

Familial hypercholesterolaemia: identification and management

Clinical guideline

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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guideline is the basis of QS41.

Overview

This guideline covers identifying and managing familial hypercholesterolaemia (FH), a specific type of high cholesterol that runs in the family, in children, young people and adults. It aims to help identify people at increased risk of coronary heart disease as a result of having FH.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- Children, young people and adults, and their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in [your care](#).

[Making decisions using NICE guidelines](#) explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Case finding and diagnosis

See also the [section on information needs and support](#).

1.1.1 Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:

- a total cholesterol level greater than 7.5 mmol/l or
- a personal or [family history](#) of premature [coronary heart disease](#) (an event before 60 years in an [index individual](#) or [first-degree relative](#)). [2008, amended 2019]

1.1.2 Systematically search primary care records for people:

- younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l and
- 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l

as these are the people who are at highest risk of FH. [2017]

1.1.3 For people with a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, offer to measure their total cholesterol. [2017]

1.1.4 Healthcare professionals should exclude [secondary causes of](#)

hypercholesterolaemia before a diagnosis of FH is considered. [2008]

- 1.1.5 Use the Simon Broome criteria (see appendix F of the full guideline) or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH in primary care settings. This should be done by a healthcare professional competent in using the criteria. [2017]
- 1.1.6 Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5. [2017]
- 1.1.7 Healthcare professionals should be aware that the absence of clinical signs (for example, tendon xanthomata) in adults and children/young people does not exclude a diagnosis of FH. [2008]
- 1.1.8 Healthcare professionals should consider a clinical diagnosis of homozygous FH in adults with a low-density lipoprotein cholesterol (LDL-C) concentration greater than 13 mmol/l and in children/young people with an LDL-C concentration greater than 11 mmol/l. All people with a clinical diagnosis of homozygous FH should be offered referral to a specialist centre. [2008]
- 1.1.9 To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs. [2008]
- 1.1.10 When considering a diagnosis of FH, healthcare professionals with expertise in FH should use standardised pedigree terminology to document, when possible, at least a three-generation pedigree. This should include relatives' age of onset of coronary heart disease, lipid concentrations and smoking history. For deceased relatives, the age and cause of death, and smoking history should be documented. If possible, the index individual should verify this information with other family members. [2008]
- 1.1.11 Ultrasonography of the Achilles tendon is not recommended in the diagnosis of FH. [2008]
- 1.1.12 Coronary heart disease risk estimation tools, such as QRISK2 and those based on the Framingham algorithm, should not be used because people with FH are

already at a high risk of [premature coronary heart disease](#). [2008, amended 2017]

- 1.1.13 Inform all people who have an identified [mutation](#) diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria (see recommendation 1.1.5). [2008, amended 2017]
- 1.1.14 In a family where a DNA mutation is identified, not all family members may have inherited the mutation. When DNA testing has excluded FH in a member of a family, healthcare professionals should manage the person's coronary heart disease risk as in the general population (see [NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification](#)). [2008]
- 1.1.15 In children aged 0–10 years at risk of FH because of 1 affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test. [2017]
- 1.1.16 In children at risk of homozygous FH because of two affected parents or because of the presence of clinical signs, for example, cutaneous lipid deposits (xanthomata), LDL-C concentration should be measured before the age of 5 years or at the earliest opportunity thereafter. If the LDL-C concentration is greater than 11 mmol/l then a clinical diagnosis of homozygous FH should be considered. [2008]

1.2 Identifying people with FH using cascade testing

- 1.2.1 Carry out [cascade testing](#) using DNA testing to identify affected first- and [second-](#) and, when possible, [third-degree biological relatives](#) of people with a genetic diagnosis of FH. [2017]
- 1.2.2 Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing. [2008]
- 1.2.3 Healthcare professionals with expertise in FH should explain what is meant by cascade testing, and discuss its implications with all people with FH. [2008]

- 1.2.4 Healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing. [2008]

1.3 Management

1.3.1 Drug treatment

Adults

Recommendations 1.3.1.4 to 1.3.1.9 have been adapted from [NICE's technology appraisal guidance on ezetimibe for treating primary \(heterozygous-familial and non-familial\) hypercholesterolaemia](#).

