Identification and management of familial hypercholesterolaemia (FH)

Full guideline

August 2008

National Collaborating Centre for Primary Care

This guideline updates NICE guideline CG71
Parts of this guideline were updated by a standing Committee in 2017.
Recommendations marked in dark grey on pages 11 to 15 were deleted and replaced by new recommendations which can be found in the addendum (evidence reviews) to this guideline. Recommendations marked in light grey on pages 11 and 12 have been edited. These can also be found in the addendum.
Nicotinic acid has been removed from the treatment recommendations. See www.nice.org.uk/guidance/CG71 for more details.

NCCPC — The National Collaborating Centre for Primary Care

RCGP — Royal College of General Practitioners

Update information
September 2023: We updated the definition of high-intensity statin.
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.
September 2019: Recommendation 1.1.1 was amended to be clearer about when to suspect familial hypercholesterolaemia.
December 2017: The definition of high-intensity statin was amended to: Statins are classified as high intensity if they produce average reductions in LDL-C greater than 40%.
November 2017: Evidence on case finding, diagnosis and statin monotherapy was reviewed. Some new recommendations were added and some recommendations were updated.
July 2016: Recommendations 1.3.1.4 to 1.3.1.9 replaced, adapted from NICE technology appraisal guidance 385.
Changes can be seen in the short version of the guidance at www.nice.org.uk/guidance/CG71

Citation

DeMott K, Nherera L, Shaw EJ, Minhas R, Humphries SE, Kathoria M, Ritchie G, Nunes V, Davies D, Lee P, McDowell I, Neil A, Qureshi N, Rowlands P, Seed M, Stracey H, Thorogood M, Watson M. *Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia.* 2008. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

Table of contents

Appendices (these are available in a separate file)

Appendix A – Scope

Appendix B - Clinical questions and search strategies

Appendix C – Clinical evidence extractions

Appendix D – Health economic extractions

Appendix E – Health economic modelling

Appendix F – Diagnostic criteria for probands and relatives

Appendix G – Declarations of Interest

Foreword

While the NHS in England and Wales has made spectacular progress in improving the secondary prevention of cardiovascular disease, we now need to work harder to identify those who are at particularly high risk of myocardial infarction.

This group includes those with familial hypercholesterolaemia who, because of their high risk of premature coronary heart disease, merit specific attention. The condition is seriously under-diagnosed so that perhaps only one in six patients is known to the NHS and, for those in whom the diagnosis is made, it is often made too late restricting the effect of the treatments available.

Since this condition is genetically determined, families must become the focus of attention so that cascade testing can identify those individuals who will benefit from early treatment and the near-normal life expectancy that can result. The innovative use of DNA testing allied with cholesterol testing will help to ensure that children, young people and adults with this condition are identified and offered timely advice and treatment.

I welcome the publication of this guideline and look forward to working with NICE during its implementation.

Professor Roger Boyle CBE

National Director for Heart Disease and Stroke

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.

The criteria the GDG used to select these key priorities for implementation included whether a recommendation is likely to:

- have a high **impact** on patients' outcomes in particular mortality and morbidity
- have a **high impact** on reducing variation in the treatment offered to patients
- lead to a **more efficient** use of NHS resources
- enable patients to **reach important points in the care pathway more rapidly**

Please note, the numbering (in square brackets) is as in the NICE guideline.

Diagnosis

- A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of FH (see Simon Broome criteria, appendix E). [1.1.8]

- In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter.
  - A DNA test if the family mutation is known.
  - LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty. [1.1.15]

- 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. [1.1.11]

Identifying people with FH using cascade testing

- 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 (see appendix D). [1.2.2]

- Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives. [1.2.4]

- The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH. [1.2.8]

Management

Adults

- Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment). [1.3.1.3]

Children and young people

- 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' (available from www.dh.gov.uk). [1.3.1.19]

Information needs and support

Information and counselling on contraception for women and girls with FH

- 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. [1.4.2.1]

Ongoing assessment and monitoring

Review

- All people with FH should be offered a regular structured review that is carried out at least annually. [1.5.1.1]

Recommendations

1.1   Diagnosis

[Hyperlink to Chapter 3](#)

See also section 1.4 on 'Information needs and support'.

1.1.1   Healthcare professionals should consider the possibility of FH in adults with raised cholesterol (total cholesterol typically greater than 7.5 mmol/l), especially when there is a personal or a family history of premature coronary heart disease.

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

1.1.3   A diagnosis of FH should be made using the Simon Broome criteria, which include a combination of family history, clinical signs (specifically tendon xanthomata), cholesterol concentration and DNA testing (see appendix E).

1.1.4   Healthcare professionals should inform people with a diagnosis of FH based on the Simon Broome criteria (see appendix E) that they have a clinical diagnosis of FH.

1.1.5   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. All people with a clinical diagnosis of homozygous FH should be offered referral to a specialist centre.

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

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. A family history of premature coronary heart

disease should always be assessed in a person being considered for a diagnosis of FH (see Simon Broome criteria, appendix E).

1.1.8   A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of FH (see Simon Broome criteria, appendix E).

1.1.9   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.

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

1.1.11   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.

1.1.12   Healthcare professionals should offer people with a clinical diagnosis of FH a DNA test to increase the certainty of their diagnosis and to aid diagnosis among their relatives.

1.1.13   Healthcare professionals should 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 appendix E).

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[1]

1.1.15   In children at risk of FH because of one affected parent, the following diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter.

- A DNA test if the family mutation is known.
- LDL-C concentration measurement if the family mutation is not known. When excluding a diagnosis of FH a further LDL-C measurement should be repeated after puberty because LDL-C concentrations change during puberty.

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.

1.2   Identifying people with FH using cascade testing

Hyperlink to Chapter 4

1.2.1   Healthcare professionals should use systematic methods (that is, cascade testing) for the identification of people with FH.

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.

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.

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[1] 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' (NICE clinical guideline 67).

1.2.4   Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives.

1.2.5   In families in which a mutation has been identified, the mutation and not LDL-C concentration should be used to identify affected relatives. This should include at least the first- and second- and, when possible, third-degree biological relatives.

1.2.6   In the absence of a DNA diagnosis, cascade testing using LDL-C concentration measurements should be undertaken to identify people with FH.

1.2.7   To diagnose FH in relatives of an index individual, the gender- and age-specific criteria for LDL-C concentration in appendix E should be used. The Simon Broome LDL-C criteria for index individuals should not be used because this will result in under diagnosis.

1.2.8   The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH.

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

1.3   Management

1.3.1   Drug treatment

[Hyperlink to Chapter 5]

Adults

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.

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

1.3.1.3 Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

1.3.1.4 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).

1.3.1.5 Healthcare professionals should offer treatment with a statin with a low acquisition cost for adults with FH in whom the diagnosis is made after the age of 60 and who do not have coronary heart disease.

1.3.1.6 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. [2]

1.3.1.7 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 recommendation 1.3.1.11) .

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[2] These recommendations are from 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines.

1.3.1.8 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[3]:

- serum total or LDL-C concentration is not appropriately controlled (as defined in recommendation 1.3.1.10) 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 1.3.1.11)

and

- consideration is being given to changing from initial statin therapy to an alternative statin.

1.3.1.9 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[3].

1.3.1.10 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations. [3]

1.3.1.11 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 tests[3]

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[3] These recommendations are from 'Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia' (NICE technology appraisal guidance 132). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines

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

1.3.1.13   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).

1.3.1.14   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.

1.3.1.15   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.

1.3.1.16   The decision to offer treatment with a bile acid sequestrant (resin), nicotinic acid or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH.

1.3.1.17   Healthcare professionals should exercise caution when adding a fibrate or nicotinic acid to a statin because of the risk of muscle-related side effects (including rhabdomyolysis). Gemfibrozil and statins should not be used together.

1.3.1.18   Adults with FH who are prescribed nicotinic acid should be offered advice on strategies that reduce flushing. Such advice should include taking low initial doses with meals and/or aspirin 30 minutes before the first daily dose.

Children and young people

1.3.1.19   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' (available from www.dh.gov.uk).

1.3.1.20   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.

1.3.1.21   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.

1.3.1.22   When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment. Healthcare professionals with expertise in FH in children and young people should choose a statin that is licensed for use in the appropriate age group.

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'.

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.

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).

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).

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

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.

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).

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.

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.

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.

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.

Diet

Hyperlink to section 6.3

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

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 www.eatwell.gov.uk/healthydiet for further practical advice.

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 www.eatwell.gov.uk/healthydiet and www.5aday.nhs.uk.

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 www.eatwell.gov.uk/healthydiet

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.

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 'MI: secondary prevention' (NICE clinical guideline 48).

Physical activity

1.3.2.8 Healthcare professionals should advise people with FH to take 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[4].

1.3.2.9 Healthcare professionals should encourage people 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 to exercise at their maximum safe capacity.

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[4].

1.3.2.11 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[4].

Weight management

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[4] See 'At least five a week: evidence on the impact of physical activity and its relationship to health. A report from the Chief Medical Officer' (2004), available from www.dh.gov.uk.

1.3.2.12   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 [5] .

Alcohol consumption

1.3.2.13   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 www.eatwell.gov.uk/healthydiet

Smoking advice

1.3.2.14   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.

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

1.3.2.16   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 [6] .

1.3.2.17   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[7] , and varenicline[8] .

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[5] 'Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children' (NICE clinical guideline 43).
[6] 'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health intervention guidance 1).
[7] 'Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation' (NICE technology appraisal guidance 39).
[8] 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123).

1.3.3 Specialist treatment

Hyperlink to Section 8.2

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 1.1.5 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

1.4   Information needs and support

1.4.1   General information and support

Hyperlink to section 6.2

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.

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.

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.

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.

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

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

Hyperlink to section 8.3.1

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.

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.

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.

1.4.3 Information for pregnant women with FH

Hyperlink to Section 8.3.3

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.

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.

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 (see appendix D) to an obstetrician for a fetal assessment. Women should be fully informed about the nature and purpose of the assessment.

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.

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 cholesterol concentrations should not be measured routinely during pregnancy.

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.

1.5   Ongoing assessment and monitoring
[Hyperlink to Chapter 7](#)

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.

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

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

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.

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 section 1.3).

1.5.2   Referral for evaluation of coronary heart disease

1.5.2.1 Healthcare professionals should offer people with FH an urgent referral (see appendix D) 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.

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.

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).

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.

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.

1   Introduction

1.1   *Epidemiology*

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 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 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 million.

1.2   Management

Early detection and treatment with hydroxy-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins) has been shown to reduce morbidity and mortality in those with heterozygous FH. LDL apheresis and liver transplantation are treatment options for individuals with homozygous FH, with LDL apheresis being occasionally used for heterozygous FH individuals who are refractory to conventional lipid-lowering therapy.

There is evidence that screening can be effective in identifying people in the early stages of FH. Methods proposed include opportunistic screening and cascade testing of the relatives of people identified as having FH ("index cases").

Currently, diagnosis involves clinical assessment and biochemical tests (lipid profile).

1.3   Aim of the guideline

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'(Institute of Medicine, 1990).

This guideline gives recommendations to clinicians and others about diagnosis; identification strategies; drug, specific and general treatments; and assessment and monitoring of FH.

1.4   How the guideline is set out

The recommendations for all the topics in each clinical chapter are listed at the start of the chapter. Both the evidence statements and narratives of the research studies on which our recommendations are based are found within each topic section. The evidence statements precede the narrative for each topic. Also

included in each chapter is a brief explanation of why the GDG made the specific recommendations. The evidence tables with details of the research studies that describe the studies reviewed are found in Appendices C and D.

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.

1.5   Scope

The guideline was developed in accordance with a scope given by the National Institute for Health and Clinical Excellence (NICE, 'the Institute'). The scope set the remit of the guideline and specified those aspects of the identification and management of FH to be included and excluded. The scope was published in January 2007 and is reproduced here in Appendix A.

Whom the guideline is intended for
This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales:

- primary, secondary or tertiary care settings dealing with case identification, diagnostic testing and the management of heterozygous FH in adults and children
- tertiary care for the rare condition of homozygous FH in all age groups.

Areas outside the remit of the guideline

- Techniques for liver transplantation.
- Measurement and reporting of blood lipids (this is covered by the NICE clinical guideline on cardiovascular risk assessment).
- Population-based screening programmes for FH.

1.6   Responsibility and support for guideline development

1.6.1   The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and was formed as a collaborating centre to develop guidelines under contract to NICE. It

is entirely funded by NICE. The NCC-PC is contracted to develop five guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres which focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as the host organisation. The Royal Pharmaceutical Society and the Community Practitioners and Health Visitors' Association are partner members with representation from other professional and lay bodies on the Board. The RCGP holds the contract with the Institute for the NCC-PC.

1.6.2   The development team

The development team had the responsibility for this guideline throughout its development. They were responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

Guideline lead

who is a senior member of the NCC-PC team who has overall responsibility for the guideline

Information scientist

who searched the bibliographic databases for evidence to answer the questions posed by the GDG

Reviewer (Health Services Research Fellow)

with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG

Health economist

who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost effectiveness

Project manager

who was responsible for organising and planning the development, for meetings and minutes and for liaising with the Institute and external bodies

Scientific advisor

with an academic understanding of the research in the area and its practical implications to the service, who advised the development team on searches and the interpretation of the literature

Chair

who was responsible for chairing and facilitating the working of the GDG meetings

Applications were invited for the post of Scientific Advisor, who was recruited to work on average, a half a day a week on the guideline. The members of the development team attended the GDG meetings and participated in them. The development team also met regularly with the Chair of the GDG during the development of the guideline to review progress and plan work.

1.6.3   The Guideline Development Group (GDG)

A Chair was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

Guideline Development Groups (GDGs) are working groups consisting of a range of members with the experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations which were sent the draft scope of the guideline with some guidance on the expertise needed. Two patient representatives and 8 healthcare professionals were invited to join the GDG as full members, with a further 6 healthcare professionals invited as co-opted experts.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments using the same process as stakeholders.

Each member of the GDG served as an individual expert in their own right and not as a representative of their nominating organisation, although they were encouraged to keep the nominating organisation informed of progress.

In accordance with guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry. Details of these can be seen in Appendix G.

The names of GDG members appear listed below.

Full GDG members
Dr Rubin Minhas (Chair)
General Practitioner, Primary Care CHD Lead, Medway Primary Care Trust and Honorary Senior Lecturer, Faculty of Science, Technology and Medical Studies, University of Kent.

Professor Steve E Humphries, PhD MRCP, FRCPath (Scientific 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 FRCPath
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 Rossi Naoumova

Honorary Consultant Physician in Lipidology and Lead Clinician (Lipid Clinic);

MRC Senior Clinical Scientist (from September to October 2006)

Dr Nadeem Qureshi

GP and Clinical Senior Lecturer in Primary Care, University of Nottingham, Derby

Mr Philip Rowlands

Patient, Penarth

Dr Mary Seed, DM FRCPath 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

Ms Melanie Watson

FH Specialist Nurse and DH Trainee Genetic Counsellor, All Wales Genetic

Service, Cardiff

Professor Margaret Thorogood PhD

Professor of Epidemiology, University of Warwick, Coventry

Members of the GDG from the NCC-PC were:

Ms Elizabeth Shaw

Guideline Lead and Deputy Chief Executive, NCC-PC (until February 2008)

Ms Nancy Turnbull

Guideline Lead and Chief Executive, NCC-PC (from February 2008)

Dr Kathleen DeMott PhD

Health Services Research Fellow, NCC-PC

Dr Meeta Kathoria PhD

Project Manager, NCC-PC (until December 2007)

Ms Vanessa Nunes

Project Manager, NCC-PC (from January 2008)

Mr Leo Nherera

Health Economist, NCC-PC

Ms Gill Ritchie

Information Scientist and Programme Manager, NCC-PC

Ms Mei-yin Tok

Health Economist, NCC-PC (from April 2007 until August 2007)

Dr Neill Calvert

Senior Health Economist, NCC-PC (from September 2007)

Co-opted GDG Members

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 Kings 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

Observers

Ms Colette Marshall

Commissioning Manager, National Institute for Health and Clinical Excellence (until August 2007)

Ms Sarah Willett

Commissioning Manager, National Institute for Health and Clinical Excellence (from December 2007)

1.6.4 Guideline Development Group meetings

The GDG met at 5 to 6 weekly intervals for 16 months to review the evidence identified by the development team, to comment on its quality and relevance, and to develop recommendations for clinical practice based on the available evidence. The recommendations were agreed by the full GDG.

1.7   Care pathways

Two clinical care pathways have been developed to indicate the key components in identification/diagnosis and management of FH in adults and children.

Individuals identified in Primary Care or by other Health Care professionals, who are suspected of having FH should be referred to a specialist centre for the following diagnostic and management procedures.

The care pathways

FH Diagnosis
Healthcare professionals should offer a referral to a specialist for confirmation of diagnosis.

Counselling for index individuals
Inform individuals of:
- Implications and limitations of LDL-C and DNA tests
- Results of tests and implications for index individuals and their families
- Clinical diagnosis of FH - if confirmed by Simon Broome criteria
- Unequivocal diagnosis of FH- if mutation identified

Diagnostic procedures in index individuals
Assessment includes:
- Personal and family history of premature CHD
- Symptoms and clinical signs
- Two measurements of LDL-C
- Exclude secondary causes of hypercholesterolaemia
- Drawing up a family pedigree
- Clinical diagnosis using Simon Broome criteria
- Following a clinical diagnosis offer DNA test

Diagnostic procedures for first-, second- and third-degree relatives of index individuals
Assessment includes:
- If mutation identified in index individual offer DNA test
- If mutation not identified in index individual offer LDL-C measurement and use gender-age specific LDL-C criteria for diagnosis
- Children with one affected parent: offer a DNA test if mutation identified in parent, and if not measure LDL-C by age 10 or earliest opportunity thereafter. Repeat after puberty before excluding FH
- For those people where the diagnosis of FH has been excluded, manage cardiovascular risk as for an individual of their age and gender in the general population (see NICE lipid modification guideline)

Counselling for first-, second- and third-degree relatives of index individuals
Inform individuals of:
- Implications and limitations of tests
- Results of tests and implications
- Clinical diagnosis - if confirmed by gender-age specific LDL-C criteria
- Unequivocal diagnosis - if mutation identified

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 CG 67)

Clinical/DNA diagnosis of FH

FH
Management

Adults with FH

Assessment

- People with FH are already at a high risk of premature CHD: the Framingham algorithm should not be used to assess their CHD risk
- Offer a referral for evaluation of CHD if family history of CHD in early adulthood is present or ≥2 other CV risk factors are present (e.g. smoking, male)
- Take at least three-generation pedigree noting age of onset of CHD, lipid levels and smoking history of relatives
- Upon diagnosis refer all adults with homozygous FH for an evaluation of CHD

- Drug therapy
- Offer a statin as the initial treatment
- Consider a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50%
- Inform women they should stop lipid-lowering medication 3 months prior to attempting to conceive
- Inform women that in the event of an unplanned pregnancy lipid-lowering medication should be stopped and medical advice should be sought.
- Prescribing should be informed by concomitant medication, comorbidities, safety and tolerability

Optimising drug therapy

- To reduce LDL-C by >50% consider increasing dose of statin to maximum licensed or tolerated dose
- Offer referral to a specialist with expertise in FH for consideration for further treatment if individual at very high risk of a coronary event, i.e.

   A. Established CHD

   B. A family history of premature CHD

   C. Two or more other CV risk factors (e.g. male, smoke, hypertension, DM)

- If the maximum licensed or tolerated dose of statin does not reduce LDL-C by greater than 50% consider adding ezetimibe, bile acid sequestrant (resin), nicotinic acid or a fibrate to initial statin therapy
- The decision to add a bile acid sequestrant (resin), nicotinic acid or a fibrate should be taken by a specialist with expertise in FH

Monitoring and review

- Offer a structured review carried out at least annually:

   - Measure fasting lipid profile

   - Assess any symptoms of coronary heart disease, and smoking status

   - Discuss concordance with medication and possible side effects

   - Discuss changes in lifestyle or lipid-modifying drug therapy that may be required to achieve recommended LDL-C concentration

- Update family pedigree with regard to CHD events
- Update family pedigree for progress with cascade testing.
- Offer an urgent referral for evaluation if signs or symptoms of possible CHD are present which are not immediately life threatening. Use a low threshold for referral

Children and young people with FH

Assessment

- Refer children and young people diagnosed with, or being investigated for a diagnosis of FH, to a specialist with expertise in FH in children and young people.
- Upon diagnosis refer all children/young people with homozygous FH for an evaluation of CHD (do not routinely offer if heterozygous FH present)

Drug therapy

- Discuss choice of treatment with the adult or child/young person and their parent/carer informed by consideration of concomitant medication, comorbidities, safety and tolerability
- Consider lipid-modifying drug therapy for a child or young person with FH, usually by the age of 10 years. Defer or offer treatment, taking into account:

   - their age

   - the age of onset of CHD within the family

   - presence of other CV risk factors including their LDL-C concentration

- Offer a statin as the initial treatment
- Statins, licensed for the appropriate age group, should be the initial treatment, usually prescribed at the doses in 'BNF for children'
- Discuss risks for future pregnancy and the fetus while taking lipid-modifying medication with women/young girls

Optimising drug therapy

- In exceptional instances, for example when there is a family history of coronary heart disease in early adulthood, consider:

   - a higher dose of statin than 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

- Consider other lipid-modifying drug therapies (such as, bile acid sequestrants [resins], fibrates or ezetimibe) if there is intolerance of statins

Monitoring and review

- Offer a structured review carried out at least annually:

   - Measure fasting lipid profile

   - Assess any symptoms of coronary heart disease, and smoking status

   - Discuss concordance with medication and possible side effects

   - Discuss changes in lifestyle or lipid-modifying drug therapy that may be required to achieve recommended LDL-C concentration

- Routinely monitor growth and pubertal development
- Discuss risks for future pregnancy and the fetus while taking lipid-modifying medication
- Offer an urgent referral for evaluation if signs or symptoms of possible CHD are present which are not immediately life threatening. Use a low threshold for referral

FH
Management (cont.)
Healthcare professionals should offer a referral to all people with FH to a specialist for initiation of cascade testing.

