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Lipid modification

Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

NICE clinical guideline 67
Developed by the National Collaborating Centre for Primary Care

NICE clinical guideline 67
Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Ordering information
You can download the following documents from www.nice.org.uk/CG067
- The NICE guideline (this document) – all the recommendations.
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – information for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:
- N1574 (quick reference guide)
- N1575 ('Understanding NICE guidance').

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death in England and Wales. In 2005, CVD was the cause of one in three deaths, accounting for 124,000 deaths; 39,000 of those who died were younger than 75[1]. For every one fatality, there are at least two people who have a major non-fatal CVD event.

CVD predominantly affects people older than 50 and age is the main determinant of risk. Apart from age and sex, three modifiable risk factors – smoking, raised blood pressure and raised cholesterol – make a major contribution to CVD risk, particularly in combination. These account for 80% of all cases of premature coronary heart disease (CHD)[2]. The risk of a future CVD event can be calculated from these risk factors and people at highest risk can be identified. There are also major identifiable population groups at particular risk. CVD is strongly associated with low income and social deprivation, the lifetime burden is greater in women because of their longevity and their increased risk of stroke over the age of 75[3]. South Asian men are more likely to develop CVD at a younger age. Family history of premature CHD identifies an important group that contains people with a genetic predisposition.

Blood cholesterol has a log–linear relationship to the risk of CHD and is a key modifiable risk factor. It is estimated that in high-income countries blood cholesterol levels in excess of 3.8 mmol/litre are responsible for more than 50% of CVD events[4]. Blood cholesterol can be reduced by dietary change, physical activity and drugs. This guideline addresses the identification of those at high risk, and the modification of lipids in these people and people with established CVD. Treatment should be aimed at reducing overall risk. It is

[1] www.statistics.gov.uk/downloads/theme_health/hsq33web.pdf
[2] Emberson JR, Whincup PH, Morris RW et al. (2003) Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. European Heart Journal 24: 1719–26.
[3] Seshadri S, Beiser A, Kelly-Hayes M et al. (2006) The lifetime risk of stroke: estimates from the Framingham Study. Stroke 37: 345–50.
[4] World Health Organization (2002) The world health report 2002. Reducing risks, promoting healthy life. World Health Organisation. www.who.int/whr/2002/en

important to stress that a multifactorial approach that addresses all risk factors yields most benefit. This is because the effect of modifying several risk factors is multiplicative.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

In February 2010 NICE Guidance Executive agreed to withdraw the recommendation that the Framingham risk equation should be the equation of choice for assessment of CVD risk, but agreed that it should be considered as one of the possible equations to use. Recommendations relating specifically to the use and modification of the Framingham risk equation have been moved to appendix D. Consider these recommendations when using the Framingham risk equation for assessment of CVD risk.

Patient-centred care

This guideline offers best practice advice on the care of adults at high risk of developing CVD or with established CVD.

Treatment and care should take into account patients' needs and preferences. People at high risk of CVD or with established CVD should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If a person does not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk). Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Key priorities for implementation

Primary prevention of CVD

- For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged 40–74 who are likely to be at high risk.
- People should be prioritised on the basis of an estimate of their CVD risk before a full formal risk assessment. Their CVD risk should be estimated using CVD risk factors already recorded in primary care electronic medical records.
- Risk equations should be used to assess CVD risk.
- People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:
  - presents individualised risk and benefit scenarios
  - presents the absolute risk of events numerically
  - uses appropriate diagrams and text.

  (See www.npci.org.uk)
- Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimised if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:
  - smoking status
  - alcohol consumption
  - blood pressure (see 'Hypertension', NICE clinical guideline 34)
  - body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)
  - fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)
  - fasting blood glucose
  - renal function

  - liver function (transaminases)
  - thyroid-stimulating hormone (TSH) if dyslipidaemia is present.
- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).[5]
- Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

Secondary prevention of CVD

- For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:
  - smoking status
  - alcohol consumption
  - blood pressure (see 'Hypertension', NICE clinical guideline 34)
  - body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)
  - fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)
  - fasting blood glucose
  - renal function
  - liver function (transaminases)
  - thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

[5] This recommendation has been taken from ‘Statins for the prevention of cardiovascular events’, NICE technology appraisal 94. See www.nice.org.uk/TA094

- Statin therapy is recommended for adults with clinical evidence of CVD.[6]
- People with acute coronary syndrome should be treated with a higher intensity statin[7]. Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.
- Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.
- In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin[7] should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

[6] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

[7] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

1 Guidance

The following guidance is based on the best available evidence. The full guideline (www.nice.org.uk/CG67/FullGuideline) gives details of the methods and the evidence used to develop the guidance.

