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**Introduction**

In some individuals, a high cholesterol concentration in the blood is caused by an inherited genetic defect known as familial hypercholesterolaemia (FH). Raised cholesterol concentrations in the blood are present from birth and lead to early development of atherosclerosis and coronary heart disease. The disease is transmitted from generation to generation in such a way that siblings and children of a person with FH have a 50 per cent risk of having FH.

Most individuals with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, an individual will inherit a genetic defect from both parents and will have homozygous FH.

The prevalence of heterozygous FH in the UK population is estimated to be 1 in 500, which means that approximately 110,000 people are affected. The elevated serum cholesterol concentrations that characterise heterozygous FH lead to a greater than 50% risk of coronary heart disease by the age of 50 years in men and at least 30% in women by the age of 60 years.

Homozygous FH is rare with symptoms appearing in childhood, and is associated with early death from coronary heart disease. Homozygous FH has an incidence of approximately one case per one million.

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


Patient-centred care

This guideline offers best practice advice on the identification and care of individuals with FH.

Treatment and care should take into account patients’ needs and preferences. People with FH should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do 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).

If the patient is under 16, healthcare professionals should follow guidelines in ‘Seeking consent: working with children’ (available from www.dh.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.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in ‘Transition: getting it right for young people’ (available from www.dh.gov.uk).

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Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with FH. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.
Key priorities for implementation

A number of key priority recommendations have been identified for implementation listed below. These recommendations are considered by the GDG to have the most significant impact on patients’ care and patients’ outcomes.

Diagnosis

- A family history should always be obtained from an individual being investigated for FH to determine if a dominant pattern of inheritance is present. [1.1.6]
- In children at risk of FH because of an affected parent, LDL-C concentrations should usually be measured by the age of ten years. This measurement should be repeated after puberty before a diagnosis of FH can be excluded. [1.1.8]
- Individuals with FH are at a very high risk of coronary heart disease. Risk estimation tools such as those based on the Framingham algorithm should not be used to assess their risk. [1.1.10]

Identifying individuals with FH using cascade testing

- All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing. [1.2.2]
- Cascade testing using a combination of lipid concentration measurement and DNA testing should be used to identify relatives of index cases with a clinical diagnosis of FH. [1.2.4]
- The establishment and use of a nationwide family based follow-up system is recommended to enable comprehensive identification of affected individuals. [1.2.8]

Management

Adults

- Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline). [1.3.1.2]
Children

- Children and young people diagnosed with, or being investigated for a diagnosis of, FH should be referred to a specialist with expertise in FH in an appropriate child focused setting. [1.3.1.14]

Women and girls

- When lipid modifying medication is first considered for girls and women, risks to the pregnancy and the fetus while taking lipid modifying medication should be discussed. This discussion should be regularly revisited. [1.4.2.1]

Ongoing assessment and monitoring

Review

- All treated individuals with FH should have a regular structured review carried out at least annually. [1.5.1.1]
1 Guidance

The following guidance is based on the best available evidence. The full guideline ([add hyperlink]) gives details of the methods and the evidence used to develop the guidance.

Unless otherwise indicated, recommendations are relevant for individuals with possible or definite FH. Recommendations are also applicable for individuals with both heterozygous and homozygous FH, unless otherwise indicated.

1.1 Diagnosis

(see also 1.4 on Information needs and support)

1.1.1 The diagnosis of FH should be made using the Simon Broome criteria which includes a combination of family history, clinical examination (specifically arcus and tendon xanthomata), lipid profile (see appendix E) or by using molecular techniques.

1.1.2 A clinical diagnosis of homozygous FH should be considered in individuals with LDL-C concentrations greater than 13mmol/l and they should be referred to a specialist centre.

1.1.3 Secondary causes of hypercholesterolaemia should be considered and excluded before a diagnosis of FH is made.

1.1.4 To confirm the diagnosis of FH, at least two measurements of elevated LDL-C concentrations are necessary because biological and analytical variability occurs.

1.1.5 Absence of clinical signs (arcus and tendon xanthomata) in adults and children does not exclude a diagnosis of FH.

1.1.6 A family history should always be obtained from an individual being investigated for FH to determine if a dominant pattern of inheritance is present.
1.1.7  Standardised pedigree terminology should be used to document a three- to four-generation pedigree including relatives’ age of onset of coronary heart disease and lipid concentrations. For deceased relatives the age and cause of death, and smoking history should be documented. If possible the proband should verify this information with other family members.