- 1.3.1.1 When offering lipid-modifying drug therapy to [adults with FH](#), healthcare professionals should inform the person that this treatment should be lifelong. [2008].
- 1.3.1.2 Offer a [high-intensity statin](#) with the lowest acquisition cost as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL-C concentration from the baseline measurement. [2017]
- 1.3.1.3 The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). [2008]
- 1.3.1.4 Ezetimibe monotherapy is recommended as an option for treating primary heterozygous-familial hypercholesterolaemia in adults in whom initial statin therapy is contraindicated. [2016]
- 1.3.1.5 Ezetimibe monotherapy is recommended as an option for treating primary heterozygous-familial hypercholesterolaemia in adults who cannot tolerate statin therapy (as defined in recommendation 1.3.1.9). [2016]
- 1.3.1.6 Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial) hypercholesterolaemia in adults who have started statin therapy when:

- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (as defined in recommendation 1.3.1.8) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in recommendation 1.3.1.9) and
- a change from initial statin therapy to an alternative statin is being considered. [2016]

1.3.1.7 When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost. [2016]

1.3.1.8 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment according to national guidance on managing cardiovascular disease in the relevant populations. [2016]

1.3.1.9 For the purposes of this guidance, intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy. [2016]

1.3.1.10 Prescribing of drug therapy for adults with homozygous FH should be undertaken within a specialist centre. [2008]

1.3.1.11 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH if treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). [2008]

1.3.1.12 Healthcare professionals should offer adults with FH a referral to a specialist with expertise in FH for consideration for further treatment if they are assessed to be at very high risk of a coronary event, that is, if they have any of the following.

- Established coronary heart disease.
- A family history of premature coronary heart disease.
- Two or more other cardiovascular risk factors (for example, they are male, they smoke, or they have hypertension or diabetes). [2008]

- 1.3.1.13 For recommendations on managing primary heterozygous familial hypercholesterolaemia in people whose LDL-C levels are not adequately controlled despite maximal tolerated lipid-lowering therapy, see the NICE technology appraisal guidance on [alirocumab](#) and [evolocumab](#). [2017]
- 1.3.1.14 Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin) or a fibrate to reduce their LDL-C concentration. [2008, amended 2017]
- 1.3.1.15 The decision to offer treatment with a bile acid sequestrant (resin) or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH. [2008, amended 2017]
- 1.3.1.16 Healthcare professionals should exercise caution when adding a fibrate to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together. [2008, amended 2017]

Children and young people

- 1.3.1.17 Healthcare professionals should offer all children and young people diagnosed with, or being investigated for, a diagnosis of FH a referral to a specialist with expertise in FH in children and young people. This should be in an appropriate child/young person-focused setting that meets the standards within the [National service framework for children, young people and maternity services](#). [2008]
- 1.3.1.18 Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. The decision to defer or offer lipid-modifying drug therapy for a child or young person should take into account:
- their age
 - the age of onset of coronary heart disease within the family, and
 - the presence of other cardiovascular risk factors, including their LDL-C concentration. [2008]
- 1.3.1.19 When offering lipid-modifying drug therapy for children or young people,

healthcare professionals should inform the child/young person and their parent/carer that this treatment should be lifelong. [2008]

1.3.1.20 Offer statins to children with FH by the age of 10 years or at the earliest opportunity thereafter. [2017]

1.3.1.21 For children and young people with FH, consider a statin that is licensed for use in the appropriate age group. [2017]

1.3.1.22 Statin therapy for children and young people should be initiated by a healthcare professional with expertise in treating children and young people with FH, and in a child-focused setting. [2008, amended 2017]

1.3.1.23 Statin therapy for children and young people with FH should usually be prescribed at the doses specified in the 'British national formulary (BNF) for children'. [2008]

1.3.1.24 In exceptional instances, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people should consider offering:

- a higher dose of statin than is licensed for use in the appropriate age group, and/or
- more than one lipid-modifying drug therapy, and/or
- lipid-modifying drug therapy before the age of 10 years. [2008]

1.3.1.25 In children and young people with homozygous FH, LDL-C concentration may be lowered by lipid-modifying drug therapy and this should be considered before LDL apheresis (see section 1.3.3). [2008]

1.3.1.26 In children and young people with FH who are intolerant of statins, healthcare professionals should consider offering other lipid-modifying drug therapies capable of reducing LDL-C concentration (such as bile acid sequestrants [resins], fibrates or ezetimibe). [2008]

1.3.1.27 Routine monitoring of growth and pubertal development in children and young people with FH is recommended. [2008]

