was the only additional new risk factor which didn't meet the inclusion criteria, as it was not statistically significant.

Overall performance of the updated QRISK3 algorithms was found to be non-inferior to the QRISK2 algorithms.

## Strengths and limitations

### *Strengths*

- Since the cohort in the study was population based, it was representative of the NHS population. This minimised the risk of selection bias.
- The study included a very large sample size and used an established approach for analysing large data sets, by randomly splitting data at the general practice rather than the individual level.

- The study is directly relevant and applicable to the QRISK2 assessment tool that is currently recommended by the guideline, and incorporates additional variables highlighted by the guideline as important risk factors for CVD.

### **Limitations**

- The authors acknowledged the limitation of lack of formal adjudication of diagnoses, which may have led to classification bias.
- The study was limited by the potential for bias owing to missing data. The authors used multiple imputations to replace missing values for body mass index, systolic blood pressure and its standard deviation, serum cholesterol, high density lipoprotein cholesterol, and smoking status.
- The validation study was dependent on data provided by the authors, and an independent study would be a more stringent test of the risk score.

### **Impact on guideline**

The guideline highlighted numerous conditions associated with increased CVD risk that may not be fully captured by QRISK2, including stage 3 kidney disease, systemic lupus erythematosus, severe mental illness, and use of atypical antipsychotics or corticosteroids. The collective new evidence and topic expert feedback indicates that the inclusion of these additional variables in QRISK3 has the potential to enable more accurate assessment of subgroups of patients with specific conditions. Incorporating additional data from the electronic health record may also improve CVD risk stratification.

The new evidence suggests that QRISK3 performs well for people with type 1 diabetes and chronic kidney disease, and may help some people with these conditions to make an informed choice on whether to take statins. There is therefore a potential impact on recommendations 1.1.9 and 1.1.11 to review the advice against using risk tools for people with type 1 diabetes and chronic kidney disease, respectively. This may also have a consequential impact on recommendations for primary prevention (see recommendations [1.3.23](#), [1.3.24](#), and [1.3.27](#)) for people with these conditions, although some topic expert feedback indicated that recommendations for people with chronic kidney disease should remain unchanged.

There is a potential need to amend the guideline recommendations ([1.1.8](#) and [1.1.10](#)) to advise the use of QRISK3 in place of QRISK2 because QRISK2 is due to be superseded by QRISK3 in 2018.

## How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of NICE's guideline on cardiovascular disease (NICE guideline CG181) in 2014.

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

## *Evidence*

We found 198 studies in a search for systematic reviews and randomised controlled trials published between 11 November 2013 and 15 March 2017. Observational studies were considered for review questions where they were included in the original protocol. We also included 15 relevant studies from a total of 35 identified by members of the guideline committee who originally worked on this guideline. A further study was identified through post-publication communications.

From all sources, we considered 214 studies to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See [appendix A](#): summary of evidence from surveillance for details of all evidence considered, and references.

## *Views of topic experts*

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

## *Views of stakeholders*

Stakeholders commented on the decision to update the guideline. Overall, 17 stakeholders commented. See [appendix B](#) for stakeholders' comments and our responses.

Seventeen stakeholders commented on the proposal to update the guideline: 14 agreed with the decision and 3 noted that they had no comments on the proposals. There was a representative mix

of patient organisations, professional bodies, private sector institutions and providers of services. These included the Association of British Clinical Diabetologists, Royal College of Nursing, clinical commissioning groups, Public Health England and HEART UK.

Several comments suggested changes to make to the review questions proposed for updating. These included a suggestion to review the recommendation relating to target based statin treatment, which will be considered in the update process. In addition, extensions to the scope were suggested, some of which were outside the remit of the guideline.

See [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual for more details on our consultation processes.

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