1.1.8  In children at risk of FH because of an affected parent, LDL-C concentrations should usually be measured by the age of ten years. This measurement should be repeated after puberty before a diagnosis of FH can be excluded.

1.1.9  Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH.

1.1.10 Individuals with FH are at a very high risk of coronary heart disease. Risk estimation tools such as those based on the Framingham algorithm should not be used to assess their risk.

1.1.11 Individuals with a clinical diagnosis of FH should be offered a DNA test to increase the certainty of their diagnosis and to aid diagnosis amongst their relatives.

1.1.12 Individuals with a clinical diagnosis of FH and their relatives who have a detected mutation should be informed they have an unequivocal diagnosis of FH.

1.1.13 Where DNA testing has excluded FH in a member of a family in which a mutation has been identified, CHD risk should be managed as in the general population (see the NICE Lipid Modification guideline).

1.2  Identifying individuals with FH using cascade testing

1.2.1 Systematic methods should be used for case identification of FH.
1.2.2 All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing.

1.2.3 Healthcare professionals should discuss the implications of cascade testing with individuals.

1.2.4 Cascade testing using a combination of lipid concentration measurement and DNA testing should be used to identify relatives of index cases with a clinical diagnosis of FH.

1.2.5 In families in which a mutation has been identified, the mutation should be used to identify affected relatives.

1.2.6 In the absence of a DNA diagnosis, cascade testing using lipid measurements should be undertaken.

1.2.7 To diagnose FH in relatives, the gender and age-specific probabilities based on LDL cholesterol concentrations in appendix E should be used. Simon Broome LDL-C criteria should not be used.

1.2.8 The establishment and use of a nationwide family based follow-up system is recommended to enable comprehensive identification of affected individuals.\(^1\)

1.3 Management

1.3.1 Drug treatment

Adults

1.3.1.1 Statins should be the initial treatment for all adults with FH.

\(^1\) See also the Department of Health FH Cascade Testing Audit Project, available at www.fhcascade.org.uk. Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)
1.3.1.2 Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline).

1.3.1.3 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who would otherwise be initiated on statin therapy but who are unable to do so because of contraindications to initial statin therapy.

1.3.1.4 Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who are intolerant to statin therapy (as defined in section 1.3.1.8).

1.3.1.5 Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who have been initiated on statin therapy when:

- serum LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and
- consideration is being given to changing from initial statin therapy to an alternative statin.

1.3.1.6 When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

1.3.1.7 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk.

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assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations (see 1.1.10).3

1.3.1.8 For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests3.

1.3.1.9 Prescribing of drugs for adults with homozygous FH should be undertaken within a specialist centre (see 1.1.2).

1.3.1.10 Individuals not achieving a reduction in LDL-C concentrations of greater than 50% from baseline should be referred to a specialist with expertise in FH.

1.3.1.11 Individuals with FH should be referred to a specialist with expertise in FH if they are assessed to be at high risk, that is, they have

- established coronary heart disease; or
- a family history of premature coronary heart disease; or
- two or more other cardiovascular risk factors (for example, smoking, hypertension, diabetes, male sex).

1.3.1.12 Individuals with intolerance or contraindications to statins or ezetimibe should be referred to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce LDL-C concentrations.

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1.3.1.13 Caution must be exercised when adding a fibrate or nicotinic acid to a statin due to the risk of muscle-related side effects including rhabdomyolysis. Gemfibrozil and statins should not be used together.

**Children and young people**

1.3.1.14 Children and young people diagnosed with, or being investigated for a diagnosis of, FH should be referred to a specialist with expertise in FH in an appropriate child focused setting.

1.3.1.15 The decision to defer or offer drug therapy for a child or young person should take into account their age, the age of onset of cardiovascular disease within the family, and presence of other cardiovascular risk factors including LDL-C concentrations greater than 6mmol/l in the child or young person.

1.3.1.16 Where the decision to initiate statins has been made in children and young people (aged 10 years upwards), those licensed for use in the appropriate age group should be chosen.

1.3.1.17 Statin therapy for children and young people with FH should usually be prescribed at the doses specified in the BNF for children.