Adults with FH		**Children and young people with FH**

General information and advice

Lifestyle advice and health education
- Strongly discourage people from starting smoking, especially children
- Recommend and support smoking cessation
- Offer dietary advice
- Offer advice on physical activity
- Offer advice on appropriate alcohol consumption

Information and support
Includes:
- Educational information about FH
- The process of family testing
- DNA testing
- Measurement of LDL-C concentration
- The individual's specific level of CHD risk
- The implications of the individual's CHD risk for their family
- Lifestyle and treatment options
- Written advice and information about patient support groups

Cascade testing for FH
- Explain cascade testing and discuss implications
- Use systematic method
- Encourage people with FH to contact their relatives to inform them of their potential risk and to enable cascade testing
- Offer to facilitate sharing of information about FH with family members

On-going monitoring of CHD risk
- Refer urgently for cardiovascular evaluation if individuals have symptoms or signs of possible CHD
- Consider referral for cardiovascular evaluation if individuals have a family history of CHD in early adulthood or two or more other cardiovascular risk factors (e.g. smoking, hypertension, diabetes, male)

Additional recommendations for Individuals with homozygous FH
- Upon diagnosis refer all adults with homozygous FH for an evaluation of CHD
- Consider LDL apheresis
- Consider liver transplantation if there is disease progression despite treatment with lipid-modifying medication and LDL apheresis

Additional recommendations for Individuals with heterozygous FH
- Where there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying medication and optimal medical and surgical therapy, consider LDL apheresis

1.8   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).

1.8.1   Identification using clinical registers

What is the clinical and cost effectiveness of identifying a person with FH (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 individuals, because currently recommended strategies are likely to lead to the identification of less than 50% of the expected number of people with FH in the UK.

These additional strategies should evaluate note searching in general practice and from secondary care coronary heart disease registers (for example, 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 recommended FH diagnostic criteria and a combination of different cut-off points for untreated raised total or LDL-C concentration, age of onset of heart disease in the index case, age of onset of heart disease in first-degree relatives, and other factors.

1.8.2   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.

1.8.3   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.

1.8.4 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 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.

1.8.5 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.

1.9   Acknowledgements

1.10   Glossary

Adults with FH	For the purpose of this guideline, 'adults' includes all persons with FH (heterozygous or homozygous) who are 16 years and older
CAD	Coronary artery disease (CAD) is an abnormal condition characterised by the narrowing of the small blood vessels that supply blood and oxygen to the heart. (CAD is synonymous with coronary heart disease (CHD).
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 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).

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
Case finding	A strategy of surveying a population to find those who have the specified disease or condition which is under investigation.
CHD	Coronary heart disease (CHD) is an abnormal condition characterised by the narrowing of the small blood vessels that supply blood and oxygen to the heart. (CHD is synonymous with coronary artery disease (CAD).
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 the service recipients.
Dominant pattern of inheritance (autosomal dominant pattern of inheritance)	An affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal (i.e. non-sex) chromosomes. Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant gene, and therefore the disorder, onto each of their children.
Family history	The structure and relationships within the family that relates information about diseases in family members.
First degree relatives	A person's biological parents, brothers and sisters and children.
Heterozygous FH	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.
High-intensity statin	High intensity statin: statins are classified as high intensity if they produce greater LDL-cholesterol reductions than simvastatin 40mg (e.g. simvastatin 80mg and appropriate doses of atorvastatin and rosuvastatin).
Homozygous FH	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. |
| Genetic counsellor | A health professional with specialised training and experience in both areas of medical genetics and counselling. |
| HDL-C | High density lipoprotein cholesterol |

Index case	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.
Index individual (Synonymous with 'proband')	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.
LDL-C	Low density lipoprotein cholesterol
Lipid measurements/ concentrations/levels	These terms refer to the measurement of total cholesterol (TC), triglycerides (TG), 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.
Molecular Genetics Diagnostic Service	The laboratory where blood samples are received, and tested for mutations causing disease. Laboratories are run under accredited schemes to ensure confidentiality and quality control of the results.
Mutation	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.
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.
Premature CHD	For the purpose of this guideline this refers to a coronary event that has occurred (1) before 55 years of age in a male index individual or 65 years of age in a female index individual or (2) before 60 years of age in first-degree relative, or (3) before 50 years of age in second-degree relative
Proband	The affected (index) individual through whom a family with a genetic disorder is ascertained.
Second-degree relatives	A person's biological grandparent, uncle, aunt, niece, nephew, half sister or half brother.
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, 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. 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.
Targeted testing	A mechanism for identifying individuals at increased risk of developing a particular condition. In the case of FH, targeted cascade testing of relatives of positively diagnosed individual aims to provide a greater rate of case identification than general population screening.
TC	Total cholesterol
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.
TG	Triglycerides
Third-degree 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.

2   Methods

2.1   Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the Institute in 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. *The Guideline Development Process – an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline.

2.2   Developing key clinical questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the Guideline Development Group (GDG).

The KCQs were developed by the GDG and with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs) specifying interventions to search and outcomes to be searched for by the methodology team and these EBQs formed the basis of the literature searching, appraisal and synthesis.

The total list of KCQs identified is listed in Appendix B. The development team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential. Also, where appropriate, high quality evidence in populations other than that of individual with FH was used to corroborate the limited direct evidence. Literature searches were not undertaken where there was already national guidance on the topic to which the guideline could cross refer. This is detailed in Appendix B.

2.3   Literature search strategy

Systematic literature searches are undertaken to identify published evidence to answer the clinical questions identified by the methodology team and the GDG. The information scientist developed search strategies for each question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and free text terms. Searches were conducted between October 2006 and September 2007. Update searches for all questions were carried out in December 2007 to identify any recently published evidence. Full details of the sources and databases searched and the strategies are available in Appendix B. In addition to the update searches, we also considered any important evidence published before the final guideline was submitted.

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED) National Research Register and Current Controlled Trials

For each clinical question the following bibliographic databases were searched from their inception to the latest date available: Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Health Technology Database (HTA), MEDLINE, MEDLINE in Process, EMBASE, CINAHL, CENTRAL (Cochrane Controlled Trials Register), Science Citation Index. When appropriate to the question PsycINFO was also searched.

The search strategies were developed in MEDLINE and then adapted for searching in other bibliographic databases. For the pharmacological questions, methodological search filters designed to limit searches to systematic reviews or

randomised controlled trials were used. These were developed by the Centre of Reviews and Dissemination and The Cochrane Collaboration. For all other questions, no restriction was placed on study design.

The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED) and in MEDLINE, MEDLINE in process, EMBASE Science Citation Index, and Social Science Citation Index using an economics search strategy developed by ScHARR at the University of Sheffield.

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

2.4   Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if they appeared to address the KCQ. The highest level of evidence was sought. However observational studies, surveys and expert formal consensus results were used when randomised control trials were not available. In general, only English language papers were reviewed however, for the questions on apheresis we also searched for foreign language papers (specifically in Japanese and German) on the advice of the GDG. Following a critical review of the full text paper, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded.

We also contacted the relevant manufacturers of key drugs for data on the safety of lipid-modifying drugs in children due to the lack of published evidence. This request was conducted according to the process outlined in the 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual.

The reasons for rejecting any paper ordered were recorded and details can be seen in Appendix C.

2.5 Critical appraisal of the evidence

From the papers retrieved, the Health Service Research Fellow (HSRF) synthesised the evidence for each question or questions into a narrative summary. These form the basis of this guideline. Each study was critically appraised using the Institute's criteria for quality assessment and the information extracted for included studies is given in Appendix C. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

2.5.1 Choice of outcomes

FH is a condition characterised by abnormally high concentrations of LDL-C. Therefore the GDG decided that only those papers reporting LDL-C as a primary outcome would therefore be included. This is also reflected in the wording of the recommendations, for example, referral specifically to the measurement of LDL-C concentration, rather than total cholesterol. Initial preference was given to interventions with evidence on clinical outcomes whether in the FH population or similar at-risk populations (persons with a myocardial infarction) where evidence in the FH population was lacking.

2.6 Economic analysis

The essence of economic evaluation is that it provides a balance sheet of the benefits and harms as well as the costs of each option. A well conducted economic evaluation will help to identify, measure, value and compare costs and consequences of alternative policy options. Thus the starting point of an economic appraisal is to ensure that healthcare interventions are clinically effective and then also cost effective. Although NICE does not have a threshold for cost effectiveness, interventions with a cost per quality adjusted life year of up to £20,000 are deemed cost effective, those between £20-30,000 may be cost effective and those above £30,000 are unlikely to be judged cost effective. If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost effectiveness of different management strategies in FH a comprehensive systematic review of the economic literature relating to FH patients was conducted. For selected components of the guideline original cost effectiveness analyses were performed. The primary criteria applied for an intervention to be considered cost effective were either:

– the intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies); or

– the intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (or usual care).

2.6.1   Health economic evidence review

Identified titles and abstracts from the economic searches were reviewed by a single health economist and full papers obtained as appropriate. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations.

Papers were included if they were full/partial economic evaluations, considered patients with FH, were written in English, and reported health economic information that could be generalised to UK.

The full papers were critically appraised by the health economist using a standard validated checklist(Kavey, R. EW, Allada, V., Daniels, S. R. et al , 2006). A general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review (see also Appendix D for the full extractions and reasons for exclusion).

Each study was categorized as one of the following: cost effectiveness analysis or cost utility analysis (i.e. cost effectiveness analysis with effectiveness measured in terms of QALYs or life year gained). Some studies were categorized as 'cost consequences analyses' or 'cost minimisation analyses'. These studies did not provide an overall measure of health gain or attempt to sythesise costs and benefits together. Such studies were considered as partial economic evaluations.

2.6.2 Cost effectiveness modelling

Some areas were selected for further economic analysis if there was likelihood that the recommendation made would substantially change clinical practice in the NHS and have important consequences for resource use.

The following areas were chosen for further analysis

1. the use of high intensity statins compared with low intensity statins in the treatment of FH. This was identified as a priority for further evaluation because statins are recommended as the initial treatment for people with FH due to their effects in reducing morbidity and mortality.

2. a cost effectiveness analysis of cascade testing for FH using DNA testing and LDL-C measurements. This was selected as a priority for further evaluation because this approach was recommended for the identification of people with FH and the resource differentials between the alternative approaches were considerable as was the potential eligible population.

Full reports for each analysis are in the Appendix E of the guideline. The GDG was consulted during the construction and interpretation of each model to ensure that appropriate assumptions, model structure and data sources were used. All models were done in accordance to the NICE reference case outlined in the 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual.

2.7   Assigning levels to the evidence

The evidence levels and recommendation are based on the Institute's technical manual 'The guidelines manual'. April 2006. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. Evidence levels for included studies were assigned based upon Table 1.

Table 1

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

2.8   Forming recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with these.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

2.9 Areas without evidence and consensus methodology

The table of clinical questions in Appendix B indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the 'Evidence to recommendations' section of each of the chapters.

2.10 Consultation

The guideline has been developed in accordance with the Institute's guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the draft of the full and short form guideline. In addition, the draft and the GDG's responses to the stakeholders were reviewed by an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the development team recorded the agreed responses.

2.11 Relationships between the guideline and other national guidance

2.11.1 National Service Frameworks

In formulating recommendations consideration was given to the National Service Framework for Coronary Heart Disease (2000) and the National Service Framework for Children, Young People and Maternity Services (2004).

2.11.2   Related NICE Guidance

It was identified that this guideline intersected with the following NICE guidelines published or in development. Cross reference was made to related guidance as appropriate.

Published

Statins for the prevention of cardiovascular events in people at increased risk of developing cardiovascular disease or those with established cardiovascular disease. NICE technology appraisal 94 (2006). Available from www.nice.org.uk/TA094

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

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

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

Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline. Available from www.nice.org.uk/CG67. Through review of published guidance, personal contact and commenting on guideline scope, endeavours were made to ensure that boundaries between guidance were clear and advice was consistent.

3 Diagnosis

[Return to recommendations](#)

3.1 Introduction

3.1.1 Diagnosis of FH

3.1.1.1 Diagnosis using clinical criteria

The clinical diagnosis of FH is based on personal and family history, physical examination, and lipid concentrations. Three groups have developed clinical diagnostic tools for FH: the US MedPed Program, the Simon Broome Register Group in the United Kingdom, and the Dutch Lipid Clinic Network.

The MedPed criteria specify cut points for total cholesterol concentrations specific to an individual's age and family history. The cut points are different for individuals who are the first-, second- or third-degree relatives of a patient with FH, and for the general population, because individuals with a relative with FH have a higher prior probability of having FH.

The Simon Broome Register criteria include cholesterol concentrations, clinical characteristics, molecular diagnosis, and family history. (Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group, 1991).

A Definite familial hypercholesterolaemia is defined as:

- total cholesterol greater than 6.7 mmol/l or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/l in a child aged younger than 16 years or total cholesterol greater than 7.5 mmol/l or LDL-C greater than 4.9 mmol/l in an adult (levels either pre-treatment or highest on treatment)

  plus

- tendon xanthomas in patient, or in first-degree relative (parent, sibling or child), or in second-degree relative (grandparent, uncle or aunt)

or

- DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

B   Possible familial hypercholesterolaemia is defined as:

- total cholesterol greater than 6.7 mmol/l or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/l in a child aged younger than 16 years or total cholesterol greater than 7.5 mmol/l or LDL-C greater than 4.9 mmol/l in an adult (levels either pre-treatment or highest on treatment)
  and at least one of the following
- family history of myocardial infarction: younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative
  or
- family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child or sibling aged younger than 16 years.

The Dutch Lipid Clinic Network criteria(World Health Organization, 1999) are similar to the Simon Broome Register criteria. Points are assigned for family history of hyperlipidaemia or heart disease, clinical characteristics such as tendinous xanthomata, elevated LDL cholesterol, and/or an identified mutation. A total point score of greater than eight is considered "definite" FH, 6-8 is "probable" FH, and 3-5 is "possible" FH. Although the Simon Broome Register criteria consider a molecular diagnosis as evidence for definite FH, the Dutch Lipid clinic Network requires that at least one other criterion be met in addition to molecular diagnosis.(Austin, M. A., Hutter, C. M., Zimmern, R. L. et al , 2004)

3.1.1.2   DNA testing

DNA tests are carried out to find the specific cause of the disorder in an individual with a clinical diagnosis of FH. The diagnostic procedures and protocols used for

FH are essentially identical to those used routinely for genetic testing for other diseases such as cystic fibrosis or familial breast cancer.

To-date, mutations in three genes have been found to cause FH, (*LDLR, APOB, PCSK9*)(Humphries, S. E., Whittall, R. A., Hubbart, C. S. et al , 2006). A number of different methods are used to test for some common mutations and to look for large deletions or re-arrangements in the *LDLR* gene. Further testing is carried out by screening the entire coding and control regions of the *LDLR* gene, using direct sequencing or by methods called fluorescent single-strand conformation polymorphism test (SSCP) and denaturing high-performance liquid chromatography test (dHPLC)(Heath, K. E., Humphries, S. E., Middleton-Price, H. et al , 2001). These tests identify the cause of FH in a significant number of individuals (70-80% of those with a clinical diagnosis of definite FH and 20-30% of those where the clinical diagnosis is less certain)(Graham, C. A., McIlhatton, B. P., Kirk, C. W. et al , 2005; Heath, K. E., Humphries, S. E., Middleton-Price, H. et al , 2001; Humphries, S. E., Whittall, R. A., Hubbart, C. S. et al , 2006). Samples from individuals where no mutation is found can be kept for further testing with the individuals' consent if, for example, other genes causing FH are subsequently identified.

Not finding a mutation does not mean that the individual does not have FH, since the molecular techniques are not 100% sensitive. In either case, the individual's LDL-C and other CHD risk factors should be actively treated.

Knowing the specific family mutation means that the individual's relatives can be offered a simple single DNA test, where the laboratory tests just for the family mutation.

3.1.2   Diagnosis in relatives

There are specific issues associated with the diagnosis of FH in relatives of the proband using LDL-C Concentration or DNA testing.

In the absence of information about the family mutation, the diagnosis of FH in a relative is made based on the elevation of fasting LDL-C concentration. Because

of the prior probability of FH in relatives (1 in 2), the cut-offs used for diagnosis in the general population are too high (where prevalence is 1 in 500). In addition, LDL-C Concentration differ in men and women and generally increase with age, and different cut-offs should be used when diagnosing FH in relatives (see appendix G for recommended cut-offs). However, because of the overlap in LDL-C levels between affected and unaffected individuals (Leonard, J. V., Whitelaw, A. G. L., Wolff, O. H. et al , 1977) the use of such cut-offs still results in diagnostic ambiguity in an estimated 15% of children (aged 5-15 years) and in nearly 50% in adults aged (45-55 years)(Starr, B., Hadfield, S. G., Hutten, B. A. et al , 2008).

Where the family mutation has been identified, this can be quickly and accurately tested for in blood samples from relatives, and further cascade testing undertaken as recommended in the guideline (see Identification strategies for a detailed review of the evidence and the health economic modelling).

3.1.3 Diagnosis in children

The Simon Broome criteria can be used to diagnose FH in children aged under 16 years of age. However, clinical signs – xanthelasma, tendinous xanthomata and corneal arcus – are rarely present in affected children. Total and LDL cholesterol concentrations increase with age and affected children can have concentrations below those expected in adults with FH.

As for diagnosis in relatives, there are issues with using LDL-C Concentration and DNA testing for diagnosis in children. For example, although it is expected that cholesterol will be greater than the 95th centile (taken from age- and sex-specific charts) in an affected child, in reality, concentrations are often much higher than this. DNA diagnosis therefore is extremely helpful in children aged under 16 years.

Children with homozygous FH often have total cholesterol concentrations greater than 11mmol/l. They generally present with cutaneous xanthomata that can be misdiagnosed as warts and may also have tendinous xanthomata and corneal arcus. Molecular evaluation is helpful to confirm the diagnosis and it is important to screen both the maternal and paternal sides of the family.

3.2   Diagnosing FH

3.2.1   Evidence statements on the effectiveness of different diagnostic strategies

Key clinical question:

In adults and children, what is the effectiveness of the following tests to diagnose heterozygous FH in individuals with a history of family history of early heart disease and/or hypercholesterolemia;

– biochemical assays?

– clinical signs and symptoms?

– DNA testing?

– combinations and/or sequences of above?

Question 1 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
No single method of diagnostic testing provides sufficient accuracy to be used exclusively. [2+] In one study(Damgaard, D., Larsen, M. L., Nissen, P. H. et al , 2005) that compared the sensitivity and specificity of different clinical criteria for diagnosing FH, the Simon Broome criteria performed at least as well as the Dutch criteria for individuals with definite FH and both Simon Broome and the Dutch criteria demonstrated better performance than MEDPED. [2+] In 25 babies at risk of FH because of an affected parent, there was significant overlap in LDL-C Concentration within mutation positive (14 babies) and mutation negative (11 babies) groups at birth(Vuorio, A. F., Turtola, H., and Kontula, K., 1997). The individual ranges of LDL-C and TC were non overlapping at one year of age. [2+] In a study of 18 children at risk of FH because of an affected parent (Kessling, A. M., Seed, M., Taylor, R. et al , 1990), serial total cholesterol measurements increased to above the 95th percentile in seven children over 1-7 years. [2+] LDL-C Concentration within the normal range for childhood do not necessarily exclude FH in children. [2+] In a single study(Assouline, L., Levy, E., Feoli-Fonseca, J. C. et al , 1995) of 88 children (mean age range 8.31-8.79 years, ±3.31-4.00) with molecularly defined FH only two children displayed arcus and none had xanthomata on clinical examination. [2+] In 21 children with molecularly defined FH(Koivunen-Niemela, T., Viikari, J., Niinikoski, H. et al , 1994), an ultrasonographic study demonstrated an average of 1.3mm thickening in Achilles tendon; this was abnormal in 8/21 of individuals. [2+] In a study(Junyent, M., Gilabert, R., Zambon, D. et al , 2005) of 290 adults, of whom 127 had FH (81 genetically ascertained), the detection rate of tendon xanthomata by clinical examination and ultrasonography were comparable [2+]	Where appropriate, the GDG considered results of diagnostic studies conducted in the UK or comparable European populations as being of greater applicability to the UK population than those from other parts of the world, due to differences in prevalence and genetic distributions. <u>Clinical diagnosis</u> The GDG considered the criteria for the initial consideration of a diagnosis of FH in people with hypercholesterolemia. The GDG consensus was that it would be reasonable practice consider a diagnosis of FH in people with elevated total cholesterol sufficient to meet the Simon Broome criteria and a personal/family history of premature coronary heart disease, Due to the increasing prevalance of CHD with age, the term premature CHD was adopted (see glossary) The term 'coronary heart disease' rather than cerebrovascular disease was adopted preferentially throughout the guideline as data from the Simon Broome register data showed that people with FH have an excess of coronary disease rather than cerebral or peripheral vascular disease. [7958] Although there was little significant difference in the accuracy of the different methods, the Simon Broome criteria were recommended for making a clinical diagnosis because they were considered to be simpler than other criteria and were developed based on a UK population and offered a comparable positive likelihood ratio to the Dutch criteria (but were more simple/pragmatic to use) and a superior positive likelihood ratio to the MEDPED criteria.. The Simon Broome criteria allow for a diagnosis of 'possible' or 'definite' FH. However in the recommendations it was not considered helpful to distinguish between 'possible' or 'definite' FH, but that where appropriate, evidence statements should reflect any difference between the groups. In relatives of people with FH, there is a higher pre-test probability if using LDL-C alone for diagnosis (thus lowering the sensitivity) so this is not a useful method of diagnosis in relatives and clinicians should use both DNA and LDL-C. Simon Broome criteria should therefore not be used when cascade testing as this would lead to considerable numbers of false negative diagnoses. The criteria should also be different for adults and children. Recommendations on the appropriate use of the

In people with FH, LDL-C Concentration may be significantly elevated from infancy and remain elevated throughout adult life, such that the cholesterol years burden accumulated by an FH individual is significantly higher than for an individual in the general population of their age and gender with similar LDL-C Concentration. [2+]

LDL-C cholesterol concentrations in the general population and individuals with FH overlap [2+]

In UK studies, with individuals from different parts of the country, DNA tests demonstrated a mutation in approx. 20% of those with a clinical diagnosis of possible FH; and up to 80% of those with a clinical diagnosis of definite FH [2+]

In individuals with a clinical diagnosis of FH, the absence of an identified DNA mutation does not exclude the possibility that they have FH [2+]

The concentrations of LDL-C recommended by the Simon Broome Register for identifying individuals in the general population who have a high probability of having FH were chosen to have an acceptable specificity and sensitivity where the expected frequency is 1 in 500. Because of the higher probability (1 in 2) of a relative of an individual with FH having the disease these concentrations have a lower discrimination and are too high.(Starr, B., Hadfield, S. G., Hutten, B. A. et al , 2008) [2+]
(see also Chapter 4)

diagnostic methods were made (see Appendix F). A report (in press but published before guideline completion) highlighted data from the large Dutch cascade project, where lipid levels were known in relatives carrying and not carrying the family mutation. These were used to determine optimal LDL-C criteria for different ages and genders (Starr et al (Starr, B., Hadfield, S. G., Hutten, B. A. et al , 2008) The GDG considered that relatives with an intermediate posterior probability of FH should be considered for other causes of hypercholesterolemia as FH is relatively rare and therefor this advice was provided with the charts.