Adults and children/young people

- 1.3.1.28 Decisions about the choice of treatment should be made following discussion with the adult or child/young person and their parent/carer, and be informed by consideration of concomitant medication, comorbidities, safety and tolerability. [2008]
- 1.3.1.29 Healthcare professionals should consider offering fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation for adults or children/young people with FH who are receiving long-term treatment with bile acid sequestrants (resins). [2008]
- 1.3.1.30 Healthcare professionals should offer people with FH a referral to a specialist with expertise in FH if they are experiencing side effects that compromise concordance with lipid-modifying drug therapy. [2008]
- 1.3.1.31 When the decision has been made to offer adults or children/young people with FH treatment with a statin, baseline liver and muscle enzymes (including transaminases and creatine kinase, respectively) should be measured before initiation of therapy. However, people with raised liver or muscle enzymes should not routinely be excluded from statin therapy. [2008]
- 1.3.1.32 Routine monitoring of creatine kinase is not recommended in asymptomatic adults or children/young people with FH who are receiving treatment with a statin. [2008]

1.3.2 Lifestyle interventions

- 1.3.2.1 Healthcare professionals should regard lifestyle advice as a component of medical management, and not as a substitute for lipid-modifying drug therapy. [2008]

Diet

- 1.3.2.2 All people with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition. [2008]
- 1.3.2.3 People with FH should be advised to consume 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
- saturated fats are replaced by increasing the intake of monounsaturated and polyunsaturated fats.

It may be helpful to suggest they look at [Live Well](#) for further practical advice. [2008]

- 1.3.2.4 Healthcare professionals should advise people with FH to eat at least five portions of fruit and vegetables a day, in line with national guidance for the general population. Examples of what constitutes a portion can be found at [Live Well](#). [2008]
- 1.3.2.5 Healthcare professionals should advise people with FH to consume at least two portions of fish a week (one of which should be oily fish). Pregnant women with FH should be advised to limit their oily fish to two portions a week. Further information and advice on healthy cooking methods can be found at [Live Well](#). [2008]
- 1.3.2.6 Healthcare professionals should advise people with FH that if they wish to consume food products containing stanols and sterols these need to be taken consistently to be effective. [2008]
- 1.3.2.7 People with FH should not routinely be recommended to take omega-3 fatty acid supplements. For people with FH who have already had a myocardial infarction (MI), refer to the NICE guideline on [myocardial infarction](#). [2008]

Physical activity

- 1.3.2.8 Healthcare professionals should advise people with FH to undertake physical activity in line with national guidance for the general population (see the [UK Chief Medical Officers' physical activity guidelines](#) for more information). [2008]
- 1.3.2.9 Healthcare professionals should encourage people who are unable to perform moderate-intensity physical activity because of comorbidity, medical conditions or personal circumstances to exercise at their maximum safe capacity (see the

UK Chief Medical Officers' physical activity guidelines for more information).
[2008]

1.3.2.10 Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling (see the UK Chief Medical Officers' physical activity guidelines for more information).
[2008]

Weight management

1.3.2.11 Healthcare professionals should offer people with FH who are overweight or obese appropriate advice and support to achieve and maintain a healthy weight in line with [NICE's guideline on obesity prevention](#). [2008]

Alcohol consumption

1.3.2.12 As for the general population, alcohol consumption for adult men with FH should be limited to up to 3–4 units a day, and for adult women with FH up to 2–3 units of alcohol a day. Binge drinking should be avoided. Further information can be found at [Live Well](#). [2008]

Smoking advice

1.3.2.13 People with FH, especially children, who do not smoke should be strongly discouraged from starting because of their already greatly increased risk of coronary heart disease. [2008]

1.3.2.14 People with FH who smoke should be advised that, because of their already greatly increased risk of coronary heart disease, they should stop. [2008]

1.3.2.15 Healthcare professionals should offer people who want to stop smoking support and advice, and referral to an intensive support service, in line with the [NICE guidance on smoking cessation](#). [2008]

1.3.2.16 People with FH who are unwilling or unable to accept a referral to an intensive support service should be offered pharmacotherapy in line with NICE guidance on nicotine replacement therapy and bupropion, and varenicline. See NICE guidance on smoking cessation, including [NICE's technology appraisal guidance on varenicline for smoking cessation](#). [2008]