1.1 Identification and assessment of CVD risk

Identifying people for full formal risk assessment

1.1.1 For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged 40–74 who are likely to be at high risk.

1.1.2 People should be prioritised on the basis of an estimate of their CVD risk before a full formal risk assessment. Their CVD risk should be estimated using CVD risk factors already recorded in primary care electronic medical records.

1.1.3 People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis.

1.1.4 People should be prioritised for a full formal risk assessment if their estimated 10-year risk of CVD is 20% or more.

1.1.5 Healthcare professionals should discuss the process of risk assessment with the person identified as being at risk, including the option of declining any formal risk assessment.

1.1.6 Opportunistic assessment should not be the main strategy used in primary care to identify CVD risk in unselected people.

Full formal risk assessment

Some recommendations from this section that relate specifically to the use and modification of the Framingham risk equation have been moved to appendix D. This follows the decision of NICE Guidance Executive in February 2010 that the Framingham risk equation should no longer be

considered the equation of choice for the assessment of CVD risk but should be considered one of the possible equations to use.

1.1.7 Healthcare professionals should always be aware that all CVD risk estimation tools can provide only an approximation of CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement.

1.1.8 Risk equations should be used to assess CVD risk[8].

1.1.9 This recommendation relates specifically to the use or modification of the Framingham risk equation and has been moved to appendix D.

1.1.10 Risk equations should not be used for people with pre-existing:

- CHD or angina
- stroke or transient ischaemic attack
- peripheral vascular disease. [8]

1.1.11 Risk equations should not be used for people who are already considered at high risk of CVD because of:

- familial hypercholesterolaemia[9] or other monogenic disorders of lipid metabolism
- diabetes, see 'Type 2 diabetes: the management of type 2 diabetes (update)' (NICE clinical guideline 66). [8]

1.1.12 This recommendation relates specifically to the use or modification of the Framingham risk equation and has been moved to appendix D.

[8] This recommendation has been modified in line with decision taken by NICE Guidance Executive in February 2010 that the Framingham risk equation should no longer be considered the equation of choice for assessment of CVD risk, but should be considered as one of the possible equations to use.

[9] See 'Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

1.1.13 When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold of 20%[10], healthcare professionals should consider other factors that:

- may predispose the person to premature CVD, and
- may not be included in calculated risk scores.

1.1.14 Ethnicity, body mass index and family history of premature heart disease should be routinely recorded in medical records.

1.1.15 This recommendation relates specifically to the use or modification of the Framingham risk equation and has been moved to appendix D.

1.1.16 This recommendation relates specifically to the use or modification of the Framingham risk equation and has been moved to appendix D.

1.1.17 This recommendation relates specifically to the use or modification of the Framingham risk equation and has been moved to appendix D.

1.1.18 Socioeconomic status should be considered when using CVD risk scores to inform treatment decisions.

1.1.19 Severe obesity (body mass index greater than 40 kg/m^2) affects CVD risk and should be considered when using risk scores to inform treatment decisions (see 'Obesity', NICE clinical guideline 43).

1.1.20 CVD risk may be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Clinical judgement should be used to decide on further treatment of risk factors in people who are below the 20% CVD risk threshold.

[10] This threshold is from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

1.1.21 CVD risk scores may not be appropriate as a way of assessing risk in people who are at increased CVD risk because of underlying medical conditions or treatments. These include people treated for HIV or with antipsychotic medication, people with chronic kidney disease[11] and people with autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.

1.1.22 People aged 75 or older should be considered at increased risk of CVD, particularly people who smoke or have raised blood pressure. They are likely to benefit from statin treatment. Assessment and treatment should be guided by the benefits and risks of treatment, informed preference and comorbidities that may make treatment inappropriate.