1.3.1.18 In children with homozygous FH, LDL concentration may be lowered by lipid modifying medication and should be considered.

1.3.1.19 In exceptional instances (for example, where there is a family history of cardiovascular disease in early adulthood) a higher dose of statin, or more than one lipid modifying treatment, may be considered for the child/young person at a younger age.

1.3.1.20 In children and young people with FH who are intolerant of statins, other drug therapies capable of reducing LDL-C (bile acid sequestrants [resins], fibrates, or ezetimibe) should be considered.
1.3.1.21 Routine monitoring of growth and pubertal development in children and young people with FH is recommended.

**Adults and children**

1.3.1.22 Decisions about the choice of treatment should be made following discussion with the individual, and be informed by consideration of concomitant medication, co-morbidities, safety, and tolerability.

1.3.1.23 The decision to add a bile acid sequestrant (resin), nicotinic acid or a fibrate should be taken in a specialist centre following consideration of the need for a further reduction in LDL-C concentrations.

1.3.1.24 Vitamin supplementation should be considered for individuals on long-term treatment with bile acid sequestrants (resins).

1.3.1.25 Individuals experiencing unusual side effects should be referred to a specialist with expertise in FH.

1.3.1.26 Individuals prescribed nicotinic acid should receive advice on strategies that reduce flushing. This includes taking low initial doses with meals and/or non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin 30 minutes prior to the first daily dose.

1.3.1.27 Baseline liver and muscle enzymes, including transaminases and creatine kinase respectively, should be measured before initiation of a statin. However individuals with raised liver or muscle enzymes should not routinely be excluded from statin therapy.

1.3.1.28 Monitoring of creatine kinase is not routinely recommended in asymptomatic individuals treated with a statin.

**1.3.2 Lifestyle interventions**

1.3.2.1 Lifestyle advice should be regarded as a component of medical management, and not as a substitute for lipid-modifying medication.

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Diet

1.3.2.2 All individuals and families with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition.

1.3.2.3 Individuals and families with FH should be given the same advice as that given to individuals with a high cardiac risk.

1.3.2.4 Individuals and families with FH 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 saturated fats are replaced by increasing the intake of monounsaturated fats and polyunsaturated fats. It may be helpful to suggest they look at www.eatwell.gov.uk/healthydiet for further practical advice.

1.3.2.5 Individuals and families with FH 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.

1.3.2.6 Individuals and families with FH should be advised to consume at least two portions of fish (one of which should be oily) per week. Pregnant women with FH should be advised to limit their oily fish to no more than two portions per week. Further information and advice on healthy cooking methods can be found at www.eatwell.gov.uk/healthydiet.

1.3.2.7 The range and costs of food products containing stanols and sterols may be discussed. Individuals should be advised that if they wish to take stanols and sterols these need to be taken consistently to be effective.
1.3.2.8 Individuals with FH should not routinely be recommended to take omega-3 fatty acid supplements. For individuals post MI cross refer to MI: secondary prevention’ (NICE clinical guideline 48).

**Physical activity**

1.3.2.9 Individuals with FH 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.\(^4\)

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

1.3.2.11 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'.)

1.3.2.12 Individuals with FH 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'.)

**Weight management**

1.3.2.13 Individuals with FH who are overweight or obese should be offered appropriate advice and support to achieve and maintain a healthy weight in line with the NICE obesity guideline.

**Alcohol consumption**

1.3.2.14 As for the general population, alcohol consumption for adult men with FH should be limited to up 3 to 4 units a day, and for adult women with FH up to 2 to 3 units of alcohol a day. Binge drinking

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should be avoided. Further information can be found on the Foods Standards Agency website www.eatwell.gov.uk/healthydiet.

**Smoking advice**

1.3.2.15 Individuals, especially children, with FH who do not smoke should be strongly discouraged from starting because of their already greatly increased CHD risk.

1.3.2.16 Individuals with FH who smoke should be advised that because of their already greatly increased CHD risk, they should stop.

1.3.2.17 Individuals who want to stop smoking should be offered support and advice, and referral to an intensive support service in line with the NICE guidance on smoking cessation\(^5\).

1.3.2.18 Individuals with FH who do not wish to accept a referral to an intensive support service should be offered pharmacotherapy in line with NICE guidance on nicotine replacement therapy, bupropion and varenicline\(^6,7\).