LDL-C Concentration were adopted for the purpose of establishing a diagnosis and also to ensure consistency both in making recommendations for diagnosis and treatment and also for clinical practice.

The GDG consensus was that a diagnosis of homozygous FH should be considered in children with an LDL cholesterol greater than 11mmol/l.

DNA testing

Mutations can be found in 80% of people with definite FH, with lower rates of mutation identification in the 'probable' group. In a family where a DNA mutation is identified, not all family members may have inherited the mutation. Where DNA testing has excluded FH in a member of a family, the GDG considered that the incidence of de novo mutations was so rare, that screening for these mutations or incorporating this issue in a recommendation did not offer sufficient practical utlity.

The GDG also considered that in some instances, cascade testing may result in the identification of 2 affected relatives and specific recommendations were made regarding this situation due to the high mortality associated with homozygous FH.

Differentiation of risk

Although DNA testing has a role in increasing the certainty of diagnosis, FH can be managed without the knowledge of DNA mutation. Also, the lack of an identified mutation does not mean that the individual is not at high risk, and the decision to offer treatment should be informed by the clinical assessment. Assessment tools based on the Framingham risk assessment equation should not be used because they have not been developed and validated in this population..

	The evidence showed that people with 'possible' FH are still at a considerable higher CHD risk and recommendations were developed that they be treated accordingly.The term 'clinical' diagnosis was used to describe both 'possible' and 'probable' FH. At this time, the evidence was not conclusive on whether different mutation patterns were associated with different risks.

3.2.2 Evidence summary on the effectiveness of different diagnostic strategies

3.2.2.1 Methods of the clinical evidence review

The searches for Question 1 were not restricted by study type or age of study participants.

Identified: 2422

Ordered: 63

Included: 21

Excluded: 42

3.2.2.2 Clinical evidence

A large retrospective, multi-centre cohort study(van Aalst Cohen, E. S., Jansen, A. C. M., Tanck, M. W. T. et al , 2006) was conducted using data on 4000 randomly selected individuals from the DNA bank at the University of Amsterdam. Each record was reviewed and 2400 individuals were defined as having FH by criteria based upon MedPed (USA), Simon Broome Register (UK) and the Dutch Lipid Clinic Network (the Netherlands). The FH diagnostic criteria for this study included the presence of a documented LDL receptor mutation (*LDLR* mutation) or an LDL cholesterol concentration above the 95th percentile for sex and age in combination with at least one of the following:

- the presence of typical tendon xanthomas in the individual or in a first degree relative
- an LDL cholesterol concentration above the 95th percentile for age and sex in a first degree relative
- proven CAD in the individual or in a first degree relative under the age of 60 years.

Patients were tested for the 14 most prevalent Dutch *LDLR* gene mutations. An *LDLR* mutation was identified in 52.3% of these individuals (*LDLR* plus), with

47.8% where no *LDLR* mutation was found (*LDLR* minus). In a random sample of 199 individuals from the *LDLR* minus group, an *LDLR* mutation was found by sequencing in 40 (20%) of these individuals. Further sequencing is currently being performed.

There were significant differences in clinical and laboratory profiles between *LDLR* plus and *LDLR* minus individuals who had been clinically diagnosed with FH. The *LDLR* minus groups had significantly higher BMI measurements as well as other risk factors including smoking and hypertension and elevated glucose concentrations. The *LDLR* plus group showed significantly higher concentrations of LDL-C, TC, and lower concentrations of TG.

Table 1

	LDLR +ve n=1255	*LDLR* -ve n=1145	Statistical significance
Male gender	45.8 % (575/680)	52.8% (605/540)	p<0.001
Age at first visit (years)	42.1 (±12.6)	47.6 (±12.2)	p<0.001
Smoking, ever	68.7% (787/359)	79.5% (811/209)	p<0.001
Hypertension	7.8% (97/1146)	11.7% (133/1000)	p<0.001
First degree relative family history	56.4% (596/460)	65.5% (664/350)	p<0.001
BMI	24.7 (±3.4)	25.6 (±3.6)	p<0.001
Systolic BP (mmHg)	133 (±19)	137 (±20)	p<0.001
Diastolic BP (mmHg)	81 (±10)	83 (±10)	p<0.001
TC (mmol/l)	10.25 (±2.13)	8.80 (±1.54)	p<0.001
LDL-C (mmol/l)	8.18 (±2.05)	6.61 (±1.47)	p<0.001
HDL-C (mmol/l)	1.19 (±0.35)	1.23 (±0.36)	p=0.003
TG (mmol/l)	1.39 (0.98-2.03)	1.71 (1.24-2.35)	p<0.001
Glucose (mmol/l)	4.9 (4.5-5.3)	5.0 (4.6-5.5)	p<0.001

Adapted from published paper(van Aalst Cohen, E. S., Jansen, A. C. M., Tanck, M. W. T. et al , 2006)

The authors discussed the value of genetic testing particularly in children who may begin to develop cardiovascular disease at a very young age and in whom clinical

manifestations such as a high LDL cholesterol and tendon xanthomas often do not appear until a later age.

A study of 1053 individuals was undertaken to determine the mutational spectra of FH among the Danish population (Brusgaard, K., Jordan, P., Hansen, H. et al , 2006). A secondary outcome of this study, which was of interest for this review, showed differences in lipid concentrations (TC significant p=0.0001) between individuals with a mutation and those with no mutation. All results are in mmol/l:

Table 2

Lipids (mmol/l)	Proband (mutation)	Proband (no mutation)	Relatives (mutation)	Relatives (no mutation)
TC	9.82±2.15	8.97±1.55	8.02±2.18	6.23±1.87
HDL-C	1.53±1.57	1.56±0.53	1.53±0.66	1.51±0.39
TG	2.05±3.25	2.01±1.13	1.43±0.70	1.48±0.96
LDL-C	7.12±1.96	6.22±1.5	5.73±1.98	4.00±1.64

Adapted from published paper(Brusgaard, K., Jordan, P., Hansen, H. et al , 2006)

Another Danish study (Damgaard, D., Larsen, M. L., Nissen, P. H. et al , 2005) aimed at testing the ability of three different sets of clinical criteria, MEDPED, Simon Broome Register and the Dutch Lipid Clinic Network, to predict the results of molecular genetic analysis and to test whether population based age and sex specific percentiles of LDL-C offer useful supplemental information in the selection of individuals for molecular genetic analysis. Four hundred and eight index individuals and 385 relatives were included. There was a 61.3% (49.4-72.4) mutation detection rate among index individuals categorized as definite FH by Simon Broome criteria. If only individuals who met Simon Broome criteria were offered molecular genetic analysis the sensitivity would be 34.1% (26.1-42.7) and specificity would be 89.4% (85.1-92.8). The false positive rate would be 10.6% (7.2-14.9).

Using the Dutch Lipid Clinic Network criteria for definite FH, a 62.9 % (52.0-72.9) mutation detection rate was noted. If the Dutch criteria positive individuals only were offered molecular genetic analysis, the sensitivity would be 41.5%

(33.1-50.3) and specificity would be 87.9% (83.4-91.5). The false positive rate would be 12.1% (8.5-16.6).

MEDPED, which used LDL-C and TC concentrations, had a mutation detection rate of 53.5% (45.4-61.6) by TC and 51.6% (43.6_59.5) by LDL-C and sensitivities of 63.4% (54.5-71.6) and 70.3% (61.2-78.4) respectively. The respective specificities were 73.4% (67.8-78.6) and 69.8% (63.8-75.3).

If individuals with a diagnosis of probable FH by Simon Broome and the Dutch criteria were included in molecular genetic analysis, both sets of criteria result in high sensitivities (90.4% and 99.3% respectively) with correspondingly lower mutation detection rates (38.%3 and 34.3% respectively).

Detection by LDL-C at the 95th percentile level and the 90th percentile level were as follows:

Table 3

	Mutation carriers	**Non- carriers**
Index individuals with LDL-C >95th percentile	94.7%	70.5%
FH relatives with LDL-C >95th percentile	67.0%	6.5%
Index individuals with LDL-C >90th percentile	99.2%	91.2%
FH relatives with LDL-C >90th percentile	76.5%	14.7%

Adapted from published paper (Damgaard, D., Larsen, M. L., Nissen, P. H. et al , 2005)

The authors concluded that either inadequacy of the molecular genetic analysis or a more complex, polygenic background for the FH phenotype must be invoked to explain that almost 40% of individuals with definite FH by clinical criteria did not have an identifiable mutation in the *LDLR* gene.

The use of corneal arcus for case finding was studied in a UK population by Winder et al (Winder, A. F., Jolleys, J. C., Day, L. B. et al , 1998). A graded

prevalence of corneal arcus with age was determined for 81 males and 73 females with newly diagnosed heterozygous FH and for 280 males and 353 females with no known disease. Arcus was recorded by one or both of two experienced observers. The proportion of individuals with any grade of arcus within age intervals of 5 years was analysed. Some degree of arcus affected 50% of individuals with FH by age 31-35 years and 50% of healthy individuals by age 41-45 years. Complete full ring arcus affected 50% of the FH group by age 50 years, with only 5% similarly affected in the healthy group. Arcus grade was not related to the presence of coronary disease.

Sonographic Achilles tendon characteristics were evaluated in 290 hypercholesterolaemic individuals (Junyent, M., Gilabert, R., Zambon, D. et al , 2005). One hundred and twenty seven individuals had FH (81 genetically ascertained); there were 88 controls and 163 further individuals with FCH and polygenic hypercholesterolemia. Tendon xanthoma were detected by clinical examination in 43% of the mutation positive group and 22% in the mutation negative group, and by ultrasound, the detection rate was not significantly different in the two groups (40% and 24% respectively).

Using data from the Netherlands FH screening programme cholesterol concentrations among 1005 *LDLR* gene mutation carriers were analysed (Asbroek, A. H., de Mheen, P. J., Defesche, J. C. et al , 2001). Results of total cholesterol concentrations in untreated screenees (n=853) using conventional cut off values (6.5 and 8.0 mmol/l) compared with FH status by DNA testing was as follows:

Table 4

	Mutation +ve (men)	Mutation – ve (men)	Mutation +ve (women)	Mutation – ve (women)
	99(22.4%)	306(75.6%)	101(22.5%)	347(77.5%)
Mean TC mmol/l	7.3(1.3)	5.7(1.1)	7.4(1.4)	5.5(1.1)
TC<6.5 mmol/l	27(27.3%)	245(80.1%)	28(27.7%)	281(81.0%)
6.5<TC<8.0 mmol/l	42(42.4%)	52(17.0%)	44(43.6%)	60(17.3%)
TC>8.0 mmol/l	30(30.3%)	9(2.9%)	29(28.7%)	6(1.7%)
%age>95th percentile	67.7%	15.0%	71.3%	13.3%

Adapted from published paper (Asbroek, A. H., de Mheen, P. J., Defesche, J. C. et al , 2001)

Another study of the Dutch screening program compared diagnosis of family members in which a functional mutation of the *LDLR* gene had been detected by DNA analysis with that by cholesterol measurement, and also assessed whether or not active identification of individuals with FH would lead to more cholesterol lowering treatment (Umans-Eckenhausen, M. A., Defesche, J. C., Sijbrands, E. J. et al , 2001). The results were as follows:

Table 5

	Carriers (n=2039) Mean (sd)	Non carriers (n=3403) Mean (sd)
TC (mmol/l)	7.43 (1.65)	5.49 (1.34)
LDL-C (mmol/l)	5.62 (1.59)	3.56 (1.11)
HDL-C (mmol/l)	1.09 (0.35)	1.20 (0.37)
TG (mmol/l)	1.47 (1.08)	1.66 (1.10)
Treatment with statins	667 (39%)	160 (5%)

Adapted from published paper (Umans-Eckenhausen, M. A., Defesche, J. C., Sijbrands, E. J. et al , 2001)

The figure used to diagnose FH in relatives by total cholesterol concentration was the age-specific and sex-specific 90th percentile. A total cholesterol concentration

below these percentiles was reported in 18% (95% CI 13-22%) of mutation positive individuals (false negatives). These individuals would have been missed if only cholesterol concentrations had been measured. The proportion of false positives was also 18% when the sample cut off was used. Given a cholesterol concentration above the 90th percentile, the post test likelihood of having a mutation detected was 1.52(1.22-1.78) corresponding to a probability of 0.60 (0.55-0.64). For cholesterol concentrations below the 90th percentile, the odds of having the disorder was 0.08 (0.05-0.10).

At the time of examination 39% of the individuals with FH were on statins. One year later after DNA diagnosis, this percentage had increased to 93%.

Genotype/phenotype correlations were studied by Graham et al (Graham, C. A., McClean, E., Ward, A. J. et al , 1999). Probands of 158 families with clinical definitions of probable (120) or definite (38) FH were studied. Mutations were identified in 52 (33%) of the families. However, eight clinically definite FH families remained who had no identified mutations. Comparisons between various mutations, lipid concentrations and tendon xanthoma were presented for 57 of the 60 families studied.

Table 6

Mutation	n	TC (mmol/l) ±sd[1]	LDL-C (mmol/l) ±sd	Tendon xanthoma	Diagnosis
Frameshift	12	38.5±12.9	11.4±1.8	9.3±1.7	83%
Nonsense	8	39.4±14.2	10.3±1.7	8.5±2.0	50%
Mis-sense	21	41.0±17.3	10.1±1.7	7.8±1.9	62%
FDB-R3500Q	8	44.3±12.2	8.8±1.3	6.4±4.1	25%
No mutation	8	47.8±9.2	10.2±1.5	8.3±1.8	100%

.* LDL-C values were not presented. Adapted from published paper (Graham, C. A., McClean, E., Ward, A. J. et al , 1999)

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[1] Assumed to be sd (for both TC and LDL-C) as not documented in the paper

DNA screening of 790 family members of molecularly characterised South African FH index individuals was undertaken to determine what percentage of adults with FH, who were heterozygous for three common mutations, could be diagnosed accurately on the basis of raised total cholesterol concentrations (Vergotine, J., Thiart, R., and Kotze, M. J., 2001). The sensitivity and specificity of FH diagnosis according to TC values (80th percentile) were reported to be 89.3% and 81.9% respectively.

Evaluation of biochemical versus DNA diagnosis revealed that 15.6% of cases may be misdiagnosed when the 80th percentile is used as a biochemical cut-off point for a diagnosis of FH compared with 12.4% using the 95th percentile for age and gender. In total, 16/150 relatives (10.7%) with an FH mutation were falsely classified as normal (negative predictive value of 89.3%), while 53/293 (18.1%) without the mutation were falsely classified as FH heterozygotes (positive predictive value of 81.9%).[2]

A study was conducted to investigate the usefulness of Achilles tendon sonography in detecting individuals with FH (Koivunen-Niemela, T., Alanen, A., and Viikari, J., 1993). One hundred and thirty individuals with hypercholesterolaemia were examined by ultrasound. Individuals with obvious secondary hypercholesterolaemias were excluded. Forty individuals had clinically evident FH. Fifty-one individuals had clinically evident hypercholesterolaemia without evidence of FH. In 19 of the 51 individuals FH had to be ruled out by DNA testing. The following results were obtained:

Table 7

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[2] The GDG questioned the statistics reported in this study. The sensitivity and specificity were re-calculated and found to be 92% and 89% respectively. The positive predictive value was 72% and negative predictive value was 94% when re-calculated.

	FH (n=40)	No FH (n=51)	Controls (n=41)
Achilles tendon thickness (mm, mean±sem)	11.0±0.5	7.3±0.2	7.1±0.2
Thickened tendons (%)	25 (63%)	2 (4%)	0
Low or mixed echogenicity of tendons (%)	36 (90%)	3 (6%)	0

Adapted from published paper (Koivunen-Niemela, T., Alanen, A., and Viikari, J., 1993)

FH could not be confirmed by DNA testing in the three individuals with high cholesterol and tendon xanthoma.

The concordance of clinical and molecular genetic diagnoses of heterozygous FH was studied in 65 participants from 10 Finnish families (Koivisto, P. V. I., Koivisto, U. M., Miettinen, T. A. et al , 1992). Using DNA testing as the 'gold standard,' a correct clinical diagnosis was made in 55 (85%) of 65 individuals. In the age group aged under 18 years only two of the five FH children were correctly diagnosed clinically, because the serum LDL-C Concentration in the other three individuals were lower than diagnostic limits. However, when age- and sex-specific LDL cholesterol concentration curves were used, this permitted correct diagnosis in 95% of those with a family history. Two of the four undiagnosed individuals were children. The other two individuals had co-morbidities.

Xanthomatosis was demonstrated in 17 of the 25 adult DNA verified individuals with FH (68%) but in none of the mutation negative individuals. Xanthomatosis was also suspected in one young and six adults with FH. Thus, only two (8%) of the 25 adults with FH were totally free of signs of xanthomatosis.

Diagnosis by statistical methods
Four studies (Kwiterovich, P. O. J., Fredrickson, D. S., and Levy, R. I., 1974; Leonard, J. V., Whitelaw, A. G. L., Wolff, O. H. et al , 1977; Mabuchi, H., Higashikata, T., Nohara, A. et al , 2005; Williams, R. R., Hunt, S. C., Schumacher, M. C. et al , 1993) used statistical methods and genetic validation to develop criteria for making the diagnosis of FH.

The statistical concept of a priori probabilities was applied by Williams et al (Williams, R. R., Hunt, S. C., Schumacher, M. C. et al , 1993) to derive two sets of practical screening criteria: one for people participating in general population screening studies and another for close relatives of confirmed FH cases. Probability distributions were generated from a population study of 48,482 persons and the relative size of the area under the FH and non FH curves were calculated. The results showed dramatic differences. At a total cholesterol (TC) concentration of 310 mg/dl (7.95 mmol/l) only 4% of people in the general population would receive a diagnosis of FH but 95% of those who were first degree relatives of known cases would have been diagnosed with FH. In population screening, the calculated FH criteria required a TC >360 mg/dl (9.23 mmol/l) for adults aged 40 years or older, or 270 mg/dl (6.92 mmol/l) in young people and children aged under 18 years. Among first degree relatives of confirmed cases in families with FH the TC is much lower: 290 mg/dl (7.44 mmol/l) for adults aged 40 years or older, and >220 mg/dl (5.64 mmol/l) in young people and children aged under 18 years. These criteria were validated among 207 people in 5 large FH pedigrees in whom genetic testing established (n=75) or ruled out (n=132) the diagnosis of FH, revealing a specificity of 98% and sensitivity of 87%. Using the proposed LDL-C criteria, the sensitivity was 91% while specificity was again 98%.

In a Japanese study of 181 individuals with FH genetically diagnosed and 100 unaffected relatives(Mabuchi, H., Higashikata, T., Nohara, A. et al , 2005), distributions of serum total cholesterol and LDL-C showed distinct bimodality when graphed, while HDL-C and log TG concentrations did not. A TC of 225 mg/dl (5.77 mmol/l) and an LDL-C of 160 mg/dl (4.10 mmol/l) were seen to be the cutoff points between normal individuals and those with FH. Sensitivity and specificity of these criteria were tested by ROC analysis of a sample of 281 sequentially sampled first- and second-degree relatives in whom the diagnosis of FH had been established using genetic testing. The proposed total cholesterol criteria of 224 mg/dl (5.74 mmol/l) and 225 mg/dl (5.77 mmol/dl) were in agreement with the DNA marker, resulting in an observed specificity of 98.5% and sensitivity of 99.4%. LDL-C cutoffs of 161 mg/dl (4.13 mmol/l) to 163 mg/dl (4.18 mmol/dl) produced an observed specificity of 98.5% and a sensitivity of 98.3%. Three of the 181

individuals with FH showed LDL-C Concentration less than 160 mg/dl (4.10 mmol/l) and none of the non-FH individuals showed LDL-C Concentration higher than 160 mg/dl. (These data may not be relevant to the UK due to very low concentrations of LDL-C in the Japanese population).

One hundred thirty four children, aged between 1 and 16 years, from 57 kinships were seen at the Hospital for Sick Children, Great Ormond Street, London because at least one first-degree relative was considered to have FH(Leonard, J. V., Whitelaw, A. G. L., Wolff, O. H. et al , 1977). Total cholesterol concentrations were taken (although not in a consistent manner) and the resulting distribution was bimodal. The two peaks represented the FH children and healthy children. The estimated mean in the unaffected group was 4.9 (3.2-7.3) mmol/l and in the FH children was 8.9 (6.6-12) mmol/l. Two curves, logarithm transformed and the fitted curves, of FH and healthy children intersected at 6.77 mmol/l. At the point of intersection, a minimum (4.25%) of the total population would be misclassified.