Lipid measurement

1.1.23 Both total and HDL cholesterol should be measured to achieve the best estimate of CVD risk[12].

1.1.24 Before starting lipid modification therapy for primary prevention, people should have at least one fasting lipid sample taken to measure total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

1.1.25 People in whom familial hypercholesterolaemia or other monogenic disorders are suspected because of a combination of clinical findings, lipid profiles and family history of premature CHD should be considered for further investigation and specialist review[13].

1.1.26 People with severe hyperlipidaemia should be considered for further investigation and/or specialist review.

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[11] See 'Chronic kidney disease' NICE clinical guideline 73). Available from www.nice.org.uk/uidance/CG73

[12] This recommendation has been modified in line with decision taken by NICE Guidance Executive in February 2010 that the Framingham risk equation should no longer be considered the equation of choice for assessment of CVD risk, but should be considered as one of the possible equations to use.

[13] See 'Identification and management of familial hypercholesterolaemia' (NICE clinical guideline 71). Available from www.nice.org.uk/guidance/CG71

1.2 Communication about risk assessment and treatment

1.2.1 Healthcare professionals should use everyday, jargon-free language to communicate information on risk. If technical terms are used, these should be clearly explained.

1.2.2 Adequate time should be set aside during the consultation to provide information on risk assessment and to allow any questions to be answered. Further consultation may be required.

1.2.3 The discussion relating to the consultation on risk assessment and the person's decision should be documented.

1.2.4 People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:

- presents individualised risk and benefit scenarios
- presents the absolute risk of events numerically
- uses appropriate diagrams and text.

(See www.npci.org.uk)

1.2.5 In order to encourage the person to participate in reducing their CVD risk, the healthcare professional should:

- find out what, if anything, the person has already been told about their CVD risk and how they feel about it
- explore the person's beliefs about what determines future health (this may affect their attitude to changing risk)
- assess their readiness to make changes to their lifestyle (diet, physical activity, smoking and alcohol consumption), to undergo investigations and to take medication
- assess their confidence in making changes to their lifestyle, undergoing investigations and taking medication
- inform them of potential future management based on current evidence and best practice

- involve them in developing a shared management plan
- check with them that they have understood what has been discussed.

1.2.6 People should be informed that CVD risk equations can only provide an estimate of risk. However, the likelihood of misclassification is reduced as the estimated CVD risk increases above the threshold of 20% risk over 10 years.

1.2.7 If the person's CVD risk is considered to be at a level that merits intervention but they decline the offer of treatment, they should be advised that their CVD risk should be considered again in the future.

1.3 Lifestyle modifications for the primary and secondary prevention of CVD

Cardioprotective diet

1.3.1 People at high risk of or with CVD should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by monounsaturated and polyunsaturated fats. It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet for further practical advice.

1.3.2 People at high risk of or with CVD should be advised to eat at least five portions of fruit and vegetables per day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk

1.3.3 People at high risk of or with CVD should be advised to consume at least two portions of fish per week, including a portion of oily fish. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet

1.3.4 Pregnant women should be advised to limit their oily fish to no more than two portions per week. Further information and advice on oily fish consumption can be found at www.eatwell.gov.uk/healthydiet

1.3.5 People should not routinely be recommended to take omega-3 fatty acid supplements for the primary prevention of CVD.

Plant stanols and sterols

1.3.6 People should not routinely be recommended to take plant sterols and stanols for the primary prevention of CVD.

Physical activity

1.3.7 People at high risk of or with CVD should be advised to take 30 minutes of physical activity a day, of at least moderate intensity, at least 5 days a week, in line with national guidance for the general population[14].

1.3.8 People who are unable to perform moderate-intensity physical activity at least 5 days a week because of comorbidity, medical conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity.

1.3.9 Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling (see 'At least five a week')[14].

1.3.10 People should be advised that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions (see 'At least five a week')[14].