**1.3.3 Specialist treatment**

**LDL-lowering apheresis**

1.3.3.1 Adults and children with clinical homozygous FH should be considered for apheresis. The timing of initiation of apheresis will depend on other factors, such as response to lipid modifying medication and presence of coronary heart disease.

1.3.3.2 In exceptional cases, individuals with heterozygous FH with progressive, symptomatic CHD, despite maximal tolerated lipid modifying medication and optimal medical therapy, should be considered for apheresis. This should be undertaken in a specialist

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6 ‘Guidance on the use of Nicotine replacement therapy (NRT) and bupropion for smoking cessation’, NICE technology appraisal guidance 39 (2002).
7 ‘Varenicline for smoking cessation’ NICE technology appraisal guidance 123 (2007).
centre on a case by case basis and data collected into an appropriate registry.

1.3.3.3 Fistulae are the preferred access in individuals treated with apheresis and individuals should be counselled about possible benefits and complications.

1.3.3.4 Routine monitoring of iron status should be carried out and iron supplementation initiated as required in individuals being treated with apheresis.

1.3.3.5 ACE inhibitors should not be used in individuals being treated with LDL apheresis, and instead substituted with angiotensin receptor blocking agents.

1.3.3.6 All hypotensive agents should be reviewed and considered for discontinuation on the morning of the day of apheresis.

1.3.3.7 Warfarin should be discontinued approximately 4 days before apheresis and substituted with low molecular weight heparin.

1.3.3.8 Anti-platelet therapy should be continued for individuals treated with apheresis.

Liver transplantation

1.3.3.9 Individuals with homozygous FH should be offered liver transplantation as an option following failure of medication and apheresis.

1.3.3.10 The decision to refer for organ transplantation should be undertaken in conjunction with the patient and/or relatives in an appropriate specialist setting, following a discussion of the benefits and potential harms of intervention.
1.4 Information needs and support

1.4.1 General information and support

1.4.1.1 During the assessment and communication of familial risk, individuals should receive clear and appropriate educational information about FH and about the process of family testing.

1.4.1.2 A specialist with expertise in FH should provide information to individuals with FH on their specific level of risk of coronary heart disease, its implications for them and their families, lifestyle advice and treatment options.

1.4.1.3 Individuals with FH should be encouraged to contact their relatives to inform them of their potential risk and to facilitate cascade testing.

1.4.1.4 When considering cascade testing, a specialist with expertise in FH should facilitate the sharing of information about FH with family members.

1.4.1.5 Individuals and families with FH should be offered written advice and information about patient support groups.

1.4.2 Information and counselling on contraception for women and girls with FH

1.4.2.1 When lipid-modifying medication is first considered for girls and women, risks to the pregnancy and the fetus while taking lipid-modifying medication should be discussed. This discussion should be regularly revisited.

1.4.2.2 Women with FH should be given specific information tailored to their needs and offered a choice of all effective contraceptive methods. Because of the small increased risk of cardiovascular events with the use of combined oral contraceptives, other forms of contraception may be considered initially.

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1.4.3 Information for pregnant women with FH

1.4.3.1 Women with FH should be advised that in general, pregnancy is not contraindicated.

1.4.3.2 Lipid-modifying medication should not be taken by women planning to conceive or during pregnancy because of the potential risk of fetal abnormality.

1.4.3.3 Lipid-modifying medication should be stopped 3 months prior to attempting to conceive.

1.4.3.4 Women with FH who conceive whilst taking statins or other systemically absorbed lipid-modifying medication should be advised to stop treatment immediately and be referred urgently to an obstetrician for fetal assessment. This assessment will then inform shared decision making about continuation of the pregnancy.

1.4.3.5 Shared care arrangements, to include expertise in cardiology and obstetrics, should be made for women with FH who are considering pregnancy or are pregnant. Such care should include an assessment of coronary heart disease risk, particularly to exclude aortic stenosis. This is essential for women with homozygous FH.

1.4.3.6 Serum lipids should not be measured routinely during pregnancy.

1.4.3.7 Breast feeding is not contraindicated in women with FH. Potential risks and benefits of re-starting lipid-modifying medication for the breast feeding mother and infant should be discussed. Resins are the only lipid-modifying medication that should be considered during lactation.
1.5 **Ongoing assessment and monitoring**

1.5.1 **Review**

1.5.1.1 All treated individuals with FH should have a regular structured review carried out at least annually.

1.5.1.2 The progress of cascade testing amongst relatives should be recorded. If there are still relatives who have not been tested, further action should be discussed.