In an early study of children aged 1-19 years who each had one parent with FH (Kwiterovich, P. O. J., Fredrickson, D. S., and Levy, R. I., 1974) the natural logarithm of LDL-C from 217 children was plotted and the observed distribution was bimodal and two populations were derived by the maximum likelihood method. The 'antimode' was 4.2 mmol/l and 55% of the observations were in the left distribution. In the normal (left) population 7.2% were above the cut point (false positives) and 9.7% of those in the affected (right) population were below the cut point (false negatives). When TC was plotted in 236 children the degree of overlap was sufficiently great so that the sum of the two populations was not bimodal but bitangential. The antimode for TC was 6.03 mmol/l. Among children in the normal (left) population, 8.5% were above the cut point (false positives) and 18.9% of the children in the affected (right) population were below the cut point (false negatives).

The analysis of the data collected for this study also supported the hypothesis (at the time of this study) that FH is inherited as a monogenic trait with early expression in children.

Diagnosis in children

Three founder related *LDLR* mutations cause FH in approximately 90% South African Afrikaners (Kotze, M. J., Peeters, A. V., Loubser, O. et al , 1998). Two hundred and twenty one children from 85 families were screened for mutations. Total and LDL-C Concentration were similar among the different mutation positive children and mean values were significantly higher compared to those without a detected mutation (p<0.0001). The results were as follows:

Table 8

Mean (sd)	FH	Non-FH
Male/female	60/56	50/54
age (years)	11 (4)	12 (4)
TC (mmol/l)	7.7(1.3)	4.7(0.7)
LDL-C (mmol/l)	6.0(1.3)	2.8(0.6)
HDL-C (mmol/l)	1.2(0.3)	1.3(0.3)
TG (mmol/l)	1.0(0.6)	1.1(0.7)

Adapted from published paper (Kotze, M. J., Peeters, A. V., Loubser, O. et al , 1998)

Among these children a TC concentration of 6 mmol/l was the best at discriminating between FH children and those without a mutation. Using this value 4.5% of the total group of 220 children would have been misdiagnosed compared with 11.4% using the 80th percentile, and 7.7% using the 95th percentile for age and sex. In total, 8/116 (6.9%) of the children with an FH mutation were falsely classified as normal (negative predictive value of 93%) whilst 2/104 (1.9%) without the mutation were falsely classified as FH (positive predictive value of 98%). The sensitivity and specificity of FH diagnosis according to TC values were 93 and 98% when testing children from FH families where the prevalence is expected to be 50%. The sensitivity, specificity and predictive values would be considerably lower in the general population.

A study of 25 babies born to 21 parents in Finland(Vuorio, A. F., Turtola, H., and Kontula, K., 1997) was designed to compare blood lipid concentrations in newborns with molecularly defined heterozygous FH to those in non-affected

babies and to clarify the value of lipid determinations in assessment of diagnosis of FH at birth and 1 year of age. Of 25 babies born to an FH parent, 14 were DNA positive and 11 were DNA negative. Mean TC and LDL cholesterol concentrations in cord serum were significantly elevated (p<0.001) in the DNA positive newborns compared to DNA negative or controls.

Table 9

	Mean TC mmol/l±sd[3]	Mean LDL-C mmol/l±sd	Mean HDL-C mmol/l±sd	Mean TG mmol/l±sd
Controls (n=30)	1.84±0.46	1.03±0.30	0.75±0.24	0.13±0.08
DNA –ve at birth (n=10)	1.54±0.23	0.78±0.15	0.63±0.14	0.28±0.23
DNA +ve at birth (n=14)	2.60±0.70	1.77±0.56	0.69±0.23	0.29±0.24
DNA –ve, aged 12 months (n=16)	4.40±0.66	2.89±0.68	1.16±0.15	0.78±0.39
DNA +ve, aged 12 months (n=18)	8.38±1.18	7.02±1.07	0.95±0.14	0.93±0.40

Adapted from published paper(Vuorio, A. F., Turtola, H., and Kontula, K., 1997)

Mean TC and LDL-C Concentration in cord serum were significantly elevated in the affected newborns compared to the non-affected or controls. There was however, a considerable overlap between the ranges of individual lipid concentrations in these three groups. The mean serum TC and LDL-C in the combined two non-affected groups would yield 95th percentile values of 2.60 and 1.44 mmol/l. If these concentrations were used as diagnostic criteria then only 5 or 6 of the 14 DNA positive newborns would have been correctly identified.

Plasma lipoprotein-lipid concentrations were compared in a cohort of 266 heterozygous FH children and adolescents (1-19 years) and a control group of 120 healthy siblings and unrelated children from Canada (Torres, A. L., Moorjani, S.,

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3 Assumed to be mean±sd for all variables

Vohl, M. C. et al , 1996). All FH children were defined by one of three mutations in the *LDLR* gene. The results were as follows:

Table 10

Mean±sd	Controls	FH>15-kb	FH C646Y	FH W66G
n	120	188	21	57
Mean age (years)	9.05±4.63	8.21±4.14	7.06±4.09	8.00±4.12
TC (mmol/l)	4.32±0.60	8.17±1.45	8.18±1.53	7.19±1.23
LDL-C (mmol/l)	2.60±0.56	6.58±1.42	6.65±1.50	5.62±1.16
HDL-C (mmol/l)	1.26±0.29	1.11±0.23	1.08±0.28	1.14±0.20
TG (mmol/l)	1.04±0.40	1.09±0.49	1.24±0.76	1.01±0.43

Plasma TC and LDL-C Concentration were significantly lower in mutation W66G which is a defective mutation compared to >15 kb and C646Y ($p<0.05$). In the latter groups, TC and LDL-C were essentially similar. The significant differences between mutation groups remained when results were analyzed by gender.

In a study of 88 unrelated French Canadian children with a persistent increase in LDL-C and a parental history of hyperlipidaemia (Assouline, L., Levy, E., Feoli-Fonseca, J. C. et al , 1995) 71% of the participants were found positive for one of the five molecular defects common in this population. The first objective was to define the molecular basis for hypercholesterolaemia in the 88 children (mean age 8 years). Heterozygosity for the common French-Canadian LDL receptor gene mutation (>10-kb deletion) was found in 50 children (57%, group 1). The presence of one of the other four *LDLR* mutations previously identified in this population was found n 12 individuals (14%, group 2). In 26 children (29%, group 3) none of these five mutations were detected.

Clinically, only one individual in group 1 displayed arcus corneae and none had xanthomas.

Table 11

Mean±sd	>10-kb Group 1	Other Group 2	None Group 3	Control	p-value compared to control
TC mmol/l	7.6 (0.1)	6.8 (0.9)	7.3 (1.5)	3.6 (0.6)	p=0.0001
LDL-C mmol/l	6.2 (1.3)	5.3 (1.1)	5.6 (1.5)	2.3 (0.03)	p=0.0001
HDL-C mmol/l	1.03 (0.03)	1.05 (0.2)	1.2 (0.3)	1.2 (0.4)	p=0.0030

Adapted from published paper (Assouline, L., Levy, E., Feoli-Fonseca, J. C. et al , 1995)

Sonography of Achilles tendon xanthomata was studied in children with FH (Koivunen-Niemela, T., Viikari, J., Niinikoski, H. et al , 1994). Both Achilles tendons of 21 FH children aged 3-18 years were examined. Seven children were studied twice. There were 68 healthy controls. All FH children had one parent with FH or had a diagnosis of FH verified by a positive DNA test. If there was controversy over the diagnosis or if the child had a serum cholesterol value less than 8 mmol/l, an *LDLR* test was done. The tendons of the FH children were significantly thicker (mean±sd 7.1±1.5, range 5-10mm) than controls (5.8±1.0, 3-7mm, p=0.0001). Achilles tendon ultrasound in FH children were abnormal in 33% (3/9) of children aged <10 years and in 42% (5/12) of children aged 10-18 years. Interestingly, only four of the eleven *LDLR* positive children had evidence of xanthomata. One was aged 3 years, one 8 years and one 15 years. One boy aged 9 years who was mutation positive developed hypoechoic areas on ultrasound when he was re-studied after two years. Five of seven children with a family history had xanthomata and the three children with a first degree relative with positive *LDLR* had no evidence of xanthomata.

Another diagnostic study of children with high cholesterol (Kessling, A. M., Seed, M., Taylor, R. et al , 1990) followed 85 children ages 4-19 years each with a first degree relative with FH. Initially, 39 had high cholesterol concentrations suggestive of FH. Mean cholesterol for all boys was higher than for all girls but not significantly different. Eighteen of the remaining 46 children with cholesterol concentrations below the childhood 95th percentile were followed with serial cholesterol measurements. Eleven of these children showed a small elevation

with a mean year to year increase of 0.096 mmol/l (sem 0.080, no significant difference to control). Seven of the children showed marked increases in serum cholesterol concentrations over an interval of 1-7 years, reaching above 95th percentile (approximately 5.6 mmol/l, as read from the graph presented in the paper), which was significantly different to control with mean year to year change of 0.34 mmol/l (sem 0.062, p<0.01). Thus children who would not have been diagnosed as having FH on initial cholesterol concentration, developed hypercholesterolaemia consistent with a diagnosis of FH. The diagnosis of FH was confirmed retrospectively by DNA analysis in three of these children. It is important to note that 6 of the 7 children were under the age of thirteen years when first tested.

Neonatal diagnosis of FH was studied in 29 infants who had one parent with FH (Kwiterovich, P. O., Jr., Levy, R. I., and Fredrickson, D. S., 1973). Cord blood was obtained from these infants and from 36 babies not related to the study sample who served as controls. Controls were compared with at risk infants considered 'positive' due to LDL-C greater than 41 mg/ml (1.05 mmol/l) and at risk infants considered 'negative' due to LDL-C less than 41 mg/ml (1.05 mmol/l).

The results were as follows:

Table 12

Mean (sd)	Controls	Positive	p-value vs controls	Negative	p-value vs controls
TC mmol/l	1.9 (0.28)	2.56 (0.38)	p<0.001	1.87 (0.33)	ns
LDL-C mmol/l	0.42 (0.09)	0.34 (0.79)	p<0.005	0.82 (0.10)	ns
HDL-C mmol/l	0.79 (0.15)	1.59 (0.41)	Not done	0.85 (0.13)	ns

Adapted from published paper (Kwiterovich, P. O., Jr., Levy, R. I., and Fredrickson, D. S., 1973)

Among 19 children from whom later samples were obtained at age 1 to 2¼ years, seven had been considered to have normal LDL-C concentration at birth and at follow up all seven had LDL-C cholesterols <4.36 mmol/l which was the upper limit

for age 1-19 years. Only one of the 12 children considered to have hyperbetalipoproteinaemia at birth had a normal LDL-C at follow up. This infant had been on a strict low cholesterol diet since birth. The correlation between TC and LDL-C improved at follow up.

3.2.2.3   *Health economic evidence*

Please see the health economic review in Chapter 4 and the full economic modelling in Appendix E.

3.2.3 Evidence statements on coronary heart disease risk of people with suspected FH

Key clinical question:

What is the coronary heart disease risk of people with suspected FH:

- who have a confirmed DNA mutation or
- who do not have a confirmed DNA mutation?

Question 2 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
Large studies have shown that in individuals with a clinical diagnosis of FH the prevalence of coronary heart disease is significantly higher in those with an identified DNA mutation compared to those without a confirmed DNA mutation [2+]	See comments above on the 'differentiation of risk' (section 3.2.1).

3.2.4 Evidence summary on coronary heart disease risk of people with suspected FH

3.2.4.1 Methods of the clinical evidence review

The searches for Question 2 were not restricted by study type or age of study participants.

Identified: 1621

Ordered: 37

Included: 8

Excluded: 29

3.2.4.2 Clinical evidence

The role of DNA testing in determining the risk of coronary heart disease in individuals with FH has been evaluated in six studies which met the inclusion criteria.

Humphries et al (Humphries, S. E., Whittall, R. A., Hubbart, C. S. et al , 2006) examined the effect of mutations in three different genes in the development of coronary heart disease in 409 individuals with clinically defined definite FH. Clinical coronary artery disease was defined as a definite myocardial infarction or having undergone a coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, having angina with an ischaemic resting echocardiogram, or a reported angiogram showing clinically important stenosis. After adjusting for age, sex smoking and systolic blood pressure, compared to those with no detectable mutation, the odds ratio of having CHD for each mutation were as follows: (p=0.001 overall).

LDLR mutation (any) OR 1.84 (95% CI 1.10 to 3.06)

APOB (R3500Q) OR 3.40 (0.71 to 16.36)

PCSK9 (D374Y) OR 19.96 (1.88 to 211.5)

Overall, there was an 84% higher risk of CHD in those with an identified *LDLR* mutation compared with those with no detected mutation. There was also a relatively high frequency and extremely high risk of CHD in carriers of the *PCSK9* (D374Y). Of particular note was the finding that the post-statin treatment lipid profile in *PCSK9* (D374Y) carriers was worse than in individuals with no identified mutation:

Table 13

	PCSK9 p.Y374	No mutation	p-value
Mean LDL-C mmol/l (sem)	6.77 (1.82)	4.19 (1.26)	p=0.001
Mean HDL-C mmol/l (sem)	1.09 (0.27)	1.36 (0.36)	p=0.03

Adapted from published paper(Humphries, S. E., Whittall, R. A., Hubbart, C. S. et al , 2006)

Clinical characteristics of index individuals were identified in the study by Damgaard et al (Damgaard, D., Larsen, M. L., Nissen, P. H. et al , 2005) reviewed for question 1. Coronary artery disease below the age of 60 was recorded by mutation status as follows:

Table 14

LDLR	Apo B	No mutations
24.8%	31.3%	22.3%

Adapted from published paper (Damgaard, D., Larsen, M. L., Nissen, P. H. et al , 2005)

The association of genetic mutations typical of FH with atherosclerosis in the coronary vessels in individuals with severe hypercholesterolaemia and a family history of early cardiovascular disease was estimated from a sample of 235 individuals (Descamps, O. S., Gilbeau, J. P., Luwaert, R. et al , 2003). FH was diagnosed according to a analysis of the *LDLR* or *APOB* genes. Coronary atherosclerosis was evaluated by performing a thoracic CT and exercise stress

test. Coronary calcification was present in 75% of FH men compared with 44% of mutation negative men (OR 3.90, 95% CI 1.85-8.18; p<0.001) and in 53% of the FH women compared with 31% in the mutation negative women (OR 2.65, 95% CI 1.14-6.15; p<0.01).

Forty two FH men, 66 mutation negative men, 32 FH women and 36 mutation negative women had an interpretable exercise stress test. Positive exercise stress test was present in 38% of the FH men compared with 9% of the mutation negative men (OR 6.15, 95% CI 2.16-17.49; p<0.01) and in 22% of FH women compared with 6% of the mutation negative women (OR 4.76, 95% CI 0.91-24.85; p=0.06). The exercise stress tests were positive only on the basis of ECG criteria and none of the individuals complained of angina-like chest pain during the test.

Data on another large cohort of individuals with FH and their unaffected relatives were collected through genetic cascade testing and examined for the influence of different mutation of the *LDLR* gene on lipoprotein concentrations and the risk of CVD(Umans-Eckenhausen, M. A., Sijbrands, E. J., Kastelein, J. J. et al , 2002). In this study cardiovascular disease was defined as angina assessed with electrocardiographic exercise testing, 70% stenosis assessed by coronary angiography, myocardial infarction or performance of coronary bypass or PTCA. The results of interest for this review are as follows:

Table 15

		Unadjusted		Adjusted for age and sex	
All mutations	**n**	**RR**	**95% CI**	**RR**	**95% CI**
	608 carriers compared with 1087 non-carriers	4.00	2.83-5.65	8.54	5.29-13.80

Adapted from published paper(Umans-Eckenhausen, M. A., Sijbrands, E. J., Kastelein, J. J. et al , 2002)

Ninety-eight unrelated Belgian individuals with a family history of autosomal dominant hypercholesterolaemia were tested for *LDLR* mutations (Van Gaal, L. F., Peeters, A. V., De Block, C. E. et al , 2001). When the mutation positive and negative individuals were compared the following results were reported:

Table 16

	Mutation +ve	**Mutation –ve**	**p-value**
Total	24	61	
Coronary heart disease*	7 (29.2%)	19 (31.1%)	ns

*CHD included
1. a medical history of coronary ischaemic heart disease documented by electrocardiography and/or cycloergometry
2. a history of acute MI
3. having undergone a CABG or PTCA.

Adapted from published paper(Van Gaal, L. F., Peeters, A. V., De Block, C. E. et al , 2001)

TC, LDL-C and HDL-C were significantly different between the two groups (p=0.0025, 0.002, and 0.03 respectively).

Two hundred and seventy three individuals with severe hypercholesterolaemia (>95th percentile) and a family history of early cardiovascular disease were genetically tested for FH and evaluated by ultrasonographic measurement of intima media thickness in the carotid and femoral arteries(Descamps, O. S., Gilbeau, J. P., Leysen, X. et al , 2001). The mean age of mutation negative men was 46.6 (sd.3) years and FH men was 44.8 (sd 10.8) years; NS. The mean age of FH women was 46.0 (sd 11.9) years and 51.5 (sd 11.0, p=0.01) years.

Table 17

	Mutation +ve	Mutation –ve	p-value (unadjusted)
Men			
Mean carotid artery IMT (mm) ± sd	1.27±0.47	1.00±0.40	p<0.001
Mean femoral artery IMT (mm) ± sd	1.30±0.53	1.08±0.46	p=0.01
Women			
Mean carotid artery IMT (mm) ± sd	1.04±0.45	0.93±0.33	p=0.15
Mean femoral artery IMT (mm) ± sd	1.05±0.49	0.84±0.32	p=0.01

Adapted from published paper(Descamps, O. S., Gilbeau, J. P., Leysen, X. et al , 2001)

Another study which evaluated carotid intima-media thickness and plaque as predictors of cardiovascular events in individuals with FH was conducted by Tonstad et al(Tonstad, S., Joakimsen, O., Stensland-Bugge, E. et al , 1998). Participants were non-smoking men and women between the ages of 26 and 46 years with a DNA based diagnosis of FH and no known cardiovascular disease. Controls were non smoking individuals from the locale who were matched to each case by age (±3 years) and sex and BMI. The results were as follows:

Table 18

	Men		Women	
	FH n=41	Controls n= 41	FH n=38	Controls n=38
Carotid IMT				
Mean far wall (mm)(sd)	0.61(0.13)	0.55 (0.14)*	0.52 (0.09)	0.63 (0.07)
Max far wall (mm) (sd)	0.74 (0.15)	0.68 (0.16)	0.65 (0.11)	0.65 (0.09)
Carotid bifurcation IMT				
Mean far wall (mm) (sd)	0.81 (0.15)	0.74 (0.19)**	0.74 (0.17)	0.66 (0.15)**
Max far wall (mm) (sd)	1.08 (0.27)	0.97 (0.35)**	0.99 (0.31)	0.85 (0.23)**
Carotid plaque (yes/no)	22/19	8/35***	21/17	3/35***

*p=0.03; **p=0.01; ***p=0.0001 compared with FH

Adapted from published paper(Tonstad, S., Joakimsen, O., Stensland-Bugge, E. et al , 1998)

A study among 120 French Canadian men aged <60 years who were heterozygous for FH and a group of 280 men without FH provides some data on CAD risk among diagnosed individuals with FH(Gaudet, D., Vohl, M. C., Perron, P. et al , 1998). All individuals in this study were screened for *LDLR* mutations .

The outcomes of interest include:

Table 19

	Mutation+ve (n=120)	Mutation – ve (n=280)	p-value
Number of diseased vessels	**n (%)**		
0 vessels with >50% stenosis	6 (5%)	31 (11%)	p=0.0001
1 vessel with >50% stenosis	27 (22.5%)	98 (35.0%)	p=0.005
2 vessels with >50% stenosis	30 (25%)	72 (25.7%)	p=0.96
3 vessels with >50% stenosis	28 (23.3%)	58 (20.7%)	p=0.65
4 vessels with >50% stenosis	29 (24.1%)	21 (7.5%)	p=0.0001

Adapted from published paper(Gaudet, D., Vohl, M. C., Perron, P. et al , 1998)

Other outcomes of interest were:

Table 20

	Mutation +ve (n=120)	Mutation – ve (n=280)	p-value
Mean BMI (sd)	26.0 (0.3)	27.9 (0.3)	p=0.0001
Mean waist circumference (sd)	92.3 (0.8)	97.6 (0.7)	p=0.0001
Mean waist-to-hip ratio (sd)	0.92 (0.01)	0.96 (0.01)	p=0.0001
Fasting insulin (mµ/L) (sd)	16.2 (0.8)	19.0 (0.7)	p=0.02

Adapted from published paper(Gaudet, D., Vohl, M. C., Perron, P. et al , 1998)

3.2.4.3 Health economic evidence

Please see the health economic review in Chapter 4 and the full economic modelling in Appendix E.

Return to recommendations

4 Identification strategies

Return to recommendations

4.1 Introduction

The prevalence of FH in the UK population is estimated to be 1 in 500, which means that approximately 110,000 people are affected. Whilst there is limited data, it appears that the prevalence of FH in people from the Indian subcontinent is similar, but with a lower prevalence in people of Afro-Caribbean origin (Austin et al 2004). Most people in the UK with FH are undiagnosed. However, it is clear that early detection and treatment can reduce morbidity and mortality. It is therefore important to determine which system of case finding for FH is the most clinical and cost effective.

4.2 Comparison of identification strategies

4.2.1 Evidence statements on the effectiveness of different identification strategies

Key clinical question:

What is effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH:

- GP note searching using electronic data bases identifying individuals with

  (i) history of early MI (<60 years) and total cholesterol (TC) >7.5mmol/l

  (ii) family history of ischemic heart disease and hypercholesterolemia, or

- secondary care registers (i) within coronary care units through identifying individuals with

  (i) history of early MI (<60 years) and total cholesterol (TC) >7.5mmol/l or

  (ii) identification of individuals through pathology registers aged <60 years and TC>9 mmol/l and LDL-C>5.5mmol/l or;

- cascade testing?