1.3.11 Advice about physical activity should take into account the person's needs, preferences and circumstances. Goals should be agreed and the person should be provided with written information about

[14] Department of Health (2004) At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer. London: Department of Health. Available from www.dh.gov.uk

the benefits of activity and local opportunities to be active, in line with 'Physical activity' (NICE public health intervention guidance 2).

Combined interventions (diet and physical activity)

1.3.12 Advice on diet[15] and physical activity[16] should be given in line with national recommendations.

Weight management

1.3.13 People at high risk of or with CVD who are overweight or obese should be offered appropriate advice and support to work towards achieving and maintaining a healthy weight, in line with 'Obesity' (NICE clinical guideline 43).

Alcohol consumption

1.3.14 Alcohol consumption for men should be limited to up to 3–4 units a day. For women, alcohol consumption should be limited to up to 2–3 units a day. People should avoid binge drinking. Further information can be found at www.eatwell.gov.uk/healthydiet.

Smoking cessation

1.3.15 All people who smoke should be advised to stop, in line with 'Smoking cessation services' (NICE public health guidance 10).

1.3.16 People who want to stop smoking should be offered support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services).

1.3.17 If a person is unable or unwilling to accept a referral to an intensive support service they should be offered pharmacotherapy in line with 'Smoking cessation services' (NICE public health guidance 10) and 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123).

[15] See www. eatwell.gov.uk/healthydiet
[16] Department of Health (2004) At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer. London: Department of Health. Available from www.dh.gov.uk

1.4 Drug therapy for the primary and secondary prevention of CVD

1.4.1 When considering lipid modification therapy in primary and secondary prevention, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality.

Drug therapy for primary prevention

1.4.2 Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimised if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- smoking status
- alcohol consumption
- blood pressure (see 'Hypertension', NICE clinical guideline 34)
- body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)
- fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)
- fasting blood glucose
- renal function
- liver function (transaminases)
- thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

Statins for primary prevention

1.4.3 Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is

not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups).[17]

1.4.4 The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy.[17]

1.4.5 If statin treatment is appropriate, it should be offered as soon as practicable after a full risk factor assessment.

1.4.6 When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).[17]

1.4.7 Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

1.4.8 Higher intensity statins[18] should not routinely be offered to people for the primary prevention of CVD.

1.4.9 A target for total or LDL cholesterol is not recommended for people who are treated with a statin for primary prevention of CVD.

1.4.10 Once a person has been started on a statin for primary prevention, repeat lipid measurement is unnecessary. Clinical judgement and patient preference should guide the review of drug therapy and whether to review the lipid profile.

[17] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094

[18] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

Fibrates for primary prevention

1.4.11 Fibrates should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, fibrates may be considered.

Nicotinic acid for primary prevention

1.4.12 Nicotinic acid should not be offered for the primary prevention of CVD.

Anion exchange resins for primary prevention

1.4.13 Anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, an anion exchange resin may be considered.

Ezetimibe for primary prevention

1.4.14 People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132).

Combination therapy for primary prevention

1.4.15 The combination of an anion exchange resin, fibrate or nicotinic acid with a statin should not be offered for the primary prevention of CVD.

1.4.16 The combination of a fish oil supplement with a statin should not be offered for the primary prevention of CVD.

Drug therapy for secondary prevention

1.4.17 For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors. Blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidaemia should be treated. Assessment should include:

- smoking status
- alcohol consumption
- blood pressure (see 'Hypertension', NICE clinical guideline 34)

- body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43)
- fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available)
- fasting blood glucose
- renal function
- liver function (transaminases)
- thyroid-stimulating hormone (TSH) if dyslipidaemia is present.

1.4.18 If a person has acute coronary syndrome, statin treatment should not be delayed until lipid levels are available. A fasting lipid sample should be taken about 3 months after the start of treatment.

Statins for secondary prevention

1.4.19 Statin therapy is recommended for adults with clinical evidence of CVD.[19]

1.4.20 The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy.[20]

1.4.21 When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).[20]

1.4.22 People with acute coronary syndrome should be treated with a higher intensity statin[21]. Any decision to offer a higher intensity statin should take into account the patient's informed preference,

[19] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094
[20] This recommendation has been taken from 'Statins for the prevention of cardiovascular events', NICE technology appraisal 94. See www.nice.org.uk/TA094
[21] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

comorbidities, multiple drug therapy, and the benefits and risks of treatment.

