

## Cardiovascular risk assessment and lipid modification:

NICE guideline

### INTRODUCTION

The National Institute for Health and Care Excellence (NICE) has updated its guidance on cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (CVD).<sup>1</sup> This article discusses the main recommendations and the implications of the update for general practice. New evidence on risk assessment tools and on statins and reduction in the cost of statins has resulted in significant changes to the level of risk at which treatment is recommended, and on the choice and dose of statins. The new guideline also incorporates guidance on lipid modification for people with type 1 and type 2 diabetes and with chronic kidney disease (CKD). See Box 1 for a summary of the main points of the revised lipid-modification guideline.

### GUIDANCE

#### Risk assessment

The guideline recommends the use of QRISK<sup>®2</sup> as a cardiovascular risk assessment tool for primary prevention, including people with type 2 diabetes. In both these groups the threshold for consideration of treatment with statins is >10% risk of CVD events in 10 years. Healthcare professionals are reminded that any risk assessment tool provides only an approximate value of CVD risk and interpretation of risk scores should always reflect informed clinical judgement. The guideline does not recommend a risk assessment tool for use for people with type 1 diabetes or for people with CKD. Although current risk assessment tools are not validated in people with these conditions, both groups are at higher risk of developing CVD. QRISK2 does provide a tick box to incorporate CKD but this should not be used. This tickbox relates to specific renal diagnosis rather than estimated glomerular filtration rate (eGFR) levels. Risk assessment tools should

also not be used in people with familial hypercholesterolaemia or other inherited disorders of lipid metabolism.

#### Use of non-HDL cholesterol

The guideline recommends the use of non-HDL (high-density lipoprotein) cholesterol rather than LDL (low density lipoprotein) cholesterol when measuring and monitoring lipid levels, and no longer requires fasting samples. Non-HDL cholesterol is less complex to calculate than LDL; the latter is calculated indirectly by subtracting HDL-cholesterol and fasting triglyceride levels, while the non-HDL calculation simply involves subtracting HDL from non-fasting total cholesterol (TC) levels. This has also been shown to give a better estimate of treatment effect and of cardiovascular risk reduction than LDL-cholesterol.<sup>2</sup> Its use will require a change in laboratory reporting and a change in the way clinicians and patients use cholesterol values.

#### Familial lipid disorders

Common secondary causes of hyperlipidaemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease, and nephrotic syndrome) should be excluded before familial lipid disorders are considered. In line with the NICE familial hypercholesterolaemia guideline,<sup>3</sup> the possibility of familial hypercholesterolaemia in those with TC concentration >7.5 mmol/L and family history of premature coronary heart disease should be considered. The guideline also recommends that those with TC >9.0 mmol/L or non-HDL cholesterol >7.5 mmol/L should be referred for specialist assessment irrespective of family history. Thresholds were based on expert opinion.

### INTERVENTIONS

#### Treatment with lipid lowering drugs

The guideline<sup>1</sup> divides statin drugs and dosages into three groups: low, medium, and high-intensity statins (Table 1).<sup>4</sup>

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## Box 1. Summary of the updated NICE lipid-modification guideline

### Identifying high risk systematically

- Prioritise those people for formal risk assessment based on an estimate of risk from information already known and recorded in the electronic medical record.
- In those with an estimated 10-year risk of a CVD event >10% prioritise for full formal risk assessment. This is a change from the previous 20% risk threshold and will involve considerably more people.
- Use the QRISK2 risk assessment tool for formal risk assessment for people age <84 years. This is a change from the choice between QRISK2 and Framingham-based assessment, previously recommended. QRISK2 is available on primary care computer systems.
- Also use QRISK2 for those people with type 2 diabetes. This is a change from previous guidance which recommended UKPDS.
- Do not use QRISK2 for people with type 1 diabetes. Because of high CVD risk, all adults with type 1 diabetes should be considered for statin therapy.
- Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> and/or albuminuria. It is known that these people already have high risk of CVD.
- Do not use QRISK2 if there is high risk of developing CVD because of familial hypercholesterolaemia or other inherited disorders of lipid metabolism. These people need specialist assessment and guidance on treatment.
- There are some groups of people who have other conditions where risk assessment will underestimate risk. Such as those with: HIV on treatment; serious mental health problems; taking antipsychotics, corticosteroids, or immunosuppressants; and systematic lupus erythematosus or other systemic inflammatory disorders.
- People will need more time set aside to discuss their risk and treatment options. There will be a need to explore their current understanding and involve them in a shared management plan. In view of the numbers involved and the importance of informed patient choice, this may require increasing time and resources, plus additional training for healthcare workers.