1.5.1.3 Family history should be updated and any changes in the coronary heart disease status of relatives should be noted.

1.5.1.4 Review should include assessment of smoking status, a fasting lipid profile, discussion about concordance with medication, side effects of treatment, and any changes that may be required to achieve recommended cholesterol concentrations.

1.5.2 **Referral**

1.5.2.1 Individuals with FH should be referred urgently\(^8\) to a specialist with expertise in cardiology for evaluation if they have signs or symptoms of possible coronary heart disease.

1.5.2.2 Individuals with FH should be considered for referral for evaluation of coronary heart disease if they have a family history of coronary heart disease in early adulthood, or two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male sex).

1.5.2.3 Adults and children with homozygous FH should be referred for an evaluation of coronary heart disease upon diagnosis.

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\(^8\) The Guideline Development Group considered 'urgently' to be within a week, depending on the severity of symptoms.

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1.5.2.4 In asymptomatic children and young people with heterozygous FH, evaluation of coronary heart disease is unlikely to detect clinically significant disease and referral is not routinely recommended.
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 http://guidance.nice.org.uk/page.aspx?o=406112.

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 by telephoning 0845 003 7783 (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.doh.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/CGXXX).

[NICE to amend list as needed at time of publication]

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

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costing template to estimate the local costs and savings involved.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- 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 Identification using clinical registers

What is the clinical and cost-effectiveness of identifying an FH patient (defined by DNA testing) from GP registers and from secondary care registers?

Why this is important

Research is needed to compare the utility of strategies other than cascade screening to identify new index cases, because currently recommended strategies are likely to lead to the identification of less than 50% of the expected number of people with this condition in the UK.

These additional strategies should evaluate note searching in general practice and from secondary care CHD registers (e.g. MINAP), using a ‘reference standard’ of known FH-causing mutations. This will require the development of different algorithms for patient identification in primary and secondary care. These algorithms should be based on the UK FH diagnostic criteria and a combination of different cut points for untreated total or LDL cholesterol, age of onset of heart disease in the index case, age of onset of heart disease in first degree relatives, and other factors.

4.2 Lipid-modifying therapy in children

What is the clinical effectiveness and safety of differing doses of lipid modifying therapy in children with FH?
Why this is important
There have been no published studies to establish target lipid concentrations in treated children with FH. Treatment is recommended from 10 years onwards, however this lack of data prevents a recommendation regarding the aim of pharmacological treatment on lipid concentrations.

Research (both cross-sectional and longitudinal) should assess the evidence of end-organ involvement (eg carotid intimal thickness, IMT) to determine at which age abnormalities can first be seen in children. The aim would be to identify a threshold effect with a cholesterol concentration below which carotid IMT is normal and where thickening is absent and above which it is abnormal and where thickening is observed. Outcomes should include fasting serum total and LDL-cholesterol concentrations, carotid artery IMT, growth, and pubertal development.

4.3 Apheresis for people with heterozygous FH

What are the appropriate indications, effectiveness, and safety of apheresis in heterozygous FH patients?

Why this is important
There is limited evidence to inform specific indications for apheresis in patients with heterozygous FH. Also there is limited published evidence on the cardiovascular outcome of such patients treated with apheresis.

Evidence on the value of investigations (various measures of vascular status, considered to reflect the extent or activity of atherosclerotic vascular disease of the coronary arteries) in predicting outcome from apheresis should ideally be based on evidence from randomised controlled trials with clinical outcomes. It is difficult to identify a suitable alternative treatment as apheresis is generally only considered in patients for whom no other treatment is available. One comparator may be novel therapies with antisense oligonucleotides (ApoB).

A national register should be established for all FH patients referred for and/or undergoing apheresis. Data should be collected on the natural history of FH.
and the temporal relationship of clinical and vascular features in relation to treatments and other parameters.

**4.4 Pregnancy in women with FH**

What are the implications of FH for the safety of a mother during pregnancy and what are the risks of fetal malformations attributable to pharmacological therapies?