1.4.23 Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

1.4.24 In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin[22] should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

1.4.25 An 'audit' level of total cholesterol of 5 mmol/litre should be used to assess progress in populations or groups of people with CVD, in recognition that more than a half of patients will not achieve a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre.

Fibrates for secondary prevention

1.4.26 Fibrates may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Nicotinic acid for secondary prevention

1.4.27 Nicotinic acid may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

Anion exchange resins for secondary prevention

1.4.28 Anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins.

[22] 'Higher intensity statins' are statins used in doses that produce greater cholesterol lowering than simvastatin 40 mg, for example simvastatin 80 mg.

Ezetimibe for secondary prevention

1.4.29 People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132).

Monitoring of statin treatment for primary and secondary prevention

1.4.30 If a person taking a statin starts taking additional drugs, or needs treatment for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions, consider reducing the dose of the statin, or temporarily or permanently stopping it.

1.4.31 People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, creatine kinase should be measured.

1.4.32 Creatine kinase should not be routinely monitored in asymptomatic people who are being treated with a statin.

1.4.33 Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.

1.4.34 People who have liver enzymes (transaminases) that are raised but are less than 3 times the upper limit of normal should not be routinely excluded from statin therapy.

1.4.35 If a person develops an unexplained peripheral neuropathy, statins should be discontinued and specialist advice sought.

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from www.nice.org.uk/CG067

This guideline is for adults (aged 18 and older) who have established CVD (including CHD [angina only], stroke or peripheral arterial disease) or who are at high risk of developing CVD because of a combination of CVD risk factors including raised blood pressure and hypertension, overweight and obesity. The following special groups have been considered for primary prevention: black and minority ethnic groups, in particular South Asians; people with a family history of CHD; low socioeconomic groups.

The guideline does not cover people with diabetes, people with familial monogenic lipid disorders or people at high risk of CVD as a result of secondary disease processes or drug treatment.

How this guideline was developed

NICE commissioned the National Collaborating Centre for Primary Care to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see appendix B).

There is more information in the booklet: 'The guideline development process: an overview for stakeholders, the public and the NHS' (third edition, published April 2007), which is available from www.nice.org.uk/guidelinesprocess or from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1233).

3 Implementation

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' (available from www.dh.gov.uk).

Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/CG067).

- Slides highlighting key messages for local discussion.
- Costing tools:
  - costing report to estimate the national savings and costs associated with implementation
  - costing template to estimate the local costs and savings involved.
- Audit support for monitoring local practice.

4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline (see section 5).

4.1 Risk estimation methods

How can CVD risk be best estimated in the population of England and Wales to identify people at high risk of developing CVD for lipid modification therapy?

Why this is important

Current risk estimation is based upon the American Framingham equations which are limited for use in the UK by their development in a historic American population. The Framingham equations overestimate risk by up to 50% in contemporary northern European populations, particularly people living in more affluent areas. They underestimate risk in higher risk populations, such as those that are most socially deprived. Framingham makes no allowance for family history of premature CHD and does not take account of ethnicity, but does have a full dataset. Two new risk scores have recently been developed in the UK. ASSIGN was developed using a Scottish cohort and QRISK using data from UK general practice databases. These scores have the advantage

of including other variables such as measures of social deprivation and family history. There is an urgent need to establish which score is most acceptable for use in the population of England and Wales. NICE should review the relevant recommendations relating to risk assessment as soon as sufficient new data are available to address this.

Research is needed:

- to adjust Framingham for use in the UK population, to assess the use of ASSIGN in UK populations outside Scotland, to validate QRISK in independent and clinical datasets and to assess the performance of the scores against each other
- to assess the feasibility of using scores with an increased number of variables, such as social deprivation, in routine clinical practice, particularly in community and secondary care settings where access to patient electronic records and computers is less likely to be available
- to assess the added value of including variables such as ethnicity, alcohol intake and chronic kidney disease to risk assessment scores.

