The NICE Guidelines for the identification and management of familial hypercholesterolaemia (FH) - An overview of the key points by HEART UK in the consultation document

What are NICE Guidelines?
NICE produce guidelines for the NHS as to how services should be delivered.

Why are they important?
The service provided for patients with FH will be affected by these Guidelines. They set out a number of recommendations based on best practice and what offers best value for money. Patients should expect to receive services in the way they are outlined in the recommendations. The guidelines are open for review and there is an opportunity to share your opinion.

About this overview by HEART UK
We have produced this quick guide of the main points based on a more detailed and comprehensive document produced by NICE. The original document by NICE details the economic and clinical research that was considered and is available from the NICE website.

Diagnosing
Think about familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:
- a total cholesterol level greater than 7.5 mmol/l, and/or
- a personal or family history of premature coronary heart disease (a coronary event before 60 years in an index individual or first-degree relative).

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.

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.

Finding FH
Systematically search primary care records for people with a total cholesterol concentration greater than 9.3 mmol/l, as these are the people who are at highest risk of FH.
For people with a personal or family history of premature coronary heart disease (a coronary event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, offer to measure their total cholesterol.

Healthcare professionals should exclude secondary causes of hypercholesterolaemia before a diagnosis of FH is considered.

Use the Simon Broome 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.

Refer 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.

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.

Everyone with a clinical diagnosis of homozygous FH should be offered referral to a specialist centre.

To confirm a diagnosis of FH, healthcare professionals should undertake two measurements of LDL-C concentration because biological and analytical variability occurs. 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.

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.

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

Coronary heart disease risk estimation tools such as 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.

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.

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.
In children at risk of FH because of one affected parent, offer a DNA test at the age of 10 years or at the earliest opportunity thereafter.

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.

Cascade testing

_Cascade testing_

_Carry out DNA cascade testing_

_Carry out cascade testing using DNA testing_ to identify affected first- and second- and, when possible, third-degree biological relatives of people with a diagnosis of FH.

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. Healthcare professionals with expertise in FH should explain what is meant by cascade testing, and discuss its implications with all people with FH.

Healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing.

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.

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

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

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- and, when possible, third-degree biological relatives. If there are still relatives who have not been tested, further action should be discussed.

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. 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.

**Treatment**

*When offering lipid-modifying drug therapy to adults with FH, healthcare professionals should inform the person that this treatment should be lifelong.*

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.

**Ezetimibe** monotherapy is recommended as an option for treating primary heterozygous-familial hypercholesterolaemia in adults who cannot tolerate statin.

**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 either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy
- a change from initial statin therapy to an alternative statin is being considered.

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

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.

*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.*

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

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).
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).

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), nicotinic acid, or a fibrate to reduce their LDL-C concentration.

**Children and Young People**

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 in an appropriate child/young person-focused setting.

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

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.

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

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

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.

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’. 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.

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.

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).

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

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.

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).

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.

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.

Routine monitoring of creatine kinase is not recommended in asymptomatic adults or children/young people with FH who are receiving treatment with a statin.

Healthy eating and lifestyle

All people with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition, this includes advising:

• at least five portions of fruit and vegetables a day, in line with national guidance for the general population.
• 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
• 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.
• people with FH should not routinely be recommended to take omega-3 fatty acid supplements.

At least 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 or for those who are unable because of comorbidity, disability, medical conditions or personal circumstances to exercise at their maximum safe capacity.

Recommended types of physical activity include those that can be incorporated into everyday life, such as brisk walking, using stairs and cycling.

Healthcare professionals should advise people with FH that bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions.

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 guidance on obesity.

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.

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.

Apherisis

LDL apheresis should be offered for the treatment of adults and children/young people with homozygous FH.

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.

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 in a case-by-case basis and data recorded in an appropriate registry.

Healthcare professionals should recommend arterio-venous fistulae as the preferred method of access for people with FH who are offered treatment with LDL apherisis. People should be counselled about possible benefits and complications of this procedure. 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.
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.

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.

People with FH who are taking warfarin should have this discontinued approximately 4 days before LDL apheresis and substituted with low molecular weight heparin.

People with FH who are receiving anti-platelet therapy should have this continued if they are receiving treatment with LDL apheresis.

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.

Pregnancy

Healthcare professionals should give women and girls with FH specific information tailored to their needs and should offer a choice of effective contraceptive methods.

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.

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.

Healthcare professionals should be aware that, in general, there is no reason to advise against pregnancy or breastfeeding in women with FH.

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.

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 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.

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.

Serum cholesterol concentrations should not be measured routinely during pregnancy.

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.

On-going care

All people with FH should be offered a regular structured review that is carried out at least annually.

A baseline electrocardiogram (ECG) should be considered for adults with FH.

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.

A person with FH with symptoms or signs of possible coronary heart disease which are immediately life-threatening (for example, acute 3 coronary syndrome) should be referred to hospital as an emergency in line with advice for the general population.

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).

Upon diagnosis, healthcare professionals should offer all adults and children/young people with homozygous FH a referral for an evaluation of coronary heart disease. 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.
What next?

HEART UK is collecting comments and views from a range of health care professionals in addition to people affected and living with FH. HEART UK will share these comments with NICE (anonymously if you prefer).

When you’ve read the document, there may be some questions you still have or think there are areas that need strengthening. Equally, you may not have anything further to add. Either way, please do get in touch and let us know what you think.

Are GPs best placed to find FH?
Will more people with FH be found if the NHS follows these Guidelines?
Is the level of diagnosis right? Is using Simon Broome and the Dutch Lipid Score the right thing to use?
Is there something more that should be considered when contacting family members for testing?
Are there any treatments or medicines that should be included, or excluded?
If you are affected or live with FH, how is your experience reflected in these proposals? Is anything missing from the proposals?
Should risk in women and men be highlighted?

If there are any specific or general points you would like to make please contact Simon Williams
sw@heartuk.org.uk