**Why this is important**

There is a paucity of information on the outcomes of pregnancy in women with FH. A small number of conflicting studies have suggested a small increase in fetal abnormalities if the mother has taken statins during the first trimester, but there are not sufficient data to provide an accurate estimate of the level of risk. There is also little information on the risk of pregnancy (including cardiac death) in a woman with FH.

Data on the incidence of cardiac problems in pregnancy and incidence of fetal malformation would inform future recommendations. This could reduce uncertainty for women, and help to identify risks during the pregnancy that could be better managed. The only feasible research method to address these questions is an observational longitudinal study following women with FH and other women (not diagnosed with FH) using statins through their pregnancies using a national register.

**4.5 Cardiovascular evaluation for people with FH**

What is the utility of routine cardiovascular evaluation for asymptomatic people with familial hypercholesterolaemia?

**Why this is important**

Because of their inherent high risk of developing CHD, a low threshold of suspicion for coronary disease is recommended for individuals with FH. Routine monitoring to detect sub-clinical atherosclerosis should be non-invasive, sensitive, specific and cost-effective. Research to assess the prevalence of both asymptomatic coronary and non-coronary atherosclerosis

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in patients with definite heterozygous familial hypercholesterolaemia is required.

As well as exercise ECG testing followed by stress echocardiography prior to possible angiography in individuals with an abnormal exercise test and ankle brachial pressure measures, it should include MRI in addition to other modalities such as carotid IMT and coronary calcification. Outcomes should include changes in exercise ECG/ankle brachial pressure testing/IMT/calcification over time.

Consideration should also be given to the feasibility of conducting a long-term randomised trial to compare the differences in morbidity or mortality attributable to early diagnosis using routine monitoring or symptom-based investigation.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, ['Full guideline title' (in quotes, no italics)] 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 [NCC website details to be added], our website (www.nice.org.uk/CGXXXfullguideline) and the National Library for Health (www.nlh.nhs.uk). [Note: these details will apply to the published full guideline.]

5.2 Quick reference guide

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

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1XXX). [Note: these details will apply when the guideline is published.]
5.3 ‘Understanding NICE guidance’

Information for patients and carers (‘Understanding NICE guidance’) is available from www.nice.org.uk/CGXXXpublicinfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1XXX). [Note: these details will apply when the guideline is published.]

6 Related NICE guidance

Published


Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)
Under development

NICE is developing the following guidance (details available from www.nice.org.uk):


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

Full GDG members were:
Dr Rubin Minhas (Chair): General Practitioner, Primary Care CHD Lead, Medway Primary Care Trust, Gillingham, Kent

Professor Steve E Humphries, PhD MRCP FRCPPath (Clinical Advisor):
Professor of Cardiovascular Genetics, British Heart Foundation Laboratories, Royal Free and University College Medical School, London

Ms Dawn Davies: Patient, Weston-Super-Mare, Director and Trustee of HEART UK

Dr Philip Lee, DM, FRCPCH, FRCP: Consultant and Honorary Reader in Metabolic Medicine, National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital for Children, London

Dr Ian McDowell, MD FRCP FRCPPath: Senior Lecturer and Consultant, University Hospital of Wales, Cardiff

Professor Andrew Neil, MA MB DSc FRCP: Professor of Clinical Epidemiology/Honorary Consulting Physician, Division of Public Health & Primary Health Care, University of Oxford, Oxford

Dr Nadeem Qureshi: GP and Clinical Senior Lecturer in Primary Care, University of Nottingham, Derby

Mr Philip Rowlands: Patient, Penarth

Dr Mary Seed, DM FRCPPath FRCP: Honorary Consulting Physician and retired Clinical Senior Lecturer, Imperial College, Faculty of Medicine, London

Ms Helen Stracey: Dietetic Services Manager/Registered Dietitian, Chelsea and Westminster NHS Foundation Trust, London

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9 See the full guidelines for a complete list of contributors.
Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)
Professor Margaret Thorogood, PhD: Professor of Epidemiology, University of Warwick, Coventry

Ms Melanie Watson: FH Specialist Nurse and DH Trainee Genetic Counsellor, All Wales Genetic Service, Cardiff

**Co-opted GDG Members were:**
Dr Mahmoud Barbir, FRCP: Consultant Cardiologist, Royal Brompton and Harefield NHS Trust, Harefield