4.2 Plant sterols and stanols

What is the effectiveness of plant sterols and stanols in people who are at high risk of a first CVD event?

Why this is important

Some people at increased risk of CVD might avoid the need to use drugs to modify their cholesterol levels if they make sufficient changes to their diet. Plant sterols and stanols have been shown to reduce cholesterol levels, but it is not known whether the consumption of plant sterols as part of a low-fat diet will provide worthwhile additional benefit and whether they reduce CVD events.

There is a need for trials to test both efficacy and effectiveness of plant sterols and stanols in people who are at high risk of a first CVD event. These trials should test whether plant sterols or stanols change lipid profiles and reduce CVD events under best possible conditions. Randomised controlled trials are

needed to test the effectiveness of advising people who are at high risk of experiencing a first CVD event to include food items containing plant sterols or stanols in a low-fat diet. The trial should last for at least 2 years and should consider appropriate outcomes.

4.3 Communication of CVD risk

How is CVD risk most effectively communicated to patients? What methods are best and how do these differ for particular groups, such as older people or members of minority ethnic groups?

Why this is important

The methods of risk communication (both the content and means of delivery) should be guided by current evidence. Controlled trials should be conducted comparing the impact of different methods of risk communication and decision aids on patient comprehension, the patient experience of decision-making and actual treatment decisions taken by patients. The aim should be to generate evidence to support the improvement of risk communication and patient decision-making. The content should include absolute rather than relative risks. Numerical data should be presented in both words and numbers, and visual and graphical aids should be used. Such studies might consider a number of delivery mechanisms, including advice from a clinician, a trained 'coach', self-accessed educational presentations via computer or DVDs, peer or lay advisers, and other appropriate means. Trials should also investigate the preferences and views of people from different ethnic groups and of different ages and sex.

4.4 Impact of decision aids

What is the impact of using clinical decision aids that include an assessment of absolute risk to prioritise the prescription of risk-reducing treatment for the primary prevention of CVD?

Why this is important

Risk scoring methods are recommended to help target preventive treatment at people who are asymptomatic but at high risk of CVD. As with any health technology, risk scoring methods should be shown to favourably influence

individual people's health outcomes or risk factors, if they are to be used in primary prevention strategies.

There are no studies involving risk scoring methods in general community populations. Importantly, there is no evidence to support the use of computer-based clinical decision support systems in the primary prevention of CVD.

Being offered long-term primary prevention treatment, or not, is highly significant for individuals, and because of the large numbers of people involved, the medical, financial and social implications for society are considerable. Although the use of clinical decision aids incorporating CVD risk assessment has intuitive appeal and is encouraged in guidelines, the components of an effective decision aid and its impact on individuals remain almost completely unknown.

Outcomes should include morbidity, individual absolute risk, adverse effects, changes in risk behaviours such as smoking, changes in treatment, and a qualitative assessment of the views of both the clinicians using the decision aids and the people being prioritised to either receive preventive treatment or not.

4.5 Treating to target

What is the clinical and cost effectiveness of incremental lipid lowering with HMG CoA reductase inhibitors (statins) and/or ezetimibe to reduce CVD events: (i) in people without established CVD disease who have a 20% or greater risk of CVD events over 10 years; (ii) in people with established CVD?

Why this is important

Several studies with CVD outcomes were identified during the development of this guideline that randomised participants to specific doses of statins to assess the additional effect of higher intensity statins versus lower intensity statins. The incremental cost effectiveness (including adverse events) of these drugs (either alone or in combination with other classes of drug) to reduce CVD events by treating to target levels of total cholesterol of either

5 mmol/litre or 4 mmol/litre (or comparable LDL cholesterol levels) is unknown.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Primary Care, and is available from our website (www.nice.org.uk/guidance/CG67/FullGuideline) and the National Library for Health (www.nlh.nhs.uk).

5.2 Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG67/QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1574).

5.3 'Understanding NICE guidance'

Information for people at high risk of or with CVD and their carers ('Understanding NICE guidance') is available from www.nice.org.uk/Guidance/CG67/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1575).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about CVD.