### Lifestyle advice

- People should be offered the opportunity of further CVD assessment after attempting to modify their risk through lifestyle, if they wish. In some patients early treatment with statin may be preferred.
- Dietary advice needs to be carefully provided, such as that available from NHS Choices.
- Physical activity advice needs to be in line with national guidance.
- Provide smoking cessation advice, support, and referral where appropriate.
- Do not advise use of plant stanols or sterols to modify diet. This includes people with type 2 diabetes.

### When to refer, when to start statins

- Estimate risk from TC and HDL-cholesterol. The best estimate of risk and treatment effect is from non-HDL cholesterol. That is, TC minus HDL-cholesterol.
- Before starting therapy for primary prevention take at least one further test for a full lipid profile, including TC, HDL-cholesterol, and triglycerides. The use of fasting samples is no longer necessary (unless initial triglyceride levels are >10 mmol/L).
- Specialist assessment should be arranged if TC is >9.0 mmol/L or non-HDL cholesterol is >7.5 mmol/L.
- Refer for urgent specialist review if triglycerides are >20 mmol/L. If triglycerides are >10 mmol/L after several measurements, also consider referral.
- Offer people opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle.
- Offer atorvastatin 20 mg daily for primary prevention of CVD in those with >10% 10-year risk of CVD, including in those with type 2 diabetes and 'significant' CKD. This is a change from offering simvastatin 40 mg daily. It is based on the change in drug prices and an analysis of safety and cost effectiveness of higher intensity treatment.
- Consider atorvastatin 20mg daily in people aged >85 years taking into account informed patient preference, comorbidities, polypharmacy, general frailty, and life expectancy. This is also a change and requires an assessment of potential for benefit in older people.
- For secondary prevention in people with established CVD start treatment with atorvastatin 80 mg daily. Use a lower dose if there is a potential for drug interactions, high risk of adverse effects, or patient preference. This may require review of patients with history of angina, stroke, TIA, peripheral vascular disease, or myocardial infarction, at their annual medication check, and change of statin to atorvastatin 80 mg.

### Monitoring treatment effect and dose increases

- Measure TC and HDL-cholesterol after 3 months of treatment. Aim for a 40% reduction in non-HDL cholesterol. Consider increasing the dose up to 80 mg atorvastatin daily, if the 40% reduction is not achieved and the person is judged to be at higher risk because of comorbidities, risk score, or clinical judgement. This is a move away from the previous single dose strategy of simvastatin 40mg daily for people without diabetes or cardiovascular disease, and the previous cholesterol targets set for those with type 2 diabetes.
- Creatine kinase should be measured in those who develop muscle symptoms such as pain, tenderness, or weakness. If >5 times the upper limit of normal the statin should be stopped. There is not normally a need for creatine kinase tests before starting a statin unless there are muscle symptoms.
- Provide annual medication reviews for all those taking statins. For those stable on low- or moderate-intensity statins discuss the likely benefits and potential risks of changing to high intensity statin. Consider an annual non-fasting test for non-HDL cholesterol. This was not thought necessary previously for primary prevention but is now a consideration to help with adherence and to inform the discussion and related lifestyle advice.

### Interventions not advised or offered

- Do not offer fibrates routinely in any patient group. The previous NICE guidance was to offer fibrates in type 2 diabetes with high triglycerides, or statin intolerance.
- Do not offer nicotinic acid (niacin) to prevent CVD.
- Do not offer bile sequestrants (anion exchange resins) to prevent CVD.
- Do not offer omega-3 fatty acid compounds to prevent CVD. These may have a role in specialist management, for example in hypertriglyceridaemia. This is a change from previous guidance which suggested a place for this treatment following myocardial infarction.
- The place of ezetimibe is covered in separate guidance.

This grouping was based on published evidence of the effects of statins and on the consensus of the guideline group. Looking at the clinical effectiveness of these drugs, in particular the high-intensity statins, the greatest reduction in cardiovascular events was associated with a 40% reduction in LDL-cholesterol, which is proportional to the same reduction in non-HDL levels.