1.3.3 Specialist treatment

LDL-lowering apheresis

- 1.3.3.1 Healthcare professionals should consider offering LDL apheresis for the treatment of adults and [children/young people](#) with [homozygous FH](#) (see [recommendations 1.1.8 and 1.1.16](#)). The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease. [2008]
- 1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with [heterozygous FH](#). This should take place in a [specialist centre](#) on a case-by-case basis and data recorded in an appropriate registry. [2008]
- 1.3.3.3 Healthcare professionals should recommend arterio-venous fistulae as the preferred method of access for people with FH who are offered treatment with LDL apheresis. People should be counselled about possible benefits and complications of this procedure. [2008]
- 1.3.3.4 Routine monitoring of the person's iron status should be carried out and iron supplementation initiated as required for people with FH who are receiving treatment with LDL apheresis. [2008]
- 1.3.3.5 Angiotensin-converting enzyme (ACE) inhibitors should not be used in people with FH who are being treated with LDL apheresis. Instead, ACE inhibitors should be substituted with angiotensin-receptor blocking agents. [2008]
- 1.3.3.6 People with FH who are receiving blood pressure-lowering drug therapy should have this reviewed and considered for discontinuation on the morning of the day of LDL apheresis. [2008]
- 1.3.3.7 People with FH who are taking warfarin should have this discontinued approximately 4 days before LDL apheresis and substituted with low molecular weight heparin. [2008]
- 1.3.3.8 People with FH who are receiving anti-platelet therapy should have this

continued if they are receiving treatment with LDL apheresis. [2008]

Liver transplantation

1.3.3.9 Healthcare professionals should consider offering liver transplantation as an option for the treatment of people with homozygous FH after treatment with lipid-modifying drug therapy and LDL apheresis. [2008]

1.3.3.10 The decision to refer for liver transplantation should take place in partnership with the patient and/or their relatives in an appropriate specialist setting, following a discussion of the benefits and potential harms of undertaking or declining transplantation. [2008]

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, people should receive clear and appropriate educational information about FH, the process of family testing, DNA testing and the measurement of LDL-C concentration. [2008]

1.4.1.2 A healthcare professional with expertise in FH should provide information to people with FH on their specific level of risk of coronary heart disease, its implications for them and their families, lifestyle advice and treatment options. [2008]

1.4.1.3 Healthcare professionals with expertise in FH should encourage people with FH to contact their relatives to inform them of their potential risk and so that cascade testing can take place. [2008]

1.4.1.4 When considering cascade testing, a healthcare professional with expertise in FH should offer to facilitate the sharing of information about FH with family members. [2008]

1.4.1.5 Healthcare professionals should offer people with FH and their families written advice and information about patient support groups. [2008]

1.4.2 Information and counselling on contraception for women

and girls with FH

- 1.4.2.1 When lipid-modifying drug therapy is first considered for women and girls, the risks for future pregnancy and the fetus while taking lipid-modifying drug therapy should be discussed. This discussion should be revisited at least annually. [2008]
- 1.4.2.2 Healthcare professionals should give women and girls with FH specific information tailored to their needs and should offer a choice of effective contraceptive methods. [2008]
- 1.4.2.3 Combined oral contraceptives (COCs) are not generally contraindicated for women and girls being treated with lipid-modifying drug therapy. However, because there is a potential small increased risk of cardiovascular events with the use of COCs, healthcare professionals should consider other forms of contraception. Prescribers should refer to the summary of product characteristics of COCs and the relevant lipid-modifying drugs for their specific contraindications. [2008]

1.4.3 Information for pregnant women with FH

- 1.4.3.1 Healthcare professionals should be aware that, in general, there is no reason to advise against pregnancy or breastfeeding in women with FH. [2008]
- 1.4.3.2 Healthcare professionals should advise women with FH that lipid-modifying drug therapy should not be taken if they are planning to conceive or during pregnancy, because of the potential risk of fetal abnormality. Women should be advised that lipid-modifying drug therapy should be stopped 3 months before they attempt to conceive. [2008]
- 1.4.3.3 Women with FH who conceive while taking statins or other systemically absorbed lipid-modifying drug therapy should be advised to stop treatment immediately and they should be offered an urgent referral to an obstetrician for a fetal assessment. Women should be fully informed about the nature and purpose of the assessment. [2008]
- 1.4.3.4 Women with FH who have conceived while taking statins or other systemically absorbed lipid-modifying drug therapy and have had a fetal assessment should be given time, opportunity and full information to consider their options

(including the advantages and disadvantages) of continuing with their pregnancy. [2008]