Question 3 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
A single retrospective study(Gray, J., Jaiyeola, A., Whiting, M. et al , 2008) in approximately 12,000 individuals in one GP practice demonstrated that electronic note searching identified 402 records that upon case note review found 2 previously unidentified individuals with definite FH and 4 previously unidentified individuals with probable FH [2+]	Primary care registers
	There is currently no evidence that note searching in primary care is effective. .
	The GDG considered the results of a single GP based study that undertook electronic note searching. Because of the high proportion of expected cases already identified in this particular practice the results may not be generalisable to the primary care in general.
No evidence using secondary care registers was identified.	
A report(Umans-Eckenhausen, M. A., Defesche, J. C., Sijbrands, E. J. et al , 2001) of the first 5-years of a national screening programme based in the Netherlands using a computerised register of pedigrees found that in relatives of probands with a positive DNA diagnosis 2039 out of 5442 were identified as having the same FH mutation as their proband. On average, 20 1st and 2nd degree relatives were tested per proband in whom the diagnosis of FH was confirmed in 8 (37%). At the time of identification of the mutation, 667 of these adults with FH (39%) received some form of lipid-lowering treatment; 1 year later, this had increased to 93%. [2+]	Primary care has a key role in the diagnosis and identification of individuals with FH and the NICE guidelines on cardiovascular risk modification can only increase the importance of this role. It is therefore necessary to identify the most effective way of finding individuals with FH in a primary care setting and a research recommendation was developed on the use of primary care records for case finding.
	Secondary care registers/records
	No evidence was identified and a research recommendation was drafted.
	Cascade testing
A Health Technology Assessment report(Marks, D., Wonderling, D., Thorogood, M. et al , 2000) which compared modelling of cascade testing of lipid measurements of 1st degree relatives vs population screening concluded that cascade testing is an efficient and cost effective means of case finding for FH [1+]	A nationwide strategy of cascade testing is feasible and would result in an improvement in identification of people with FH (with associated higher rates of treatment).
	Two studies showed the feasibility of cascade testing in the UK, and also showed the value of approaching relatives directly. The average age of diagnosis is reduced using this strategy.
Two cost-effectiveness studies (Marks, D., Thorogood, M., Neil, H. A. et al , 2003b), (Marks, D., Wonderling, D., Thorogood, M. et al , 2002) concluded that family tracing is the cost-effective compared to no tracing or universal screening.	Overall, the evidence supported the use of a nationwide strategy of cascade testing as this would not then be limited by geographical boundaries. The evidence supported a direct approach to relatives.
	A nationwide, proactive, systematic approach to cascade testing is recommended but will need to be evaluated.
Two cost-effectiveness studies (Wonderling, D., Umans-Eckenhausen, M. A., Marks, D. et al , 2004), (Marang-van de Mheen, P. J., ten Asbroek, A. H., Bonneux, L. et al , 2002) also found that genetic based method (DNA) is cost-effective compared to no screening	
An economic analysis done for the guideline also found that the most cost-effective	

method for cascade testing is using DNA testing plus cascading from both DFH and PFH mutation negative index cases compared to the Cholesterol method. The model results are stable in sensitivity analysis.	
A retrospective study(Bhatnagar, D., Morgan, J., Siddiq, S. et al , 2000) of cascade testing using lipid measurements in two specialized hospital clinics identified 285 1st degree relatives from 259 probands with definite FH. 200 relatives were tested of whom 121 (60%) were found to have FH, demonstrating the feasibility of cascade testing using direct contact by a clinic nurse. [2+]

A prospective study(Marks, D., Thorogood, M., Neil, S. M. et al , 2006) using cascade testing of lipid measurements from a specialized hospital clinic covering a defined geographical area identified 227 eligible adult index cases who had 1075 1st degree relatives. Using indirect contact via the probands 23% of adult relatives who lived within the catchment area were tested of whom 29% had lipid concentrations indicative of FH. 97% of children/young people under 18 years, where the parents were directly approached were tested, of whom 32% had lipid concentrations indicative of FH [2+] | |

4.2.2 Evidence summary on the effectiveness of different identification strategies

4.2.2.1 Methods of the clinical evidence review

The searches for this review were not restricted by study type or age of individuals.

Identified: 380

Ordered: 16

Included: 6

Excluded: 10

4.2.2.2 Clinical evidence

GP note searching

A study(Gray, J., Jaiyeola, A., Whiting, M. et al , 2008) was conducted to assess the utility of combined computer and notes-based searches in a GP practice to identify index cases of FH. This retrospective chart review used computer searches in a South London practice with 12,100 individuals. Four searches were done using practice coding levels:

1. for ischaemic heart disease (IHD) in the record

2. for lipid disorder in the record

3. for statin prescribing in the record, and

4. for cholesterol search in the record.

Selected notes were reviewed by a GP and consultant lipidologist to give a Dutch score for the probability of FH.

Case finding for FH in this practice identified 12 individuals scoring more than 8 (definite), eight individuals scoring between 6 and 8 (probable) and after

exclusions, 47 scoring between 3 and 5 (possible) on the Dutch scale. Of the 12 definite cases 2/12 (16.6%) and 4/8 (50%) of the probable cases were not already known to a secondary care lipid clinic. A combined search of IHD, lipid diagnosis or statin use showed a sensitivity of 100% and a yield of 5.83%. In this study the combined search plus the use of cholesterol >7.0mmol/l showed a sensitivity of 100% and a yield of 4.98%. A total of 3.3% of the registered practice population had their notes searched. It took approximately half an hour to search a set of notes. The combined and cholesterol search required 20.1 sets of notes to be searched to find one case of definite or probable FH.

This study demonstrated that is it possible to use note searching to define a population of FH individuals in primary care. Although results showed that the combined search resulted in the highest sensitivity and yield, the authors did not recommend ignoring the cholesterol search as, "… there are bound to be individuals in other practices whose elevated cholesterol is the only marker of the diagnosis." The authors also recommended that where records are incomplete face to face interviews would be required to establish a diagnosis. In addition, the effect of variable practice coding levels and information derived from individuals must be considered.

Secondary care registers
No evidence was identified.

Cascade testing
Targeted testing of relatives of index individuals (probands) with definite FH is known as cascade testing. The purpose is to identify new cases among those at highest risk 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.

A well documented active case finding program for individuals with FH was established in the Netherlands in 1994. In a narrative paper Defesche et al(Defesche, J. C., Lansberg, P. J., Umans-Eckenhausen, M. A. et al , 2004) described the Dutch method for identification of individuals with FH which incorporates active family testing supported by DNA diagnostics. The program is

based on principles for large scale screening programs which include the following:

- The condition should be recognizable at a latent or early symptomatic stage
- The natural history of the condition should be understood
- The condition must be considered to be an important health hazard
- A suitable diagnostic test should be available
- The diagnostic test should be acceptable
- The cost of case finding should be economically balanced
- Facilities for diagnosis and treatment should be available
- There should be consensus on whom to treat
- Acceptable treatment for individuals with recognized disease should be available
- Case finding should be an ongoing process.

Individuals in the Netherlands with a clinical diagnosis of FH are referred for DNA testing. Once a mutation has been identified the individual becomes an index case. With the help of the index individual, information is collected on all family members and these individuals are tested for the mutation of the index case and for non fasting lipid concentrations. During the years 1994 to 1998 over 5400 individuals were enrolled in the identification program. In this group, starting from 237 index cases, more than 2000 individuals were diagnosed as having FH.

The Umans-Eckenhausen et al(Umans-Eckenhausen, M. A., Defesche, J. C., Sijbrands, E. J. et al , 2001) (also reviewed for Question 1 on the diagnosis of FH) described the Dutch program of active family testing supported by DNA diagnostics. A clinical diagnosis was made according to a uniform diagnostic protocol which included LDL-C, physical signs, and personal and family history in a scoring system. All individuals with clinical FH were tested for DNA mutations. Index cases were those with both a clinical diagnosis and a confirmed DNA mutation. First degree relatives of index cases were contacted by a specialist nurse after written consent was obtained; 5442 relatives of 237 people with FH were tested; 2039 individuals were identified as heterozygous by LDL-C receptor

gene mutation analysis. At the time of examination, 667 of these adults with FH (39%) received some form of lipid-lowering treatment; 1 year later, this percentage had increased to 93%.

A Health Technology Assessment(Marks, D., Wonderling, D., Thorogood, M. et al , 2000) evaluated screening for hypercholesterolaemia versus case finding for FH. Danish population screening of school entrants by testing capillary blood samples was shown to be more efficient than screening for FH by first identifying children with a positive family history. However, the prevalence of FH in this population was higher (about 1 in 300) compared to the UK (1 in 500). Population screening in an American study was not considered cost effective. Population screening cost US $1600 per new case identified while tracing relatives of identified index cases cost US $400. Data reviewed for family tracing /case finding (cascade testing) was poorly described and the paucity of studies made it difficult to reach firm conclusions about relative effectiveness or cost of different strategies. However the HTA economic model concluded that cascade testing would be the most effective and least costly option of identifying undiagnosed FH. Screening all 16 year olds using clinical methods of diagnosis appeared to be similarly cost-effective, assuming that such screening was acceptable and that at least 55% of those invited for screening attended. See also Section 4.2.2.3 and Appendix E for further details.

Researchers at the University of Manchester(Bhatnagar, D., Morgan, J., Siddiq, S. et al , 2000) used detailed family history records of FH probands to identify first degree relatives. Two hundred first degree relatives were tested and 121 (60%) were found to have inherited FH. To detect a similar number by population screening over 60,000 tests would be required and only a few of these individuals would have been detected had cholesterol testing been restricted to those with other risk factors for coronary heart disease. The newly diagnosed individuals were younger than the probands and were generally detected before they had clinically overt atherosclerosis. Concentrations of serum cholesterol were respectively 8.4 (1.7 SD) mmol/l and 8.1 (1.9 s) mmol/l in affected men and women and 5.6 (1.0 sd) mmol/l and 5.6 (1.1 mmol/l in unaffected men and women. Screening for risk factors would have failed to identify most of the

affected relatives in whom hypertension, diabetes mellitus, cigarette smoking and obesity were uncommon.

Another UK based study(Marks, D., Thorogood, M., Neil, S. M. et al , 2006) conducted cascade testing among individuals attending the Oxford lipid clinic and meeting the diagnostic criteria of the Simon Broome Familial Hyperlipidaemia Register for definite or probable FH. Index cases in this study were asked to contact their first degree relatives. The positive diagnostic rate among those resident in the Oxfordshire area was 29% (15/52) in adults and 32% (36/113) in children. DNA testing was not done. Testing increased prevalence by 14.4% from 0.58/1000 (95% CI 0.52-0.65) to 0.67/1000 (95% CI 0.60-0.73), representing 33.5% of predicted cases. The authors concluded that cascade testing conducted by a specialist hospital clinic within its population catchment area did not substantially increase the prevalence of diagnosed FH. For cascade testing to identify most individuals with FH, a comprehensive national programme would be needed.

A study conducted by Starr et al(Starr, B., Hadfield, S. G., Hutten, B. A. et al , 2008) aimed to demonstrate that the plasma LDL-C concentration used as diagnostic criteria for FH probands in the general population are too stringent for use when cascade testing in 1st degree relatives, given that they have a 50% probability of having FH. A Bayesian model of LDL-C cut offs for 1st degree relatives was shown to have a higher sensitivity than MedPed for identification of potential FH individuals. Serum LDL-C results of 1st degree relatives of FH probands in the Netherlands, Denmark and Norway were compared according to both the Bayesian model and the MedPed model. In the Netherlands, the cut offs performed best for the youngest cohort (aged under 15 years) where sensitivity was 85% and specificity 93%. Sensitivity decreased with age from 85% in the younger cohort to 38% in over 55 year olds. This means that specificity dropped rapidly after 14 years of age (93% to 85%) and then remained fairly constant at between 83-86%. The accuracy (as assessed by Youden's index) was 0.53, but the cut offs performed significantly better amongst younger 1st degree relatives (aged under 45 years) compared to those older (Youden's Index, 0.59 vs. 0.33 p<0.001). The Norwegian and Danish values were adjusted to take into account

the higher concentrations seen in these countries. The pattern of greater accuracy in younger age groups seen in the Dutch cohort was mirrored in the Norwegian data whilst for the Danish cohort the pattern was reversed and sensitivity increased with age. Overall the Youden's index in the Norwegian data was 0.68 and in the Danish data was 0.64, 84% and 81% accuracy respectively. Overall the LDL-C cut offs gave a significantly better performance (p<0.001) than the MedPed cut offs when tested on the Dutch sample and at least as well for the Norwegian and Danish data sets. The sensitivity was higher for all datasets when using the LDL-C cut offs and specificity consistently lower.

4.2.2.3   Health economic evidence

Published analyses

The literature search retrieved 185 abstracts and 10 papers were ordered for further consideration. Only five papers met the inclusion criterion, all of which were published between 2000 and 2004. One of the publications (Marks, D., Wonderling, D., Thorogood, M. et al , 2002) was a follow up to the Health Technology Assessment report undertaken in 2000 (Marks, D., Wonderling, D., Thorogood, M. et al , 2000) by the same authors, and only the updated version is reported here.

Marks et al (Marks, D., Wonderling, D., Thorogood, M. et al , 2002) undertook a cost-effectiveness analysis from the NHS perspective which considered the different approaches to screening for FH patients aged between 16 and 54 years. Strategies considered were universal screening, opportunistic screening of patients consulting for unrelated reasons in primary care, opportunistic screening of patients admitted to hospital with premature myocardial infarction and systematic screening of first degree relatives of people with diagnosed familial hypercholesterolemia. They used life table analysis to construct the life years gained and data from the Simon Broome Register (The Simon Broome Register Group.Scientific Steering Committee on behalf of The Simon Broome Register Group: 1991) aided in the construction of life tables. Tracing of family members was the most cost-effective strategy with an estimated ICER of about £3,097/LY compared to no screening. Universal population screening was the least cost-

effective strategy with an estimated ICER of £13,029/LYG compared to no screening. They also found that it was more cost-effective to screen younger people and women. There was no incremental analysis comparing these strategies against each other or comparing clinical versus diagnostic testing.

Marks et al (Marks, D., Thorogood, M., Neil, H. A. et al , 2003b) also undertook a cost-effectiveness study over a 10 year period of the different strategies for FH screening. The strategies compared were family tracing strategy, in which a clinic nurse collects family histories from index cases, and universal screening of 16 year olds. They used a combination of life table analysis and decision analysis to estimate the life years gained from each strategy. They concluded that screening 16 year olds will avert 11.7 deaths over 10 years from 470 new cases identified. The cost per case identified and treated was £13, 141 and cost per death averted was about £1.6m. Family tracing would result in 13,248 new cases identified and 560 deaths averted over 10 years. The cost per case identified and treated was £3,505 and cost per death averted was £3,187. This result was explained by the fact that using family screening only needed 2.6 people to be screened in order to identify one positive case, whereas for universal screening of 16 year olds, about 1370 people were needed to find one positive case. The analysis was assessed using the Drummond checklist as being well conducted with appropriate methodology used by the authors. However an incremental analysis between the two methods was not undertaken as they only reported results compared to doing nothing. However, in previous work, the authors had shown that the two identification methods have a similar lifetime cost per life year gained.

Wonderling et al (Wonderling, D., Umans-Eckenhausen, M. A., Marks, D. et al , 2004) evaluated the cost-effectiveness of a Dutch genetic screening programme of FH patients compared to no screening. They used data from the Dutch screening programme in the year 2000. New cases identified by the screening programme gained an average of 3.3 years of life (undiscounted) and 0.9 years discounted. The model estimated that 26 myocardial infarctions would be avoided for every 100 persons aged between 18 and 60 years who were treated with statins. The cost per new case identified was US$7, 500. The cost per life-year gained was US$8, 800. The result was sensitive to the price of statin treatment and the

number of life-years gained. If all of these parameters were set to the value most unfavorable (worst case scenario), within their respective range, the incremental cost-effectiveness ratio (ICER) of the genetic identification programme relative to no intervention rises to rises to $38, 300 per life-year gained. This study was assessed as being of good methodological quality, with excellent internal validity. However, the generalisability of the result to the context of the NHS is unclear due to different resource use valuations between countries.

Marang-van de Mheen et al (Marang-van de Mheen, P. J., ten Asbroek, A. H., Bonneux, L. et al , 2002) evaluated the cost-effectiveness of five DNA-based genetic screening programmes in FH patients compared no screening. The methods compared were 1) treating all individuals with a cholesterol level above the 95th percentile of the general Dutch population, 2) individuals who fulfil the treatment criteria in the Dutch Institute on Health Care Improvement (CBO) consensus guideline on hypercholesterolemia, 3) as in 1, but only if untreated at screening, 4) as in 2, but only if untreated at screening, 5) all FH positive patients. The authors used data from the Dutch screening programme and combined this with Framingham risk functions to estimate patient survival and costs. Results were evaluated for each strategy using cost per life year gained (LYG). Treating all FH positive patients had an estimated ICER of about €31,260/LYG. All FH positive patients with elevated cholesterol concentrations above the 95th percentile of the Dutch general population had an estimated ICER of €29,957 per LYG, individuals who fulfil the treatment criteria in the Dutch Institute on Health Care Improvement (CBO) consensus guideline on hypercholesterolemia had an estimated ICER of €24,376. Those individuals with a cholesterol level above the 95th percentile of the general Dutch population and untreated at screening had an estimated ICER of €30,558 and lastly untreated FH+ as in cholesterol consensus had an estimated ICER of €27,700. The paper was assessed as being of fair quality using the Drummond checklist, but had weaknesses, including the lack of discounting. Also, the generalisability of the result to the NHS is unclear. Furthermore, the lack of incremental analysis between options is not justified.

In conclusion, screening programmes using DNA based methods have been found to be cost-effective.

Modelling of cascade testing - analysis

Above we have summarised the results of four studies, found in a literature search, which compared the cost-effectiveness of different identification methods in patients with FH. The GDG requested a de novo economic analysis with an NHS costing perspective to help inform the guideline recommendations about cascade testing. The following is an overview of this economic modelling analysis. The details the model and the economic analysis can be found in Appendix E.

A decision tree was constructed in Excel to estimate the numbers of "affected patients". The standard method of clinical diagnosis and identification of affected relatives using elevation of LDL-C concentration is the base line comparator, and is referred to in this model as the Simon Broome criteria, "Cholesterol" method. The UK FH Cascade Audit Project (FHCAP) has shown that, 30% of the patients currently being treated in lipid clinics have definite FH (DFH), 60% have probable FH (PFH), and 10% fail to meet either criterion (Hadfield, S. G., Horara, S., Starr, B. J. et al , 2008). Only patients meeting the criteria of DFH or PFH were included for cascade testing. The second method is based on the identification of an FH-causing mutation by molecular genetic methods, called the "DNA" method in this model. Here, only patients with an identified mutation were included for cascade testing, and the relatives tested for the family mutation. This is the model used in the Netherlands (Umans-Eckenhausen, M. A., Defesche, J. C., Sijbrands, E. J. et al , 2001).

Strategy 1:
Cascade testing is carried out from all DFH and PFH probands. All relatives with elevated LDL-C Concentration are offered appropriate treatment and used as secondary index cases for further cascade testing.

Strategy 2:
Following DNA testing of the probands, cascade testing of relatives is undertaken in all mutation-positive probands i.e. using the DNA information to offer appropriate lipid-lowering treatment and to select those from whom secondary cascading will be undertaken.

Strategy 3:

Following DNA testing of the probands, cascade testing of relatives is undertaken in all mutation-positive probands , and cascade testing is also undertaken in the relatives of DFH probands using measures of LDL-C Concentration to identify "affected" relatives for treatments and for secondary cascading (DNA+DFH method).

Strategy 4:

Cascade testing is undertaken in all mutation-positive probands as above and additionally from both DFH and PFH probands using measures of LDL-C Concentration to identify "affected" relatives for treatments and for secondary cascading (DNA+DFH+PFH method[L1]).

In each strategy, all individuals with elevated LDL-C are offered lipid-lowering therapies. For the purposes of the analysis a true-positive index case is defined as one who has a monogenic cause of FH who is selected for cascade testing, while a false-positive case is defined as one who does not actually have a monogenic cause but who is selected for cascade testing (i.e. fulfils the clinical criteria of FH but the cause is due to polygenic plus environmental causes). A false-negative subject is one who is not selected for cascade testing but who actually does have a monogenic cause of FH, and a true-negative subject is defined as one who does not actually have a monogenic cause, and who is not selected for cascade testing (i.e. does not fulfill the clinical criteria of FH).

For relatives, a true-positive is defined as one who has a monogenic cause of FH who is correctly identified by the strategy in use (i.e. by elevated LDL-C Concentration or by being a carrier for the family mutation) and who is offered treatment and selected for cascade testing, while a false-positive case is defined as one who does not actually have a monogenic cause but who is offered treatment and selected for cascade testing (i.e. has LDL-C concentration above the diagnostic cut-off for age and gender but the cause is due to polygenic plus environmental causes). A false-negative subject is one who actually does have a monogenic cause of FH but who is not offered treatment or selected for cascade testing (i.e. with LDL-C Concentration below the diagnostic cut-off for age and

gender due to "protective" polygenic plus environmental causes), and a true-negative subject is defined as one who does not have a monogenic cause, and who is not offered treatment or selected for cascade testing (i.e. with LDL-C Concentration below the diagnostic cut-off for age and gender or who does not carry the family mutation).

In the model it is assumed that 65% of the first degree relatives and 60% of the second degree relatives will agree to testing. In FHCAP, these values were 85% and 80% respectively. Data on sensitivity and specificity of the Cholesterol method were taken from Hadfield 2007 and for the DNA method, the mutation detection rate in DFH was taken to be 80% (Graham, C. A., McIlhatton, B. P., Kirk, C. W. et al , 2005),(Humphries, S. E., Whittall, R. A., Hubbart, C. S. et al , 2006),(Heath, K. E., Gudnason, V., Humphries, S. E. et al , 1999). Unit costs for health care professional time, blood tests, and invitation letters were taken from Curtis 2007(PSSRU, 2005) and GDG estimates.