Analysis developed for the guideline found that it was cost effective to offer high intensity statins, up to a dose of atorvastatin 80 mg daily for all groups, including people being treated for primary prevention. The threshold for treatment for primary prevention is 10% using QRISK2 – based on a cost-effectiveness model which included the cost of drugs and of the assessment and monitoring of the patient and possible adverse drug effects. When the 2008 guideline was developed these doses were cost effective only in people at highest risk (those with post-acute coronary syndrome) because of the cost of statins at that time. A 40% reduction in LDL (or non-HDL) may be achieved with atorvastatin 20 mg in many people. Individuals respond differently to drugs and there is concern about more adverse events at higher doses. Hence, the guideline group consensus was to recommend atorvastatin 20 mg for initiation of statins in primary prevention, including people with type 1 and type 2 diabetes. Titration to higher doses may be appropriate and considered depending on response to treatment. The guideline recommends using atorvastatin 80 mg for people for secondary prevention as these people are at highest risk. Because of altered drug excretion, people with CKD should be started on atorvastatin 20 mg whether they are being treated for primary or secondary prevention, and the dose titrated up according to response. Doses of atorvastatin >20 mg should not be used for people with severe CKD (eGFR <30 mL/min/1.73 m<sup>2</sup>) without specialist guidance.

### Monitoring

The guidance allows for all people taking statins to take a maximum tolerated dose of statin (atorvastatin <80 mg daily), based on informed choice. Repeated cholesterol levels are not strictly necessary once a person is taking their maximum tolerated dose. The guideline recognises that people take an interest in their cholesterol, highlights the potential usefulness of checking cholesterol levels to inform discussions about adherence, and therefore suggests consideration of an annual cholesterol review.

**Table 1. Grouping of statins used in this guideline<sup>1</sup>**

Statin, mg/day	Reduction in low-density lipoprotein cholesterol, %				
	5	10	20	40	80
Fluvastatin	–	–	21 <sup>a</sup>	27 <sup>a</sup>	33 <sup>a</sup>
Pravastatin	–	20 <sup>a</sup>	24 <sup>a</sup>	29 <sup>a</sup>	–
Simvastatin	–	27 <sup>a</sup>	32 <sup>b</sup>	37 <sup>b</sup>	[42] <sup>c,d</sup>
Atorvastatin	–	37 <sup>b</sup>	43 <sup>c</sup>	49 <sup>c</sup>	55 <sup>c</sup>
Rosuvastatin	38 <sup>b</sup>	43 <sup>c</sup>	48 <sup>c</sup>	53 <sup>c</sup>	–

<sup>a</sup>20%–30%: low intensity. <sup>b</sup>31%–40%: medium intensity. <sup>c</sup>>40%: high intensity. <sup>d</sup>Advice from the MHRA: there is an increased risk of myopathy associated with high dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients 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 risks.

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## Other interventions

Fibrates, anion-exchange resins and nicotinic acid are not recommended by the guideline because of the lack of evidence of beneficial effect on cardiovascular outcomes.

## DISCUSSION

The publication of the guideline resulted in widespread debate in the media, and between healthcare professionals, particularly about the move from the >20% 10-year risk threshold to a >10% threshold.<sup>5</sup> Similar debate has taken place in the US where the recommended threshold is even lower.<sup>6</sup> The main concerns relate to 'mass medication' and to tolerability and safety of statins in those without disease, with concern that they may cause more harm than good in low-risk people. Recent published evidence from both trial data and observational studies supports the NICE assessment of the relative safety of statins.<sup>7,8</sup> The guideline group considered that there was significant potential to prevent and delay subsequent cardiovascular events on a population basis. An estimate of benefit is the prevention of 8000 deaths in 3 years and over 28 000 heart attacks and 16 000 strokes annually in England and Wales.<sup>9</sup> From an individual perspective it has been estimated that for primary prevention, at around the 10% level of risk, 74 people need to take a statin for 5 years to prevent one cardiovascular event (number needed to treat) whereas the number needed to harm for significant harm is many times higher (>500).<sup>10</sup> This is a level of benefit and risk similar to treating mild to moderate hypertension.

The decision to take statins for primary prevention will depend on patient values and preference, as does the choice to increase the dose if 40% reduction in non-HDL cholesterol is not seen. It may be that many people wish to persist with risk-reducing

lifestyle changes alone rather than start statins, but the guideline group believed that both clinician and patient should be informed of the potential benefits and risk of treatment. The guideline presents an opportunity for GPs to explain risk to their patients and help them make informed decisions. Patient-centred care and choice are fundamental components of this approach. NICE has developed a decision aid to help with these discussions (available on NICE website).

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