- 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. [2008]
- 1.4.3.6 Serum cholesterol concentrations should not be measured routinely during pregnancy. [2008]
- 1.4.3.7 Women with FH who are pregnant should be advised on the potential risks and benefits of re-starting lipid-modifying drug therapy for the mother and breastfed infant. Resins are the only lipid-modifying drug therapy that should be considered during lactation. [2008]

1.5 Ongoing assessment and monitoring

1.5.1 Review

- 1.5.1.1 All people with FH should be offered a regular structured review that is carried out at least annually. [2008]
- 1.5.1.2 A baseline electrocardiogram (ECG) should be considered for adults with FH. [2008]
- 1.5.1.3 Healthcare professionals should record the progress of cascade testing among the relatives of a person with FH as part of the structured review. This should include at least the first- and second-degree relatives- and, when possible, third-degree biological relatives. If there are still relatives who have not been tested, further action should be discussed. [2008]
- 1.5.1.4 Healthcare professionals should update the family pedigree of a person with FH and note any changes in the coronary heart disease status of their relatives as part of the structured review. This should include at least the first- and second- and, when possible, third-degree biological relatives. [2008]

1.5.1.5 Structured review should include assessment of any symptoms of coronary heart disease and smoking status, a fasting lipid profile, and discussion about concordance with medication, possible side effects of treatment the patient may be experiencing, and any changes in lifestyle or lipid-modifying drug therapy that may be required to achieve the recommended LDL-C concentration (see the [section on management](#)). [2008]

1.5.2 Referral for evaluation of coronary heart disease

1.5.2.1 Healthcare professionals should offer people with FH an [urgent referral](#) to a specialist with expertise in cardiology for evaluation if they have symptoms or signs of possible coronary heart disease which are not immediately life-threatening. A low threshold for referral is recommended. [2008]

1.5.2.2 A person with FH with symptoms or signs of possible coronary heart disease which are immediately life-threatening (for example, acute coronary syndrome) should be referred to hospital as an emergency in line with advice for the general population. [2008]

1.5.2.3 Healthcare professionals should consider offering people with FH a 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 (for example, they are male, they smoke, or they have hypertension or diabetes). [2008]

1.5.2.4 Upon diagnosis, healthcare professionals should offer all adults and [children/young people](#) with [homozygous FH](#) a referral for an evaluation of coronary heart disease. [2008]

1.5.2.5 In asymptomatic children and young people with [heterozygous FH](#), evaluation of coronary heart disease is unlikely to detect clinically significant disease and referral should not be routinely offered. [2008]

Terms used in this guideline

Adults with FH

For the purposes of this guideline, 'adults' includes all persons with familial hypercholesterolaemia (FH; heterozygous or homozygous) who are 16 years and older.

Cascade testing

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 a DNA test where a disease-causing mutation has been identified in the index individual/proband.

Children/young people

For the purposes of this guideline, 'children' refers to persons younger than 10 years; 'young people' refers to persons from 10 years of age up to the age of 15 years. The definitions used here are not prescriptive and healthcare professionals are expected to exercise their judgement and consider the wishes of the patients, and their families or carers when interpreting these terms in individual instances.

Child-focused setting

Child-focused refers to valuing the child's view and validating their voice in making decisions impacting their lives. A child-focused facility or space is one designed from the viewpoint of the service recipients.

Coronary heart disease

An event is defined as angina, acute coronary syndrome, myocardial infarction, need for coronary artery bypass grafting, need for percutaneous coronary intervention or definite coronary artery disease on coronary angiography.

Dutch Lipid Clinic Network (DLCN) criteria/score

A method of assessing whether a person has FH. It is based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score is attributed to each component; the higher the score, the higher the likelihood of the person having FH.

Family history

The structure and relationships within the family that relates information about diseases in family members.

First-degree relative

A person's biological parents, brothers and sisters, and children.

Heterozygous FH

High LDL-C concentration in the blood caused by an inherited mutation from one parent only. People with FH are at increased risk of cardiovascular disease.

High-intensity statin

Statins are classified as high intensity if they produce average reductions in LDL-C greater than 40%. See [appendix A of NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification](#).

Homozygous FH

Very high LDL-C concentration in the blood caused by an inherited mutation from both parents. When 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-C 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.

Index individual (synonymous with 'proband')

The original patient 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.

Lipid measurements/concentrations/levels

These terms refer to the measurement of total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and LDL-C. LDL-C is not usually measured directly but calculated from the TC, TGs and HDL-C, ideally using a fasting sample.