Dr Anneke Lucassen, DPhil, FRCP: Professor of Clinical Genetics, University of Southampton and Wessex Clinical Genetics Service

Ms Aileen Parke, BSc, MSc: Pharmacy Team Leader for Women's and Children's Services, King's College Hospital, London

Dr Anthony Wierzbicki: Consultant Chemical Pathologist, Guy's and St Thomas' Hospitals, London

Ms Helen Williams: Specialist Cardiac Pharmacist, Lambeth and Southwark PCTs and King's College Hospital and CHD Adviser to East and South East Specialist Pharmacy Services

Dr Richard Wray: Consultant Cardiologist, Conquest Hospital, The Ridge St Leonards-on-Sea

**Members of the GDG from the NCC-PC were:**
Ms Elizabeth Shaw: Guideline Lead and Deputy Chief Executive, National Collaborating Centre for Primary Care (until Feb 2008)

Dr Kathleen DeMott: Health Services Research Fellow, National Collaborating Centre for Primary Care

Dr Meeta Kathoria: Project Manager, National Collaborating Centre for Primary Care (until Dec 2007)

Vanessa Nunes: Project Manager, National Collaborating Centre for Primary Care (from Jan 2008)
Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)
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, secondary care, lay, public health and industry.

[NICE to add]

[Name; style = Unnumbered bold heading]
[job title and location; style = NICE normal]
Appendix C: The algorithms

**FH Diagnosis**

**Counselling for probands**
- Inform individuals of implications and limitations of lipid and DNA tests
- Inform individuals of results of tests and discuss implications for them and their families
- Inform individuals with diagnostic LDL-C levels and other Simon Broome criteria they have a diagnosis of FH
- Inform individuals with a detected mutation and clinical diagnosis they have FH

**Diagnostic procedures in adult probands (first identified family member)**
- Measure LDL-C at least twice before confirming diagnosis
- Examine for secondary causes of hypercholesterolaemia
- Examine for clinical signs and symptoms, including tendon xanthomata and corneal arcus
- Take personal and family medical history, especially CHD
- Make a clinical diagnosis using the Simon Broome criteria
- Record 3-generation pedigree, noting age of onset of CHD and lipid levels of relatives
- Offer a DNA test to those individuals with a clinical diagnosis of FH
- Consider a diagnosis of homozygous FH if LDL-C is >13mmol/l

**Counselling for relatives**
- Inform individuals of implications and limitations of lipid and DNA tests
- Inform individuals of results of tests and discuss implications for them and their families
- Inform those who have inherited the family mutation that they have FH
- Measure those in whom the family mutation is not found that they do not have FH

**Diagnostic procedures in relatives and children of proband**
- Offer a DNA test for the family mutation to those individuals where a mutation is found in the proband
- Do not use the Simon Broome criteria to diagnose FH in relatives
- Use adjusted LDL-C criteria to make a diagnosis (see NICE version for details), not Simon Broome criteria for probands
- Measure LDL-C in at-risk children by the age of 10 years
- Repeat LDL-C measurement in at-risk children before and after puberty
- Consider a diagnosis of homozygous FH if LDL-C is >13mmol/l

**Diagnosis of FH excluded**
- Manage cardiovascular risk as for an individual of their age and gender in the general population (See NICE Lipid Modification guideline)

**Clinical/DNA diagnosis of FH**
Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)
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### Appendix D: Definitions used in the guideline