6 Related NICE guidance

Published

Familial hypercholesterolaemia: identification and management of familial hypercholesterolaemia. NICE clinical guideline 71 (2008). Available from www.nice.org.uk/CG071

Type 2 diabetes: the management of type 2 diabetes (update). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/CG066

Reducing the rate of premature deaths from cardiovascular disease and other smoking-related diseases: finding and supporting those most at risk and improving access to services. NICE public health guidance 15 (2008). Available from www.nice.org.uk/PH015

Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. NICE public health guidance 10 (2008). Available from www.nice.org.uk/PH010

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. NICE technology appraisal guidance 132 (2007). Available from www.nice.org.uk/TA132

Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/TA123

MI: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/CG048

Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/CG043

Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from www.nice.org.uk/CG034

Statins for the prevention of cardiovascular events. NICE technology appraisal guidance 94 (2006). Available from www.nice.org.uk/TA094

Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health intervention guidance 1 (2006). Available from www.nice.org.uk/PHI001

Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. NICE public health intervention guidance 2 (2006). Available from www.nice.org.uk/PHI002

7 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

Appendix A: The Guideline Development Group

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Mr Alaster Rutherford (until June 2007)
Head of Medicines Management, Bristol Primary Care Trust

Professor Margaret Thorogood
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Professor David Wood

Garfield Weston Chair of Cardiovascular Medicine, Imperial College London

Co-opted GDG members

The following people attended meetings at which their expertise was required.

Professor Phillip Bath (co-optee for secondary prevention who attended the meetings for secondary prevention)

Stroke Association Professor of Stroke Medicine, University of Nottingham

Dr Jane Skinner (Clinical Adviser for the 'Secondary prevention of MI' guideline)

Consultant Community Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust

Ms Alison Mead

Cardiac Prevention and Rehabilitation Dietitian, Hammersmith NHS Trust and Imperial College, London

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National Collaborating Centre for Primary Care

Dr Tim Stokes (until December 2006)

Clinical Director and Guideline Lead

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Ms Nicola Browne (from August 2006 until September 2007)

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Ms Gabrielle Shaw (until December 2005)
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Ms Charmaine Larment (until July 2006)
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Mr Christopher Rule (from August 2006 until September 2007)
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Mr Leo Nherera
Health Economist

Mrs Janette Camosso-Stefinovic
Information Scientist

Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The Panel includes members from the following perspectives: primary care, lay, public health and industry.

Dr Robert Walker
General Practitioner, Workington, Cumbria

Mrs Ailsa Donnelly
Lay member

Dr Mark Hill
Head of Medical Affairs, Novartis Pharmaceuticals

Dr John Harley
Clinical Governance and Prescribing Lead, North Tees Primary Care Trust, Stockton-on-Tees

Appendix C: The algorithms

The pathway of care can be found on page 6 of the quick reference guide, available from www.nice.org.uk/CG67/QuickRefGuide

Appendix D: Recommendations relating specifically to the use and modification of the Framingham risk equation for the assessment of CVD risk

In February 2010 NICE Guidance Executive agreed to withdraw the recommendation that the Framingham risk equation should be the equation of choice for assessment of CVD risk, but agreed that it should be considered as one of the possible equations to use. Recommendations relating specifically to the use and modification of the Framingham risk equation have been moved to this appendix. Consider these recommendations when using the Framingham risk equation for assessment of CVD risk.

1.1.9 The following variables should be used for formal estimation of CVD risk with the Framingham 1991 equations:

- age
- sex
- systolic blood pressure (mean of previous two systolic readings)
- total cholesterol
- HDL cholesterol
- smoking status
- presence of left ventricular hypertrophy.

1.1.12 Healthcare professionals should be aware that Framingham 1991 risk equations may overestimate risk in UK populations.

1.1.15 The estimated CVD risk should be increased by a factor of 1.5 in people with a first-degree relative with a history of premature CHD (age at onset younger than 55 in fathers, sons or brothers or younger than 65 in mothers, daughters or sisters).

1.1.16 The estimated CVD risk should be increased by a factor of between 1.5 and 2.0 if more than one first-degree relative has a history of premature CHD.

1.1.17 The estimated CVD risk for men with a South Asian background should be increased by a factor of 1.4.