Such tests are usually done in a clinical biochemistry laboratory.

Mutation

An identified change in the DNA sequence of a gene that is predicted to damage the normal function of the gene and so cause disease.

Pedigree

A method of characterising the relatives of an index individual/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 individual). The pedigree is drawn as the relatives are described. One begins with the siblings of the index individual and proceeds to the parents; relatives of the parents, including brothers, sisters, nephews, nieces, grandparents, and so on. At least three generations are usually included. Illnesses, hospitalisations, causes of death, miscarriages, abortions, congenital anomalies, and any other unusual features are recorded.

Premature coronary heart disease

For the purpose of this guideline, this refers to a coronary event that has occurred before 60 years of age in an index individual or first-degree relative.

Proband

The affected (index) individual through whom a family with a genetic disorder is ascertained.

Second-degree relative

A person's biological grandparent, grandchild, uncle, aunt, niece, nephew, half sister or half brother.

Secondary causes of hypercholesterolaemia

Causes of hyperlipidaemia other than familial, including uncontrolled diabetes mellitus, obesity, excess alcohol consumption, untreated hypothyroidism and some medications, for example, thiazide diuretics and ciclosporin.

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 people attending there, the presence of a multi-disciplinary team (which may include, for example, physicians, lipidologists, specialist nurses, pharmacists and dietitians), 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. Although 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 least annually for review.

Tendon xanthomata

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 that most frequently affects the Achilles tendons but can also involve tendons on the back of the hands, elbows and knees.

Third-degree biological relative

A person's biological great grandparent, great grandchild, great aunt, great uncle, first cousin, grand nephew or grand niece.

Urgent referral

For the purposes of this guideline, urgent referral is as soon as possible with a maximum of 14 days.

Context

In some people, a high cholesterol concentration in the blood is caused by an inherited genetic defect known as familial hypercholesterolaemia (FH). A raised cholesterol concentration in the blood is present from birth and may lead to early development of atherosclerotic disease like coronary heart disease. The disease shows an autosomal dominant pattern of inheritance, being transmitted from generation to generation in such a way that siblings and children of a person with FH have a 50% risk of inheriting FH.

Most people with FH have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, a person will inherit a genetic defect from both parents and will have homozygous FH or compound heterozygous FH, which will be collectively termed homozygous FH for the purpose of this guideline.

The prevalence of heterozygous FH in the UK population is estimated to be somewhere between 1 in 250 and 1 in 500, which means that between approximately 130,000 and 260,000 people are affected. The elevated serum cholesterol concentration that characterises heterozygous FH leads to a greater than 50% risk of coronary heart disease in men by the age of 50 years 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.

In 2017 the areas on case-finding, diagnosis and pharmacological monotherapy (statin v placebo) were updated. Since the original guideline was published in 2008, cascade testing may now be more cost-effective, and DNA diagnosis technology has changed greatly. In addition, more evidence has been identified on the use of high-intensity statins, and on the safety profile of statins in children and young people.

Recommendations for research

The guideline committee has made the following recommendations for research.

As part of the 2017 update, the standing committee made research recommendations on using different thresholds of low-density lipoprotein cholesterol (LDL-C) concentration in primary care case finding and on long-term monitoring of sub-clinical atherosclerosis in children with familial hypercholesterolaemia (FH) who are treated with statins (see below). The committee also made 3 other research recommendations, on secondary care case finding, cascade testing and the use of clinical scoring criteria. One research recommendation on identification using clinical registers was removed. Details can be found in the [evidence reviews](#).

1 Using different thresholds of low-density lipoprotein cholesterol concentration in primary care case finding

What is the clinical and cost effectiveness of using different thresholds of LDL-C concentration in primary care case finding?

Why this is important

The clinical community recognises that FH is underdiagnosed, with prevalence more likely to be approximately 1 in 250 rather than the widely cited 1 in 500. Searching electronic primary care databases is an effective way of identifying people with FH. One of the ways in which people are identified through electronic primary care database searching is to search using total cholesterol or LDL-C concentration. Currently, the entire evidence base for identifying cohorts of people with FH through primary care case finding uses a total cholesterol concentration cut-off of 9.3 mmol/l. This is a very high concentration and anecdotal evidence suggests that this identifies older people but may miss younger people with FH. This could lead to missed opportunities to identify and treat people with FH at an earlier age. Research is needed to identify whether using different total cholesterol and LDL-C concentrations to identify people with FH through primary care database searching affects the diagnostic yield of FH. Additionally, there is a lack of data on the ethnicity, age and triglyceride concentration of people with FH identified through primary care database searching. These should be included as outcomes in future research. [2017]

2 Long-term monitoring of sub-clinical atherosclerosis in children with FH who are treated with statin therapy

What are the long-term effects of statin therapy on sub-clinical atherosclerosis in children with FH who are treated with statin therapy?