All index cases and all relatives with elevated LDL-C levels were offered statin treatment. True and false positives were offered high intensity statins while true and false negatives were offered low intensity statins for their elevated lipids for both index cases and relatives. A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins compared with low intensity statins (simvastatin 40mg) from a UK NHS perspective. The baseline age for the index case was 50 years and the age for the relative was 30 years.

The intermediate outcomes included in the model include MI, stroke, PAD, heart failure, revascularisation, unstable angina and death from CVD and other causes. Effectiveness data were drawn from TNT (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005) and IDEAL (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) which were meta-analysed. Health state utility values were taken from published sources (Appendix E). All cause mortality rates are from the Government Actuarial Department (Government Actuaries Department., 2006). The model makes the assumption of no adverse events from treatment using high intensity statins which will result in under-estimation of the true cost effectiveness.

Costs of drugs were taken from Drug tariff March 2008(Prescription Pricing Division., 2006). Costs of cardiovascular events were taken from the NICE TA94 on statins (Kwiterovich, P. O., Jr., Levy, R. I., and Fredrickson, D. S., 1973). In order to reflect social values for time preference as is standard in economic models; costs and QALYs have been discounted at 3.5% as recommended by NICE (National Institute for Health and Clinical Excellence, 2006c). All of these and other model assumptions have been tested in sensitivity analyses.

Modelling of cascade testing - results

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY. The table below shows the lifetime costs and QALY gains per patient by strategy. Cholesterol method dominates DNA alone and DNA + DF, that means Cholesterol method is cheaper and generates more QALYs compared to the two methods that it dominates. The model results indicate that the use of DNA testing plus cascading from both mutation negative definite FH individuals and individuals with possible FH is cost-effective when compared to the Cholesterol method. The estimated ICER is about £2,700/QALY.

Table 1 Base case results for the Incremental cost-effectiveness of the four strategies for cascade testing

Strategy	Cost (£)	Effect (QALYs)	Incremental cost (£)	Incremental effect (QALY)	ICER (£/QALY)
Cholesterol	£38,921	32.87			
DNA	£44,816	30.63	-	-	-
DNA + Chol M-ve DF	£46,479	31.91	-	-	-
DNA + Chol M-ve DF +PFH	£51,924	37.73	£13,003	4.86	£2,676

In conclusion, using a threshold of £20,000/QALY, the most cost-effective method for cascade testing is strategy using DNA testing plus cascading from both DFH and PFH mutation negative index cases compared to the Cholesterol method.

DNA alone and DNA + cascading from DFH mutation negative index cases are ruled out by simple dominance. The model results are stable in sensitivity analysis.

Return to recommendations

5 Management (pharmacological treatment)

[Return to recommendations](#)

5.1 Introduction

Current clinical management of FH routinely includes drug treatment with HMG CoA (hydroxymethylglutaryl co-enzyme A) reductase inhibitors or statins. When statins are not tolerated bile acid sequestrants, fibrates, nicotinic acid and dietary measures areused. Most recently ezetimibe has been introduced for the treatment of FH. Although the heterozygous condition affects about 1 in 500 of the UK population, there is little published data about the risks of coronary heart disease in treated heterozygous individuals and it would no longer be ethical to conduct placebo controlled trials to obtain more data. Therefore, it is necessary to rely upon the few studies conducted before the use of statins became usual practice to evaluate the effectiveness of monotherapy in adults with FH in randomized control trials.

In 1999, the Scientific Steering Committee of the Simon Broome Register published statistics on the largest cohort of individuals with heterozygous FH (FH) to date(Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group, 1999). This report divided the person-years observation into two periods: before 1 January 1992 and from 1 January 1992 onward, by which date statins were being widely prescribed for people with FH. Over the whole period, the Relative Risk of CHD mortality in women was higher than in men (125 fold vs 48 fold in 20-39 year olds and 8.4 vs 3.5 in 40-49 year olds). Although there was no evidence of a substantial decline in coronary mortality across all ages at that time, there was a large reduction in mortality in individuals aged 20-59 with relative risk declining from 8 (95% CI 4.8-12.6) to 3.7 (95% CI 1.6-7.2) (not statistically significant however, $p < 0.081$). This corresponded to an absolute reduction from 523 to 190 in the annual excess number of deaths per 100,000.

5.2   *Pharmacological treatment*

5.2.1   Evidence statements on the effectiveness of monotherapy in adults

Key clinical question:

What is the effectiveness in improving outcome in adults with FH of the following monotherapies (i.e.: statins versus placebo, resins (bile acid sequestrants) versus placebo, nicotinic acid versus placebo, fibrates versus placebo, fish oils (omega 3 fatty oils) versus placebo, ezetimibe versus placebo) in improving outcome in adults with FH?

Questions 8a-f of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
Statins lower LDL-C and TC in people with FH. There was no statistically valid data quantifying side effects in the FH population. [1+] The biochemical responses to statins in people with FH are comparable with those of other hyperlipaedaemic individuals. [1+] Bile acid sequestrants significantly reduce total cholesterol and LDL-C Concentration when compared with placebo. [2 studies; quality ratings 1+ and 1+](Betteridge, D. J., Bhatnager, D., Bing, R. F. et al , 1992; Wiklund, O., Angelin, B., Fager, G. et al , 1990) Nicotinic acid significantly reduces LDL-C, TC, and triglyceride concentrations when compared with placebo. HDL-C concentration are also raised significantly with nicotinic acid therapy. [One study; quality rating 1+](Davignon, J., Roederer, G., Montigny, M. et al , 1994) There is good supportive evidence, based on a published systematic review, for the use of acetyl salicylic acid in reducing the severity of flushing related to the use of nicotinic acid. Indomethacin 100mg was also shown to significantly reduce the incidence of flushing due to nicotinic acid.(Oberwittler, H. and Baccara-Dinet, M., 2006) Fibrates significantly reduce LDL-C, TC, and triglyceride concentrations when compared with placebo. HDL-C concentration are also raised significantly with fibrate therapy. [Two studies; quality ratings 1+ and 1+](Brown, W. V., Dujovne, C. A., Farquhar, J. W. et al , 1986; Illingworth, D. R., Olsen, G. D., Cook, S. F. et al , 1982) No studies were identified for the use of omega 3 acid ethyl esters treatment in the FH population. Evidence from the post MI population showed that advice to increase consumption of oily fish reduced all-cause mortality [1++].(Cooper, A., Skinner, J., Nherera, L. et al , 2007) There was no evidence for the use of ezetimibe monotherapy in the FH population. See also NICE TA(Starr, B.,	FH is a condition that is characterised by elevated LDL-C concentrations. This was agreed as the primary target of drug therapy and in the absence of direct evidence in FH populations, drug treatment of other lipid fractions was not supported.The reviewed evidence showed that statins reduce both TC and LDL-C in adults with FH and adverse events are rare in the general population (based on evidence reviewed in the NICE TA (National Institute for Health and Clinical Excellence, 2006b)). Although the Simon Broome data (Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group, 1999) shows a non significant decrease in CHD mortality following the advent of statins, statins are associated with a lowering of total and coronary mortality in post MI patients (see NICE Guideline 'Secondary Prevention Post MI'), the only class of lipid lowering drug therapy to do so. Based on this evidence of safety, tolerability and efficacy, the GDG agreed that adults with FH should be treated with statins as initial therapy. Evidence showed that nicotinic acid and fibrates affect outcomes other than LDL-C, including TG and HDL-C, so these may be additional factors in the clinical decision making around drug choice. The BNF states that: • resins affect the absorption of other medication, and this must be taken into account when prescribing, and • resins may affect vitamin absorption. Recommendations were drafted to include the NICE TA ezetimibe recommendations(National Institute for Health and Clinical Excellence, 2007) and to give clear and practical guidance to prescribers, recognising that clinicians need to be able to choose the most appropriate drugs in conjunction with the individual. The GDG agreed that pre-treatment LDL-C concentration should be used as the baseline when considering offering treatment with a statin. The GDG believed that confirmation of the cholesterol concentration at diagnosis should be undertaken before considering patients for further lifelong management and investigation for FH. Recommendations on the sequencing of different drugs were based on the consideration of indirect evidence and clinical experience, as no head-to-head trials were identified. Efficacy, safety, and tolerability

Evidence statements	Evidence into recommendations
Hadfield, S. G., Hutten, B. A. et al , 2008) An economic model done for the guideline showed that high intensity statins are cost effective in the management of FH patients who are aged below 60 years when compared with low intensity statins.	were key factors considered and consideration to drug selection should be based on these factors in addition to informed patient preferences. Due to these considerations and the lack of trial evidence of significant improvement in clinical outcomes such as total mortality in either the FH or non FH populations, no sequencing of second line drugs was specified. Initiation of second line therapies with respect to healthcare setting or referral was based on the GDGs experience or knowledge of the known efficacy of statins, likelihood of high baseline LDL-concentrations, experience of use of second line drug treatments in primary care, safety and tolerability. Due to variations in individual patient characteristics, dose titrations, timing of access and additional treatment options, it is not possible to specify an arbitrary time point after initiation of treatment when all patients should be referred. The draft recommendations were written so as to alert prescribers to clinical factors (risk) and the response of LDL-C (biochemical response). Although non-aspirin NSAIDS have been shown to reduce the incidence of flushing with nicotinic acid their routine use was not recommended because of the potential increase in cardiovascular events highlighted by the Medicines and Health Regulatory Agency (MHRA) despite the short term use of lower dose NSAID's in this situation. It should be noted that people with FH may be prescribed drugs for lipid lowering at much earlier ages (see recommendations for drug use in children) and therefore, although the side effects may be rare, the duration of drug treatment may be much longer that in the general population. Therefore, safety and tolerability were key to the discussions on drug use and strategies were recommended to prevent and manage adverse effects based on both BNF guidance, and clinical and individual experience. The economic model showed that if the current prices of non generic statins were to decrease, they will become cost effective for all age groups. Thus assuming the current costs of simvastatin 80mg will result in high intensity statins dominating lower intensity statins.Higher intensity statins (simvastatin 80mg and appropriate doses of atorvastatin and rosuvastatin) were cost effective when compared with lower intensity treatment with simvastatin 40mg. Children and Young People. The GDG discussed the management of children and

Evidence statements	Evidence into recommendations
	young people with FH. It was agreed that they should be referred to a healthcare professional with expertise in providing both holistic, integrated care (in accordance with the National Service Framework for Children, Young People and Maternity Services) and managing the specific condition (FH). Ethnic groups All FH patients are considered as high risk of premature CHD so no distinctions between patients of different ethnic origin should be made when treating with statins. .

5.2.2 Evidence summary on the effectiveness of monotherapy in adults

5.2.2.1 Methods of the clinical evidence review

For this review we included only randomised controlled trials conducted in the FH population. Search for statin monotherapy:

Identified: 1113 studies

Ordered: 166 studies

Included: 16 studies

Excluded: 150 studies

Search for monotherapy with bile acid sequestrants, fibrates, nicotinic acid, fish oil:

Identified: 789 studies

Ordered: 62 studies

Included: 11 studies

Excluded: 51 studies

5.2.2.2   Clinical evidence

Statins versus placebo

Two systematic reviews were identified in the literature search. One systematic review met the agreed inclusion criteria. Marks et al (2002)(Marks, D., Thorogood, M., Neil, H. A. et al , 2003a) reviewed the evidence on diagnosis, natural history and treatment of FH. There were no placebo controlled trials identified which studied statin use in people with FH. A review of rosuvastatin treatment (Chong & Yim, 2002)(Chong, P. H. and Yim, B. T., 2002) included abstracts, proceedings and unpublished data on file from the manufacturer and therefore did not meet NICE quality criteria for systematic reviews. Several of the studies specific to individuals with primary hypercholesterolemia or heterozygous familial hypercholesterolemia included in the Chong and Yim review also did not meet GDG inclusion criteria. Studies which did meet criteria have been reviewed individually.

Four studies were identified which included a simvastatin versus placebo phase in the treatment of individuals with FH. Phase 1 of a study conducted by Berger et al (1989)(Berger, G. M., Marais, A. D., Seftel, H. C. et al , 1989) in 44 South African individuals included a 4 week randomised placebo controlled dose response trial in which six different doses (2.5mg-80mg) were administered and then compared to placebo. After 4 weeks of therapy the placebo group showed a 4.6% reduction in LDL-C; the simvastatin groups showed reductions of 14.9% (2.5mg), 31.7% (20mg), 44.6% (40mg) and 46.5% (80mg) (significance levels not given). Total cholesterol levels were not reported.

In a placebo controlled trial (LeClercq, 1989)(Leclercq, V. and Harvengt, C., 1989)19 individuals received placebo or simvastatin tablets ranging from 2.5mg up to 80mg daily. On 20 mg simvastatin there was a 50% decrease in LDL-C at week 12 (p<0.005), a 47% decrease at week 77 (p<0.05) and a 42% decrease at week 104 (p<0.04). On 40mg simvastatin LDL-C Concentration were lowered by 37% (p<0.005), 41% (p<0.005) and 35% (p<0.05) at week 12, 77 and 104, respectively.

The decrease in TC was similar. On 20 mg simvastatin there was a 40% decrease in TC at week 12 (p<0.05), a 29% decrease at week 77 (p<0.05) and a 32% decrease at week 104 (p<0.05). On 40mg simvastatin TC concentrations were lowered by 32% (p<0.005), 35% (p<0.005) and 3% (p<0.005) at week 12, 77 and 104, respectively

An Italian research team (Valerio et al, 1990)(Valerio, G., Vigna, G. B., Vitale, E. et al , 1990) evaluated the efficacy and tolerability of simvastatin 10mg versus placebo in a double blind RCT of 12 individuals with FH. At the end of treatment, the simvastatin treated group showed a significant (p<0.001) decrease in LDL-C (35%), and a 26% decrease in total cholesterol.

McDowell et al (1991)(Mcdowell, I. F. W., Smye, M., Trinick, T. et al , 1991) studied the effect of simvastatin 10mg in 27 individuals with severe primary hypercholesterolaemia in a double blind randomised placebo controlled parallel group trial. LDL-C fell by 39% and total cholesterol fell by 32% (p<0.05 for both LDL-C and TC).

Simvastatin was well tolerated in all trials and appeared to be uniformly effective in reducing LDL-C as well as total cholesterol, triglycerides and Apo B concentrations.

A further double blind parallel, placebo controlled study (Hunninghake et al, 1990)(Hunninghake, D. B., Stein, E. A., and Mellies, M. J., 1993) evaluated the safety and efficacy of pravastatin 40mg (on various dosing schedules) versus placebo. One hundred and ninety six individuals with primary hypercholesterolaemia were randomised to treatment or placebo. Significant reductions in both total and LDL cholesterol were observed in all three pravastatin treatment groups throughout the study (p<0.001). Pravastatin treatment reduced mean total cholesterol more than 15% from baseline and mean LDL cholesterol more than 19% from baseline as early as the end of the first week of treatment.

Bile acid sequestrants versus placebo
Cholestyramine versus placebo was evaluated by Wiklund et al in a Swedish study(Wiklund, O., Angelin, B., Fager, G. et al , 1990). One hundred and twenty

individuals with FH were randomized into three groups: pravastatin (10 mg for 6 weeks; 20 mg for 6 weeks), cholestyramine (24 g or highest dose tolerated) or placebo. The cholestyramine versus placebo group showed an LDL-C reduction of approximately 30% after 12 weeks (mean±sd: 5.6±1.8 mmol/l versus 8.3±2.3 mmol/l). In the pravastatin group LDL-C was reduced by 28% after 12 weeks (5.9±1.5 mmol/l versus 8.3±2.3 mmol/l).   At 12 weeks total cholesterol was reduced 24% in the cholestyramine versus placebo group (7.3±1.7 mmol/l versus 10.1±2.15 mmol/l and by 23% in the pravastatin versus placebo group (7.6±1.5 mmol/l versus 10.1±2.2 mmol/l). HDL-C concentration was increased for the pravastatin group only and there were no significant changes in triglyceride concentrations. The differences between the placebo group and the two treatment groups were highly significant for reduction of LDL-C and TC ($p<0.001$). However, after 12 weeks there was no significant difference between the treatment groups. HDL cholesterol increased significantly on pravastatin ($p<0.01$); TGs were variable with no significant increase in any group at 12 weeks.

Another placebo controlled parallel study of cholestyramine and pravastatin 40mg per day was carried out by Betteridge et al(Betteridge, D. J., Bhatnager, D., Bing, R. F. et al , 1992) in 128 people with heterozygous FH. Pravastatin 40mg/day led to a 25% reduction in total cholesterol (mean±sem: 9.9mmol/l±1.3 baseline) and a reduction in LDL-C of 30% (mean±sem: 7.8mmol/l±0.3 baseline). Cholestyramine 24g/day led to similar reductions in concentrations of TC (23%; baseline mean±sem: 9.51mmol/l±1.23) and LDL-C (31%; baseline mean±sem: 7.6mmol/l±0.2). No consistent changes occurred in HDL-C. There was a small rise (18%; baseline 1.4mmol/l± 0.1) in TG with bile acid sequestrant therapy. The reductions in TC and LDL-C were similar when compared with placebo, $p<0.001$. There was no change in the concentration of high density lipoprotein cholesterol. Plasma triglyceride concentration fell but was not significantly different from placebo; however it was significantly different from baseline ($p<0.05$).

Nicotinic acid versus placebo
In a multicentre placebo controlled trial(Davignon, J., Roederer, G., Montigny, M. et al , 1994) 158 individuals with type IIa or IIb primary hypercholesterolaemia (115 FH individuals) were randomised to either placebo, nicotinic acid extended

release 500mg bid, pravastatin 40 mg at bedtime or a combination of nicotinic acid 500 mg bid and pravastatin 40 mg for 8 weeks. Percent change was reported. LDL-C concentration were 21% lower than placebo with nicotinic acid, 33% lower than placebo with pravastatin 40 mg, and 49% lower with combination therapy. At week 8 HDL-C concentration were increased in relation to placebo by nicotinic acid (12%), pravastatin (13%) and combination therapy (16%). Total cholesterol decreased by 11.3% with nicotinic acid, 23.1% with pravastatin and 31.6% with combination therapy. TG decreases were as follows: 11.4% with nicotinic acid, 14.38 % with pravastatin and 34.9% with combination therapy. In comparison with placebo, nicotinic acid, pravastatin and combination therapy was associated with significantly lower TC and LDL-C ($p<0.05$) and combination therapy was significantly lower than the other 3 treatments at all weeks measured ($p<0.05$). HDL-C was significantly higher at week 8 in all treatment groups ($p<0.05$) but there were no between group differences. Adverse events were less frequent in the pravastatin and placebo groups ($p≤0.05$). Treatment with nicotinic acid had no statistically significant effects on triglyceride concentrations in relation to placebo but treatment with pravastatin and with combination therapy resulted in significantly lower triglyceride concentrations ($p<0.05$).

At the request of the GDG a systematic review on the use of acetyl salicylic acid (ASA) to control flushing related to nicotinic acid treatment was reviewed(Oberwittler, H. and Baccara-Dinet, M., 2006). This review identified four studies specifically exploring the utility of ASA in preventing flushing due to nicotinic acid in healthy volunteers. Twenty-three studies using nicotinic acid where ASA was mandatory or optional within the protocol and four studies where ASA therapy was reported in most participants were also identified. Discontinuation rates with nicotinic acid commonly reported in the literature were up to 40%. However with the use of ASA discontinuation rates due to flushing were low (mean 7.7%). Indomethacin 100mg was also shown to significantly reduce the incidence of flushing following intravenous nicotinic acid.

Fibrates versus placebo
Two studies were identified which evaluated fibrates versus placebo in people with FH.

Brown et al(Brown, W. V., Dujovne, C. A., Farquhar, J. W. et al , 1986) randomised 227 individuals with type IIa and IIb hypercholesterolaemia (181 and 46 respectively) to double blind treatment with either fenofibrate (100 mg three times a day) or matching placebo for 24 weeks. For the 92 type IIa individuals receiving fenofibrate there were significant reductions ($p<0.01$) in total cholesterol from 8.0mmol/l in placebo to 6.4mmol/l in the treatment group (18%); LDL cholesterol 5.7mmol/l in placebo to 4.5mmol/l in the treatment group (20%) and TG 2.3mmol/l in placebo to 1.3 in treatment group (38%). Mean plasma HDL-C increased by 11% ($p<0.01$) 1.2mmol/l in placebo to 1.4 in treatment group. Fenofibrate significantly ($p<0.01$) reduced mean plasma concentrations of TC, LDL-C and TG. Mean plasma HDL-C increased significantly ($p<0.01$).

The hypolipidaemic efficacy of ciprofibrate was evaluated in individuals with type II hypercholesterolaemia by Illingworth et al(Illingworth, D. R., Olsen, G. D., Cook, S. F. et al , 1982). Twenty seven of the 31 participants were classified with type IIa phenotype. Individuals were randomised to placebo or ciprofibrate 50mg or 100 mg for 12 weeks. Total and LDL cholesterol decreased 11% (8.0mmol/l to 7.2mmol/l; $p<0.05$) and 13% (6.1mmol/l to 5.3mmol/l; $p<0.025$) on the 50mg dose whereas HDL-C increased 8% (1.1mmol/l to 1.4mmol/l; $p<0.01$). TG fell by 22% (1.9mmol/l to 3.2 mmol/l; $p<0.025$). In individuals receiving 100 mg ciprofibrate total and LDL cholesterol fell by 20% (to 6.9mmol/l; $p<0.005$) and 24 % (to 5.1mmol/l; $p<0.005$) respectively. HDL-C increased 9.8% (1.4mmol/l; $p<0.01$) and TG decreased by 30% (to 0.8mmol/l; $p<0.05$).

Fish oils versus placebo
No studies were identified.

Ezetimibe versus placebo
No studies were identified for the populations searched. These were those with homozygous FH and children. The ezetimibe TA 94 (National Institute for Health and Clinical Excellence, 2007) has addressed treatment for adults with heterozygous FH.