<table>
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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td><strong>Cascade testing</strong></td>
<td>Cascade testing is a mechanism for identifying people at risk of a genetic condition by a process of family tracing. For FH the test employed is measurement of (LDL) cholesterol in the blood, and/or a DNA test if a disease-causing mutation has been identified in the proband (see below).</td>
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<tr>
<td><strong>Family history</strong></td>
<td>The structure and relationships within the family that relates information about diseases in family members.</td>
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<td><strong>First degree relatives</strong></td>
<td>Parents, siblings, and children of an individual.</td>
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<tr>
<td><strong>Heterozygous FH</strong></td>
<td>High LDL cholesterol concentration in the blood caused by an inherited mutation from one parent only. Individuals with FH are at increased risk of cardiovascular disease.</td>
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<tr>
<td><strong>Homozygous FH</strong></td>
<td>Very high LDL cholesterol level in the blood caused by an inherited mutation from both parents. Where a person inherits exactly the same affected gene from both parents this is called truly “homozygous” FH. When the mutations in the LDL receptor gene (or equivalent) are different, this state is called “compound heterozygous”. In general the overall effect in both states is similar, in that LDL cholesterol concentrations are very high. Both groups of patients have the same clinical pattern and high risk of cardiovascular disease. For clinical purposes both homozygous FH and compound heterozygous FH can be regarded as behaving in a similar manner. Therefore, for the purposes of this guideline the term “homozygous FH” is used to also encompass compound heterozygous FH.</td>
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<td><strong>Index case</strong></td>
<td>The original patient (proband) who is the starting point for follow up of other members of a family when investigating for possible causative genetic factors of the presenting condition.</td>
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<td><strong>Lipid measurements or concentrations</strong></td>
<td>These terms refer to the measurement of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol. LDL cholesterol is not usually measured directly but calculated from the total cholesterol, triglycerides and HDL cholesterol, ideally using a fasting sample. Such tests are usually done in a clinical biochemistry laboratory.</td>
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<td><strong>Mutation</strong></td>
<td>An identified change in the DNA sequence of a gene which is predicted to damage the normal function of the gene and so cause disease.</td>
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</table>
Pedigree  A method of characterizing the relatives of an index case and their family relationship as well as problems or illnesses within the family. This information, often represented graphically as a family tree, facilitates analysis of inheritance patterns. Study of a trait or disease begins with the affected person (the index case). The pedigree is drawn as the relatives are described. One begins with the siblings of the proband and proceeds to the parents; relatives of the parents, including brothers, sisters, nephews, and nieces; grandparents; and so on. At least 3 generations are usually included. Illnesses, hospitalizations, causes of death, miscarriages, abortions, congenital anomalies, and any other unusual features are recorded.

Proband  The affected individual through whom a family with a genetic disorder is ascertained.

Simon Broome register  A computerized research register of individuals with FH, based in Oxford. Research from this voluntary register has lead to several publications describing the natural history of FH in the UK. The “Simon Broome Criteria” for diagnosis were based on study of this group of individuals with FH.

Specialist  One who has expertise in a particular field of medicine by virtue of additional training and experience. For this guideline, we use specialist to refer to a healthcare professional with an expertise in FH.

Specialist centre  The definition of a specialist centre is not rigid and is based on a combination of patient treatment services, numbers and ages of individuals attending there, the presence of a multi-disciplinary team (which may include for example, physicians, lipidologists, specialist nurses, dieticians), the ability to manage the more unusual manifestations of the condition and the additional functions such as research, education and standard setting. Care is supervised by expert healthcare professionals but shared with local hospitals and primary care teams. Whilst details of the model may vary between patients and areas, the key is that specialist supervision oversees local provision with the patient seen at diagnosis for initial assessment and then at minimum, annually for review.

Tendon xanthoma  A clinically detectable nodularity and/or thickening of the tendons caused by infiltration with lipid-laden histiocytes (macrophages in connective tissue). A distinctive feature of FH which most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows, and knees.
Appendix E: Diagnostic criteria for probands (Simon Broome) and relatives

Simon Broome diagnostic criteria for probands
Definite familial hypercholesterolaemia is defined as:

- total cholesterol above 6.7mmol/l or LDL cholesterol above 4.0mmol/l in a child aged under 16 years or total cholesterol above 7.5mmol/l or LDL cholesterol above 4.9mmol/l in an adult (levels either pre-treatment or highest on treatment) plus
- tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt) or
- DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Possible familial hypercholesterolaemia is defined as above plus one of the criteria below:

- family history of myocardial infarction: below age of 50 years in 2nd degree relative or below age 60 years in 1st degree relative
- family history of raised total cholesterol: above 7.5mmol/l in adult 1st or 2nd degree relative or above 6.7mmol/l in child or sibling aged under 16 years.
Diagnostic criteria for relatives

**LDL diagnostic tables**

**LDL-C diagnostic table for first degree relatives**

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**Legend**

- **Red** = Likely FH
- **Grey** = Uncertain
- **Green** = Unlikely FH

Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)
### TC diagnostic tables

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</table>

**Legend**

- **Red** = Likely FH
- **Grey** = Uncertain
- **Green** = Unlikely FH

Familial hypercholesterolaemia: NICE guideline DRAFT (February 2008)