Why this is important

Although statins are increasing in use, there is still a lack of data on the long-term effects of statins in children. It is particularly important to determine any long-term adverse effects of statin treatment in a population with FH, as people generally take statins for the rest of their lives once treatment starts. [2017]

3 Lipid-modifying drug 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 serum LDL-C concentration in treated children with FH receiving lipid-modifying drug therapy. Treatment is recommended from 10 years onwards, however this lack of data prevents a recommendation regarding the aim of pharmacological treatment on serum LDL-C concentrations.

Research (both cross-sectional and longitudinal) should assess the evidence of end-organ involvement (for example, carotid intima medial thickness [IMT]) to determine at which age abnormalities can first be seen in children. The aim would be to identify a threshold effect, with an LDL-C 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-C concentration, carotid artery IMT, and growth and pubertal development. [2008]

4 LDL apheresis for people with heterozygous FH

What are the appropriate indications, effectiveness and safety of LDL apheresis in people with heterozygous FH?

Why this is important

There is limited evidence to inform specific indications for LDL apheresis in people with heterozygous FH. In addition, there is limited published evidence on the cardiovascular outcome of such patients treated with LDL 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 LDL apheresis should ideally be based on evidence from randomised controlled trials with clinical outcomes. It is difficult to identify a suitable alternative treatment because LDL apheresis is generally only considered in people 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 people with FH who are referred for and/or are undergoing LDL 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. [2008]

5 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 little 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 limited 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. [2008]

6 Cardiovascular evaluation for people with FH

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

Why this is important

Because of their inherent high risk of developing premature coronary heart disease, a low threshold of suspicion for coronary disease is recommended for people 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 in people with definite heterozygous FH is required.

As well as exercise ECG testing followed by stress echocardiography before possible angiography in people with an abnormal exercise test and ankle brachial pressure measures, research should include magnetic resonance imaging (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. [2008]

Finding more information and committee details

You can see everything NICE says on this topic in the [NICE Pathway on familial hypercholesterolaemia](#).

To find NICE guidance on related topics, including guidance in development, see the [NICE webpage on lipid disorders](#).

For full details of the evidence and the guideline committee's discussions, see the [full guideline and appendices](#). You can also find information about [how the guideline was developed, including details of the committee](#).

NICE has produced [tools and resources to help you put this guideline into practice](#). For general help and advice on putting our guidelines into practice, see [resources to help you put NICE guidance into practice](#).

Update information

October 2019: Recommendation 1.1.1 was amended to be clearer about when to suspect familial hypercholesterolaemia.

November 2017: We reviewed the evidence and made new recommendations on case finding, diagnosis and statin monotherapy. These recommendations are marked [2017].

We also made some changes without an evidence review:

- Some wording was updated to emphasise that familial hypercholesterolaemia should be thought about as a potential diagnosis.
- A clarification was added about the QRISK2 score.
- Nicotinic acid was removed from the recommendations.
- Recommendations on statins were updated.
- A new recommendation cross-referring to the [NICE technology appraisal guidance on alirocumab](#) and [evolocumab](#) was added to section 1.3.1.

These recommendations are marked [2008, amended 2017].

Recommendations marked [2016] last had an evidence review in 2016, and those marked [2008] last had an evidence review in 2008. In some cases minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

July 2016: Recommendations 1.3.1.4 to 1.3.1.9 have been replaced and are adapted from [NICE technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia](#). TA385 has replaced TA132, the original source for these recommendations. They have been changed to remove reference to non-familial hypercholesterolaemia, which TA385 also covers.

Minor changes since publication

November 2020: Recommendations 1.3.2.8 to 1.3.2.10 were amended to direct readers to the 2019 UK Chief Medical Officers' physical activity guidelines, and the original recommendation

1.3.2.11 was removed as it is now covered by the changes made to recommendation 1.3.2.8. Footnotes were incorporated into the text to improve accessibility.

December 2017: The definition of high-intensity statin was amended.

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