5.2.2.3   *Health economic evidence*

No relevant health economic studies were identified.

5.2.3   Evidence statements on the effectiveness of monotherapy in children

Key clinical question:

What is the effectiveness in improving outcome in children with FH of the following monotherapies (i.e.: statins versus placebo, bile acid sequestrants versus placebo, nicotinic acid versus placebo, fibrates versus placebo, fish oils (omega 3 fatty oils) versus placebo, ezetimibe versus placebo) in improving outcome in children with FH?

Questions 8a-f of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
Statins are effective in lowering LDL and TC, and raising HDL-C in children aged 8-18 years (numbers of children aged below 10 years were very small). [1+] In short-term studies of statin use in children there were no adverse effects in terms of growth rate or pubertal development. [1+] In short-term studies (up to 2 years) statins have not been associated with significant adverse effects in children aged 8-18 years. Longer term studies are not available. [1+] Bile acid sequestrant therapy is effective in lowering and LDL-C and TC in children aged 6-15 years. [1+] The palatability and side effects of bile acid sequestrants reduces compliance with therapy. [1+] The safety of bile acid sequestrants in children has not been evaluated for greater than 5 years. No studies were identified for nicotinic acid use in children. Fibrate therapy lowered TC and raised HDL-C concentration in children ages 4-15 years in one small short-term study. [1+](Wheeler, K. A., West, R. J., Lloyd, J. K. et al , 1985) In a short-term study(Wheeler, K. A., West, R. J., Lloyd, J. K. et al , 1985) fibrates have not been associated with significant adverse effects with children ages 4-15 years. [1+] Longer term studies are not available. No studies were identified for fish oils use in children.	Children and Young People. The GDG discussed the management of children and young people with FH. It was agreed that they should be referred to a healthcare professional with expertise in providing both holistic, integrated care (in accordance with the National Service Framework for Children, Young People and Maternity Services) and managing the specific condition (FH). Treatment for children with heterozygous FH should be started early, with general agreement that this should be usually be by aged 10 years (based on the median age of the included study populations, and very limited data on the use of drugs in younger children). Evidence from post-mortem studies (not individually reviewed in this guideline) showed that atherosclerosis is not evident in children younger than 10 years, but is evident in older children so treatment should be initiated before significant atherosclerosis has developed. The evidence for children was more limited than for adults, so the recommendations were drafted to allow for the possible use of different drugs as first line treatment, based on clinical judgment and patient and parent/carer preference. The age of onset of cardiovascular disease within the family and presence of other cardiovascular risk factors including LDL-C concentrations in the child/young person should also be taken into account. 'Target LDL-C' levels were not specified in this guideline for children as there was an absence of evidence and values change with growth. Recommendations for monitoring cholesterol were as for people with FH (inclusive of children), again due to an absence of evidence specific for children. As for adults, safety and tolerability were considered paramount and monitoring recommendations were agreed to be the same as for adults. Routine monitoring of growth and pubertal monitoring was also recommended, although the limited evidence does not show any disturbances in growth or pubertal development. This is standard paediatric care, as is monitoring of BMI/weight in adults, but the reasons for monitoring of growth/weight are different in children and adults (the effect on growth compared with overweight/obesity respectively). Parents may be concerned that the drugs will affect the child's growth, so any drug should be initiated in children only after a full, informed discussion. The use of nicotinic acid in children was not recommended as these drugs are not licensed in this age group.

Evidence statements	Evidence into recommendations
No studies were identified for ezetimibe use in children.	

5.2.4 Evidence summary on the effectiveness of monotherapy in children

5.2.4.1 Methods of the clinical evidence review

Inclusion criteria for Q7b, 8a-f, 9a-f specified randomised controlled trials conducted in the FH paediatric population. The paediatric population was included in the original search terms for statins (1113) and the searches for other cholesterol lowering drugs (789).

Identified: 1902 total

Ordered: 34 studies

Included: 7 studies

Excluded: 27 studies

Studies for each comparison were as follows:

- statins versus placebo – 4 studies
- bile acid sequestrants versus placebo – 2 studies
- nicotinic acid versus placebo – no studies identified
- fibrates versus placebo – 1 study
- fish oils (omega 3 fatty oils) versus placebo – no studies identified
- ezetimibe versus placebo – no studies identified.

5.2.4.2 Clinical evidence

Statins versus placebo

Researchers from the Department of Public Health and Primary Health Care, University of Oxford (Arambepola et al, 2007)(Arambepola, C., Farmer, A. J.,

Perera, R. et al , 2006) recently conducted a systematic review and meta analyses of clinical trials and observational studies to assess the evidence for efficacy and safety of statin therapy in children and adolescents with heterozygous FH. Eight RCTs were included in the review which evaluated statin therapy against placebo. Two other trials used active treatment control groups. Statin therapy varied by type and dosage. In total 947 individuals (548 males) were included in the RCTs with an age range of 8-18 years. Median duration of the trials was 27 weeks (6-96). Total exposure was estimated at 850 person-years.

All trials measured mean changes in LDL-C, HDL-C and total cholesterol and triglycerides from baseline to the end follow up point as primary efficacy outcome measures. Five studies were included in a pooled analysis of LDL-C and HDL-C outcomes. The pooled reduction in LDL cholesterol due to statins was 1.89mmol/l (95% CI 1.58-2.19) compared to placebo (p<0.0001). There was a significant heterogeneity within the pooled LDL cholesterol changes (p=0.04). All reduced LDL-C but efficacy varied by the statin used and dose. Due to this variability, individual studies are described 1 which has been expanded from the systematic review paper and the original studies. 2 reports the outcome data for each of these studies.

Eighteen studies in total (11 trials and 7 prospective case series) provided information on safety outcomes for an estimated total exposure of 1162 child-years. There were no significant adverse events. In the RCTs, adverse events were equally distributed between statin treatment and placebo. Adverse events did not appear to vary by type or dose of statin when groups were compared within trials.

Table 1 Included studies on statin treatment in children with FH - description (Adapted from published review(Arambepola, C., Farmer, A. J., Perera, R. et al , 2006))

Study	Study design	Follow up	Characteristics of participants			Intervention	Control	Jadad score (quality assessment)
			Age range	n (males)	Criteria of LDL-C (mmol/l) for inclusion			
Wiegman (2004)	RCT	96w	8-18 years	214 (100)	≥ 4.0	Pravastatin 40mg/d if ≥14 y of age; 20mg/d if <14 y of age	Placebo	5
de Jongh (2002a)	RCT	48w	10-17 years	175 (99)	4.9-13.0	Simvastatin10mg/d for 8w; 20mg/d/ for 8w; 40 mg/d	Placebo	4
Stein (1999)	RCT	48w	10-17 years	132 (132)	≥ 4.9	Lovastatin 10mg/d for 8w; 20mg/d for 8w; 40mg/d	Placebo	4
de Jongh (2002b)	RCT	28w	9-18 years	50 (26)	Above 95th percentile for age and sex	Simvastatin10mg/d for 8w; 20mg/d for 8w; 40mg/d	Placebo	1
McCrindle (2003)	RCT	26w	10-17 years	187 (120)	> 4.1	Atorvastatin 10mg/d; 20mg/d if LDL-C ≥3.4 at week 4	Placebo	3
Clauss (2005)	RCT	24w	10-17 years post menarche females	54 (0)	4.1-10.3	Lovastatin 20mg/d for 4w; 40 mg/d	Placebo	5

Study	Study design	Follow up	Characteristics of participants			Intervention	Control	Jadad score (quality assessment)
			Age range	n (males)	Criteria of LDL-C (mmol/l) for inclusion			
Knipscheer (1996)	RCT (4 randomised arms)	12w	8-16 years	72 (25)	Above 95th percentile for age and sex	Pravastatin: (1) 5 mg/d (2) 10 mg/d (3) 20 mg/d	Placebo	3
Couture (1998)	RCT	6w	8-17 years	63 (37)	Above 95th percentile for age and sex	Simvastatin 20 mg/d (for 3 groups according - gene mutations)	Placebo	3
McCrindle (2002)	Randomised cross over trial	18w	8-18 years	40 (25)	> 4.15	Pravastatin 10mg/d + colestipol5g/d	Colestipol 10g/d	-
Stefanutti (2005)	Non-randomised parallel matched trial	48w	4-11 years	16 (7)	Not stated	Simvastatin 10mg/d + step II AHA diet	Step II AHA diet	-
Lambert (1996)	Time series comparison (4 randomised arms)	8w	≤ 17 years	69 (69)	Above 95th percentile for age and sex	Lovastatin: (1) 10 mg/d (2) 20 mg/d (3) 30 mg/d (4) 40 mg/d	Placebo/4w prior to randomisation	-

	changes (±sd) in lipid profiles from baseline (mmol/l)	changes(±sd) in lipid profiles from baseline (mmol/l)	function	(mm)
Wiegman (2004)	2 year follow-up: TC: pravastatin 20mg (under 14yrs) and 40mg over 14 years +1.44 ($\pm$1.1), p<0.001. LDL-C: pravastatin 20mg (under 14yrs) and 40mg over 14 years +1.46 ($\pm$1.0), p<0.001 HDL-C: pravastatin 20mg (under 14yrs) and 40mg over 14 years +0.03 ns			2 year follow-up: pravastatin 20mg (under 14yrs) and 40mg over 14 years -0.010 ($\pm$0.048) p=0.02
de Jongh (2002a)		Week 48: TC: simvastatin 40mg -30.9% ($\pm$11.5); LDL-C: simvastatin 40mg -40.7% ($\pm$39.2) HDL-C: simvastatin 40mg +3.3% ($\pm$14.9).		
Stein (1999)	Week 48: TC: lovastatin 40mg +0.51 ($\pm$0.5), p<0.001 vs placebo; LDL-C: lovastatin 40mg +0.64 ($\pm$0.5), p<0.001 vs placebo; HDL-C: lovastatin 40mg +0.01 ns			
de Jongh (2002b)	Week 28: TC: simvastatin 40mg -2.16 ($\pm$1.04), p=0.0001; LDL-C: simvastatin 40 mg -2.13 ($\pm$0.99) p=0.0001; HDL-C: simvastatin 40 mg -0.05 ($\pm$0.17) p=0.08.		Week 28: FMD significant increase in simvastatin FH group (p<0.0001).	

	baseline (mmol/l)	from baseline (mmol/l		
McCrindle (2003)		Week 26: TC: atorvastatin 10-20mg titrated depending upon response, -31.4% (+ 1.0); LDL-C: atorvastatin 10-20mg titrated depending upon response, -39.6% (+ 1.1); HDL-C: atorvastatin 10-20mg titrated depending upon response, +2.8% (+ 1.3);		
Clauss (2005)]		Week 24: TC: lovastatin 40mg -21.8% (+2.5); LDL-C: lovastatin 40mg -26.8% (+3.4); HDL-C: lovastatin 40mg +2.5% (+2.5);		
Knipscheer (1996)		Week 12: TC: pravastatin 20mg -24.6% (95% CI 21.0 to 28.1); LDL-C: pravastatin 20mg -32.9% (95% CI 28.6 to 37.0); HDL-C: pravastatin 20mg + 10.8% mean change (95% CI 3.4 to 18.8).		

	baseline (mmol/l)	from baseline (mmol/l		
McCrindle (2002)	Week 18: TC: colestipol 10g only -0.63+0.80; colestipol 5g + pravastatin 10mg -1.06+1.11 p=0.041; LDL-C: colestipol 10g only -0.65+0.80; colestipol 5g + pravastatin 10mg -1.07+ 1.06 p=0.066; HDL-C: colestipol 10g only -0.01+0.18; colestipol 5g + pravastatin 10mg +0.03+ 0.13 p=0.63;			
Stefanutti (2005)		Month 12 TC: simvastatin 10mg -24%; LDL-C: simvastatin 10mg -29% p<0.01; HDL-C: simvastatin 10mg +7% (no sd reported)		
Lambert (1996)		Week 8: TC: lovastatin 40mg +29% (26-32); LDL-C: lovastatin 40mg +36% (33-39) ; HDL-C: lovastatin 40mg +3%		

Duplaga (1999)(Duplaga, B. A., 1999) published an early review of literature regarding the safety and efficacy of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) when used during childhood and adolescence. Six clinical studies were reviewed after a Medline search of the literature (children aged 0-18 years), including case series and RCTs (Stein, 1989;Ducobu et al, 1992; Sinzinger et al, 1992; Lambert et al, 1996; Stein et al, 1999; Knipscheer et al, 1996). Three of these studies are included in the 2007 Arambepola et al review (Lambert et al, 1996; Stein et al, 1999; Knipscheer et al, 1996). This review suggested that the addition of statins to diet therapy in children aged >10 years may be effective when diet therapy alone has failed to reduce LDL-C. In children and adolescents TC and LDL-C can be expected to decrease by 25% when statins are used in conjunction with lipid lowering diet but HDL-C is not significantly improved. Statins appear to be well tolerated and generally safe to use in children and adolescents who took part in these studies, including growth parameters of male children before and after puberty. Effects on girls are not known.

Two guidelines for the treatment of children with FH were also reviewed. The Finnish Medical Society (2004)(Finnish Medical Society Duodecim., 2005) guideline, based on a systematic review and quality assessment of the literature made the following recommendation regarding drug therapy in children with FH:

'The need for drug therapy is decided mainly on family history of coronary heart disease. Drug therapy (a bile acid sequestrant is the first line drug; a statin may be used as an alternative) is initiated by an experienced paediatrician.'

The evidence base for this recommendation is Wiegman et al, 2004(Wiegman, A., Hutten, B. A., de, GrootE et al , 2004) and is summarized as follows:

'Two years of pravastatin therapy appear to induce a significant regression of carotid atherosclerosis in children with familial hypercholesterolemia.'

An American guideline from the Institute for Clinical Systems Improvement (2005)(Institute for Clinical Systems Improvement., 2003) based on a 'search of electronic databases' also cites Wiegman et al, 2004(Wiegman, A., Hutten, B. A.,

de, GrootE et al , 2004) regarding treatment of children and adolescents with familial hyperlipidaemia:

'A long-term study demonstrates that statin therapy for FH is safe and effective in children.'

Bile acid sequestrants versus placebo

Two studies on the effects of bile acid sequestrants in children with FH were identified. Groot et al (1983)(Groot, P. H., jkhuis-Stoffelsma, R., Grose, W. F. et al , 1983) studied 33 children aged 7-15 years, who were matched on age, sex and serum cholesterol and received either colestipol or placebo in a 16 week crossover trial. The treatment effects for colestipol v placebo were:

- TC -0.89 (p<0.001); percent change -12.8%
- LDL-C +VLDL -0.91(p<0.001); percent change -15.7%
- HDL-C +0.02 (ns); percent change +1.7%
- TG -0.10 (ns); percent change -9.3%
- Apo B -0.18 (p<0.001); percent change -13.5%
- Apo A +0.02 (ns); percent change +1.7%.

Five children did not complete the study because of aversion to the sandy tasting medication. There were no other complaints.

Tonstad et al (1996)(Tonstad, S., Knudtzon, J., Sivertsen, M. et al , 1996) conducted a one year RCT comparison of 8g/l cholestyramine versus placebo among 72 children with FH and a mean age of 8.4±1.4[1] years. Percent change was reported; absolute values were not given. After one year of treatment the following percent changes were reported for the cholestyramine versus placebo group:

- TC -11.5% (p<0.001) (further statistics not provided in paper)
- LDL-C -16.9% to -18.6% versus 0 to +1.5% in placebo (p<0.0001)
- HDL-C +8.2% to +13.4% versus +2.4% to +8.8% in placebo (not significant)
- Mean triglyceride remained unchanged in both groups

- Apo B was reduced from 2.1±0.4gm/l to 1.8±0.4 gm/l (p value not given).

Mean height velocity standard deviation scores during 1 year for the children in the cholestyramine and placebo groups who had not started puberty were 0.24±1.14 and 0.11±0.68, respectively (not significant). Mean levels of 25-hydroxyvitamin D in the cholestyramine group decreased. Unpalatability of the drug caused 21 withdrawals. Abdominal pain and/or loose stools or nausea were reported in 3 placebo and 5 treatment individuals. One case of intestinal obstruction after taking two doses of cholestyramine was reported.

Nicotinic acid versus placebo

No studies were identified.

Fibrates versus placebo

One study was identified which evaluated the use of bezafibrate in 14 children, aged 4-15 years, with FH (Wheeler, 1985)(Wheeler, K. A., West, R. J., Lloyd, J. K. et al , 1985). Bezafibrate was given twice daily in a dose of 10 to 20 mg/kg/day in a 6 month double placebo randomised crossover trial. LDL-C was not reported. The results of other lipid values were as follows:

TC:

mean baseline TC: 9.3 (sd 1.5); mean TC on bezafibrate 7.8 (sd 3.0); mean placebo TC 10.0 (sd 1.6). Mean plasma total cholesterol while on bezafibrate was 22% lower than during the placebo period and 16% lower than in the period before the trial.

HDL-C:

mean baseline HDL-C: 1.44 (sd 0.2); mean HDL-C on bezafibrate 1.30 (sd 0.36); mean placebo HDL-C 1.43 (sd 10.2). There was a mean rise in HDL-C on bezafibrate of 15% compared with placebo and 25% compared to pre-trial values. There was a mean rise in HDL-C on bezafibrate of 15% compared with placebo and 25% compared to pre-trial values.

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[1] Assumed to be mean±sd throughout, but not reported explicitly in paper

TG:

mean baseline TG:1.00 (sd 0.26); mean TG on bezafibrate 0.67 (sd 0.37); mean placebo TG 0.87 (sd 0.35). There was a mean fall of TG on bezafibrate treatment of 23% compared with placebo and 33% compared with pre trial values. This was not statistically significant.

One child had an elevated alkaline phosphatase due to intercurrent infection and a second child had a transient rise in alanine transaminase . Both of these children returned to normal at the end of the third month and there were no other abnormal blood results. Growth was satisfactory and no reported clinical side effects.

Fish oils versus placebo

No studies were identified.

Ezetimibe versus placebo

No additional studies were identified.

5.2.4.3   Health economic evidence

No relevant health economic evidence was identified for any comparison.

5.2.4.4   Drug safety

At the request of the GDG chair and clinical advisor an additional search was carried out for studies of 'long term' bile acid sequestrant and fibrate safety in children. 'Long term' was determined to be five years or greater.

Identified: 107 total

Ordered: 26 studies

Included: 1 study

Excluded: 25 studies

Only one reference study followed children for more than five years. Hansen et al (1992)(Hansen, D., Michaelsen, K. F., and Skovby, F., 1992) evaluated 30 children for the effects of low fat diet alone or diet and colestipol. The median age

at the start of the study was 3.0 years in the diet only group and 5.0 years in the diet and colestipol group. The median duration of treatment was 8.5 years in 13 children on diet only and 5.5 years in 17 children treated with diet followed by diet and colestipol. The children were not randomized to treatment. The decision to prescribe colestipol was based upon the concentrations of serum lipids and the response to dietary measures, the age and sex of the child and the family history of early ischemic heart disease. The scores for both height/age and weight/age decreased by approximately 0.4 during dietary treatment ($p < 0.05$), but were not affected by treatment with colestipol.

5.2.5 Evidence statements on the effectiveness of combined therapy in adults

Key clinical question:

What is the effectiveness of adjunctive pharmacotherapy with statins (statins and bile acid sequestrants, statins and nicotinic acid, statins and fibrates, statins and fish oils, statins and bile acid sequestrants with nicotinic acid, statins and ezetimibe, or statins plus bile acid sequestrants versus statins plus fibrates) in adults with FH?

Question 9 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
The use of statin and bile acid sequestrant in combination significantly reduces LDL-C and TC when compared with placebo and appears to have a greater effect when compared with either drug alone. The effect of combination therapy on HDL-C and triglycerides does not appear to be consistent. [1+]

The use of statin and nicotinic acid in combination significantly reduces LDL-C, TC, and triglycerides and increases HDL-C when compared with placebo. The combination appears to have a greater effect when compared with either drug alone. [1+]

The use of statin and fibrate in combination significantly reduces LDL-C, TC, and triglycerides and increases HDL-C when compared with placebo. (Reduction in total cholesterol (29.0%), LDL-C (37.1%), TG (41.7%) and increased HDL-C by 16.8%). The combination appears to have a greater effect when compared with either drug alone. [1+]

There was no evidence for the use of a combination of statins and omega-3-ethyl esters treatment in the FH population.

There was no evidence for the use of a combination of statins and bile acid sequestrants with nicotinic acid in the FH population.

One RCT showed that the addition of fibrates or bile acid sequestrants to statin therapy, showed similar reductions in LDL-C or TC. In this trial fibrates were more effective than bile acid sequestrants in reducing TG and raising HDL-C concentration. [1+](Leitersdorf, E., Muratti, E. N., Eliav, O. et al , 1994)

See the NICE TA for evidence on the use of ezetimibe in adults with heterozygous FH(National Institute for Health and Clinical Excellence, 2007).

No evidence on the use of ezetimibe in individuals with homozygous FH, or children with FH was identified.

In summary, combination therapy is superior to monotherapy in the treatment of FH individuals to lower LDL-C and TC. | Clinical practice on the use of combination therapy or higher intensity statins may differ depending on the side effect profile for the individual statin, the results of monitoring, and the response of the individual (where the dose response curve may flatten off considerably). None of the included studies titrated to maximal dose.

There was no direct evidence for the differential choice of drugs within the treatment pathway, so recommendations were made based on clinical judgment and considerations of efficacy, safety, and tolerability.

The combination of statin with fibrates has specific safety issues which have been highlighted in the recommendations.

In the clinical experience of the GDG, the pattern of side effects tend to show peaks at initiation and when used long term, so rather than define regular monitoring, people experiencing unusual side effects should be referred. However, BNF monitoring recommendations for each drug should be followed. |

5.2.6 Evidence summary on the effectiveness of combined therapy in adults

5.2.6.1 Methods of the clinical evidence review

This review included only trials in which individuals with FH taking combined therapy were randomized and compared either to a placebo control group or a statin only group...

Identified: 789 studies

Ordered: 62 studies

Included: 11 studies

Excluded: 51 studies

5.2.6.2 Clinical evidence

Statins in combination with bile acid sequestrants

An early randomised follow on study from 1988(Erkelens, D. W., Baggen, M. G., Van Doormaal, J. J. et al , 1988) evaluated the response of 60 individuals with heterozygous FH to treatment with cholestyramine (8-16 g) or simvastatin 20mg for 6 weeks then on 40mg for a further 6 weeks. At the end of 12 weeks 50 of 60 participants were placed on 40mg simvastatin in combination with 8-16 g cholestyramine. There were significant differences (p<0.05) between each treatment. Percent changes in lipid concentrations were reported:

Table 3

	TC	LDL-C	HDL-C	TG
Cholestyramine	-23%	-30%	+9%	+11%
Simvastatin	-36%	-43%	+16%	-21%
Combination	-45%	-54%	+20%	-17%

A study conducted in Holland in 1990(Hoogerbrugge, N., Mol, M. J., Van Dormaal, J. J. et al , 1990) randomised 40 heterozygous FH individuals to pravastatin 40mg and 22 individuals to placebo. If serum LDL-C concentration did not fall below 5.0mmol/l 8 weeks after randomization, bile acid sequestrants were added starting 10 weeks after randomization. These were given at the maximum tolerable dose per individual. After 8 weeks of treatment, TC had decreased from 10.6 (sd±1.7 mmol/l to 7.6±1.3 mmol/l (28%; $p<0.01$). When pravastatin was supplemented with bile acid sequestrants, there was an additional reduction in TC of 8% ($p<0.01$) by week 24. LDL-C decreased after 8 weeks from 8.7±mmol/l to 5.8±1.3 mmol/l (33%, $p<0.01$). In 30 individuals treated with combination therapy the LDL-C decreased an additional 12% ($p<0.01$). HDL-C was not affected by bile acid sequestrants. The addition of bile acid sequestrants to pravastatin caused TG concentrations to increase by 7% compared to pravastatin monotherapy.

Tsai et al(Tsai, C. H., Ding, Y. A., and Hao, K. L., 1995) conducted a randomized parallel group study comparing pravastatin 20mg/day with a combination of pravastatin 10mg/day plus cholestyramine 8g/day for 24 weeks in 30 individuals with primary hypercholesterolaemia. The low dose combination of pravastatin and cholestyramine was significantly more effective than pravastatin alone in higher doses in terms of LDL-C reduction (mean±sem): 25% reduction with pravastatin alone (4.7mmol/l±0.3 to 3.5mmol/l±0.3); 34% reduction (4.7± 0.3 to 3.1±33) with the pravastatin/cholestyramine combination ($p<0.01$ between groups). There was no significant change in total cholesterol or in HDL-C. TG increased by 18% (4.9±0.6 to 3.1±0.3) in the combination treatment group (between group p-value not reported).

Pravastatin was studied at doses of 20 or 40mg twice daily alone or 20mg twice daily with cholestyramine, 12g twice daily vs. placebo in an 8 week RCT in 311 individuals with primary hypercholesterolaemia(Knopp, R. H., Brown, W. V., Corder, C. N. et al , 1993). TC and LDL-C reductions were substantially greater than with either drug alone ($p<0.001$). At 8 weeks pravastatin 20mg bid reduced TC by 23.8% (7.9 mmol/l±0.18 placebo versus 6.0mmol/l± 0.16); pravastatin 40mg bid reduced TC by 29.8% (7.9mmol/l±0.18 placebo versus 5.7mmol/l±0.13);cholestyramine 12g bid reduced TC by 18.3% (7.9 mmol/l±0.18

placebo versus 6.6mmol/l±0.20); pravastatin 20mg bid plus cholestyramine 12g bid reduced TC by 32.2% (7.9 mmol/l±0.18 placebo versus 5.4mmol/l±0.15). LDL-C reductions were as follows: placebo 5.9 mmol/l±0.18; pravastatin 20mg bid 31.7% change (4.1mmol/l±0.13); pravastatin 40mg bid 38.9% change (3.7mmol/l±0.13); cholestyramine 12g bid 28.3% change (4.4mmol/l±0.19); pravastatin 20mg bid plus cholestyramine 45.4% change (3.3 mmol/l±0.14). For the study as a whole, HDL-C concentration increased about 5% with either drug alone or in combination. Both pravastatin regimes after eight weeks of therapy reduced plasma TG concentrations by 13-14% (p<0.01) versus placebo. Cholestyramine significantly elevated plasma TG from baseline (12.1%, p<0.01).

The effect of the combination of low dose lovastatin and low dose colestipol versus placebo was studied among 57 individuals with moderate to severe primary hypercholesterolaemia(Tonstad, S., Ose, L., Gorbitz, C. et al , 1993). Subjects received either colestipol 5g at breakfast and lovastatin 20mg at bedtime; colestipol 10g and lovastatin 20mg; or placebo. Compared to placebo, 20mg of lovastatin and 5g of colestipol reduced TC concentrations from 7.9±0.8mmol/l to 5.6±0.7mmol/l after 8 weeks of treatment (p<0.0001). LDL-C Concentration were reduced from 5.9±0.8mmol/l to 3.9±0.7mmol/l (34%; p<0.0001). In the lovastatin 20mg and 10g colestipol group TC was reduced to 5.5mmol/l and LDL-C was 3.6±0.8mmol/l representing a 35% decrease (p<0.0001 in both groups). Triglycerides and HDL-C remained unchanged.

Statins in combination with nicotinic acid
See Evidence statements on information for pregnant women with FH

Return to recommendations

Statins in combination with fibrates
Only one study of pravastatin and gemfibrozil alone and in combination for the treatment of primary hypercholesterolaemia was identified(Wiklund, O., Angelin, B., Bergman, M. et al , 1993). Individuals with primary hypercholesterolaemia (n=266) were randomised to either pravastatin 40mg once daily, gemfibrozil 600 mg twice daily, combination therapy with pravastatin and gemfibrozil or placebo. Pravastatin reduced total cholesterol more than gemfibrozil (26.3% versus 15.2%,

p≤0.01) and LDL-C (35.5% versus16.8%, p≤0.01). Gemfibrozil reduced triglycerides (42.2% versus 14.2%, p≤0.01) and increased HDL-C (15.2% versus 5.9%, p≤0.01) more than pravastatin. The combination significantly (p≤0.01) reduced total cholesterol (29.0%), LDL-C (37.1%), TG (41.7%) and increased HDL-C by 16.8%). The absolute mean values (sem) were as follows:

- TC: placebo 7.13mmol/l (0.12), -1.72% change; pravastatin 5.44mmol/l (0.11), -26.25% change; gemfibrozil 6.20mmol/l (0.12), -15.18% change; combination 5.10mmol/l (0.12), -28.98% change

- LDL-C: placebo 5.02mmol/l (0.13), -1.88% change; pravastatin 3.44mmol/l (0.11), -33.54% change; gemfibrozil 4.29mmol/l (0.11), -16.80% change; combination 3.17mmol/l (0.10), -37.06% change

- VLDL: placebo 0.65mmol/l (0.05), +2.17% change; pravastatin 0.49mmol/l (0.04), -21.85% change; gemfibrozil 0.32mmol/l (0.02), -49.06% change; combination 0.32mmol/l (0.03), -49.43% change

- TG: placebo 1.83mmol/l (0.10), +1.87% change; pravastatin 1.53 mmol/l (0.08), -14.17% change; gemfibrozil 1.03mmol/l (0.05), -42.16% change; combination 1.01mmol/l (0.06), -41.68%change

- HDL-C: placebo 1.16 mmol/l (0.03), -4.44% change; pravastatin 1.32mmol/l (0.04), -5.93% change; gemfibrozil 1.39mmol/l (0.04), 15.21% change; combination 1.46mmol/l (0.05), 16.81% change.

Statins in combination with fish oils

No studies identified. The GDG extrapolated from evidence reviewed in the Clinical Guidelines and Evidence Review for Post Myocardial Infarction(Cooper, A., Skinner, J., Nherera, L. et al , 2007).

Statins in combination with bile acid sequestrants and nicotinic acid

No studies were identified.

Statins in combination with ezetimibe

For a review of the evidence in adults with heterozygous FH, see the NICE TA on the use of ezetimibe(National Institute for Health and Clinical Excellence, 2007). No evidence on the use of ezetimibe in adults with homozygous FH was identified.

Statins in combination with bile acid sequestrants versus statins in combination with fibrates

It was decided to review one additional study by Leitersdorf et al(Leitersdorf, E., Muratti, E. N., Eliav, O. et al , 1994) as it contributed to the evidence base for determining second and third line treatment options in FH. This study was a double blind, double placebo randomized parallel group investigation in 38 individuals with heterozygous FH. During weeks 13-18 of this study 18 individuals (Group 1) received 8g cholestyramine and 40mg fluvastatin daily and 20 individuals (Group 2) received 400 mg bezafibrate and 40mg fluvastatin. Percent change (mean±sd) from baseline was reported in both groups. Total cholesterol in Group 1 changed by 23.9±10.7% and in Group 2, 28.6±11.7%; TG increased in Group 1 by 14.2±35.8% and decreased in Group 2, 25.1±29.7%; HDL-C increased in Group 1 2.9±11.0% and in Group 2 13.0±13.4%; LDL-C decreased by 21.3±7.9% in Group 1 and 25.0±13.5%. There was no significant difference in total cholesterol or LDL-C between groups; however, there were significant differences between triglyceride and HDL-C concentration (p<0.001 and p<0.05 respectively).

5.2.6.3   Health economic evidence

No studies were found looking at high versus low dose statins or any lipid lowering drug compared with placebo from the literature search. However there was one cost utility analysis found comparing fluvastatin 80mg versus simvastatin 40mg in FH patients by Metcalfe(Metcalfe, S., 1997) for PHARMAC a pharmaceutical management agency established by the New Zealand Public Health and Disability Act of 2000. The authors of the report used data from the Simon Broome register, other observational data and effectiveness data from the 4S trial. Most of the data was presented as graphs, but the authors were transparent with the sources of data and the methodology used except for utility data which was not well reported.

The authors reported that simvastatin 40mg resulted in more QALYs compared to fluvastatin 80mg. (1.03 vs. 0.89 discounted QALYs respectively) The estimated ICERs were approximately $32,947 for those aged 35-59. The ICERs ranged

between $28,112 in men aged 55-59 years, to about $77,000 in children. The cost effectiveness improved with age.

The authors did not undertake a sensitivity analysis which weakens their study. In their base case model they assumed fluvastatin will cause a disutility of 0.01 (compared to a disutility of 0.00 for simvastatin), while in their discussion they acknowledge that published studies did not find any difference in utility between the two statins. The implications, which the authors acknowledge, are to exaggerate the QALY gains by simvastatin; hence making the ICERs favourable. It would be more helpful if they had fully explored this in sensitivity analysis or assumed no difference in the base model.

In conclusion, simvastatin 40mg compared with fluvastatin 80mg used in patients with FH appears to have value for money; this finding is weakened by a lack of sensitivity analysis and, especially, the assumptions about utility loss between the two statins. Their finding seem to contradict our finding that in FH patients, cost effectiveness is favourable for those aged less than 60 years compared to those aged over 60 years.

5.2.6.4 *Modelling the cost effectiveness of high intensity statins compared with low intensity statins in the management of FH*

When initial searches were undertaken, no studies were found which compared cost-effectiveness of higher intensity statins with lower intensity statins in patients with FH. Consequently, the GDG requested the development of a *de novo* economic model to help inform the guideline recommendations.

A Markov model was developed to estimate the incremental cost per quality adjusted life year (QALY) of lifetime treatment with high intensity statins atorvastatin 80mg compared with low intensity statins simvastatin 40mg. The base case models a cohort of hypothetical patients aged 50 years of age.

Baseline risks were taken from the Statins TA 94(Kwiterovich, P. O., Jr., Levy, R. I., and Fredrickson, D. S., 1973) which shows the prevalence of CHD in the general population. This is different from the population with FH therefore the age-

adjusted risk of cardiovascular disease reported in the updated Simon Broome paper (Neil 2008)(Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group, 1999) was applied. Thus for ages groups 20-39 the risk of developing cardiovascular disease by a factor of 84.3 was increased, for those aged 40-59 a factor of 5.76 was used and those over 60 a factor of 1.2. Stroke and PAD were assumed to be the same as seen in the general population. The intermediate outcomes include MI, stroke, TIA, PAD, heart failure, revascularisation, unstable angina and death from CVD and other causes. There was no trial evidence considering the effectiveness of high intensity statins with low intensity statins in FH patients. The only available evidence was observational data from the Simon Broom register which showed benefit from treatment before and after the use of statins. For the main analysis we assumed that FH patients do not benefit differently from statin treatment from patients with after myocardial infarction with stable coronary disease (CAD). This enabled us to use reduction in cardiovascular events reported by the TNT (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al , 2005) and IDEAL ((Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al , 2005) trials which we meta-analysed and used in sensitivity analysis. We then used data from the Simon Broome(Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group, 1999) in sensitivity analysis to estimate statins benefit.

Health state utility values were taken from published sources (Appendix E). All cause mortality rates are from the Government Actuarial Department (Government Actuaries Department., 2006). The model makes the assumption of no adverse events from treatment using high intensity statins. Costs of drugs were taken from the Drug tariff March 2008 (atorvastatin 80mg £367.74/year, simvastatin 40mg, £18.12/year) (Prescription Pricing Division., 2006). Costs of cardiovascular events were taken from the NICE TA94 on statins (Kwiterovich, P. O., Jr., Levy, R. I., and Fredrickson, D. S., 1973). In order to reflect social values for time preference as is standard in economic models; costs and QALYs have been discounted at 3.5% as recommended by NICE (National Institute for Health and

Clinical Excellence, 2006c). All of these and other model assumptions have been tested in sensitivity analyses.

Results

The base case results are presented below, and cost-effectiveness is assessed against a threshold of £20,000/QALY.

### Results for patients with FH effectiveness data from Simon Broome

Table 4 indicates the modelled number of events for the hypothetical 1,000 patients who are taking high intensity or low intensity statins. The table indicates that fewer cardiovascular events occur in the population treated high intensity statins. More people will die from other causes and fewer people will die from cardiovascular mortality for people taking high intensity statins. This translates to a gain of 0.34 discounted QALYs when compared with low intensity statins.

Table 4 Lifetime event outputs modelled for a cohort of 1,000 patients high intensity statins compared with low intensity treatment strategy for patients with FH

Health state	Low intensity (number of events)	High intensity (number of events)
MI	443	348
Stroke	313	251
PAD	66	67
Heart failure	220	153
Revascularisations	266	203
Unstable angina	140	117
Cardiovascular mortality	370	329
Death from other causes	612	650

Scatter Plot

The scatter plot visually illustrates that high intensity statins cost more per patient and also generates more QALYs.
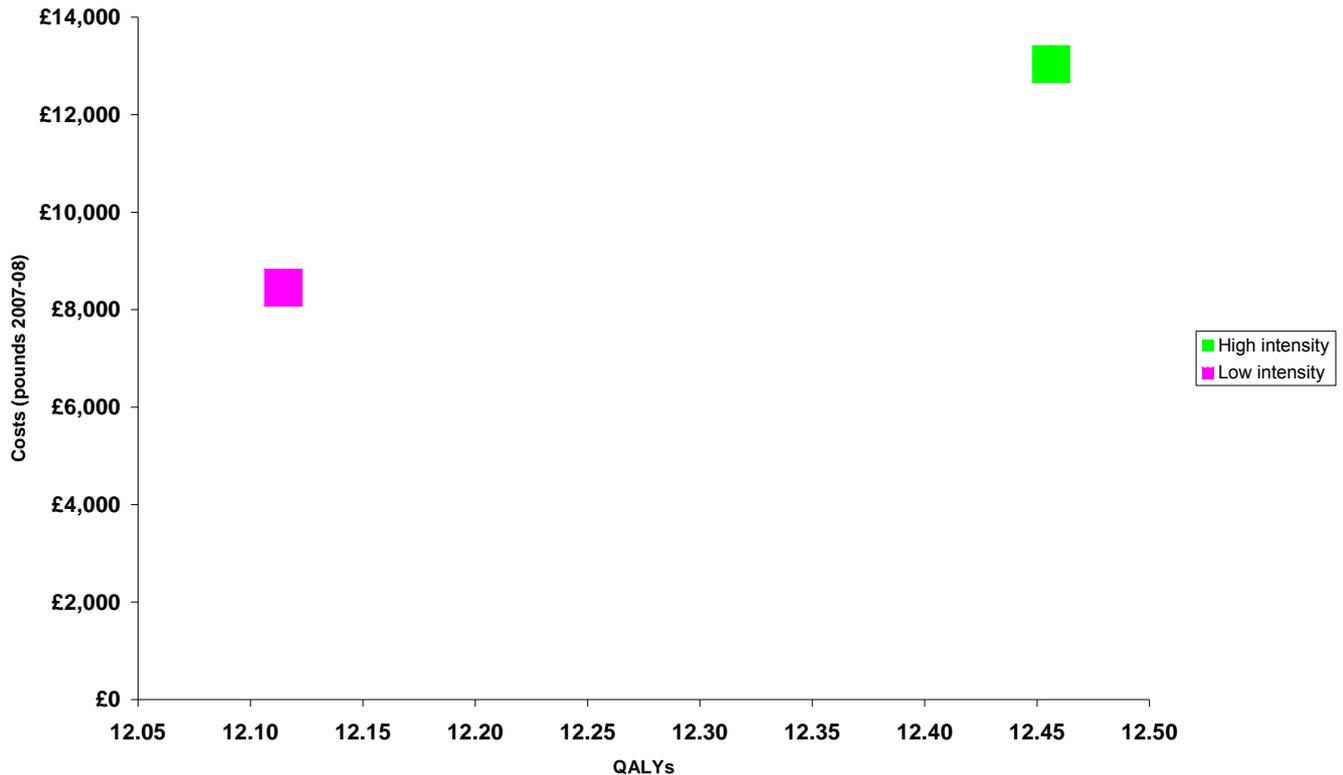
The incremental cost per patient is estimated to be about £4,591.when compared with low intensity statins. The estimated ICER is about £13,437/QALY suggesting that high intensity statins are cost effective.

Rosuvastatin was not considered on the grounds that it did not have clinical outcome data, however assumptions can be made about its cost effectiveness based on its efficacy in reducing cholesterol (STELLAR trial). Assuming the reduction in cholesterol translates to reduction in final outcomes, Rosuvastatin will be cost effective. A threshold analysis showed that as long as rosuvastatin was more than 0.7% more effective (in the STELLAR trial, rosuvastatin is said to be 8.2% more effective in lowering cholesterol than Atorvastatin 80mg), then the choice will be Rosuvastatin 40mg.

If it is assumed that Simvastatin 80mg was has the same effectiveness as Atorvastatin 80, then Simvastatin 80 will be more cost effective as it is cheaper than Atorvastatin 80. If however it is assumed that Simvastatin 80mg was 5% less effective than Atorvastatin 80mg (as in the STELLAR study), the result is high intensity treatment will dominate low intensity treatment.

Due to a lack of data on the effectiveness of simvastatin and rosuvastatin at maximal dose, and lack of long term, credible safety data for atorvastatin, simvastatin and rosuvastatin at these doses, the incremental cost effectiveness was not further examined. If high intensity treatment with Simvastatin 80mg, Atorvastatin 80mg, Rosuvastatin 40mg are considered individually, they are all cost effective options compared to S40.

However this result is sensitive to age and effect of statins on cardiovascular mortality. If the average FH patient is aged over 60 years, it's no longer cost effective to give atorvastatin 80mg as the ICERs increase to £26,254/QALY. When upper limit of the 95% CI for treatmnment effect is used, thus assuming high intensity will result in more cardiovascular death, low inensity statins will dominate high intensity. When we assumed the cost of atorvastatin 80mg were to fall to the price of generic simvastatin 80mg (£64,53/year), high intensity became cost effective for all age groups.

The limitations of this model are that it is based on extrapolated baseline risks from a non FH population adjusted for the FH population andthe model assumes that there is no loss in utility due to treatment side effects which may not be the case. In this respect our model may overestimate the cost-effectiveness of high intensity statins (make them look more favorable). The model is also based on observational data, and there is a lack of direct effectiveness data for this population. However as the ICER for atorvastatin 80mg is considerably lower than the £20,000 cost/QALY threshold, any plausible variance in the size of treatment effect in the FH population would be unlikely to effect the acceptability of the cost effectiveness.

In conclusion, high intensity statins are cost effective for the treatment adults with FH below age 60 years. For adults with FH who are first identified over the age 60 years and do not have coronary heart disease, the economic analysis shows that only lower intensity statins (i.e. simvastatin) are cost effective.

5.2.7 Evidence statements on the effectiveness of combined therapy in children

Key clinical question:

What is the effectiveness of adjunctive pharmacotherapy with statins (statins and bile acid sequestrants, statins and nicotinic acid, statins and fibrates, statins and fish oils, statins and bile acid sequestrants with nicotinic acid, statins and ezetimibe, or statins plus bile acid sequestrants versus statins plus fibrates) in children with FH?

Question 9 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
No evidence was identified.	See also above for issues on ezetimibe.

5.2.8 Evidence summary on the effectiveness of combined therapy in children

5.2.8.1 Methods of the clinical evidence review

This review included only trials in which individuals with FH taking combined therapy were randomized and compared either to a placebo control group or a statin only group.The paediatric population was included in the original search terms for statins (1113) and the searches for other cholesterol lowering drugs (789).

Identified: 1902 total

Ordered: 34 studies

Included: 0 studies

Excluded: 34 studies

A separate search was carried out to review the literature on the use of ezetimibe in children and individuals with homozygous FH. These two populations were not included in NICE ezetimibe TA(Starr, B., Hadfield, S. G., Hutten, B. A. et al , 2008). For this review we included only randomised controlled trials conducted in the paediatric and homozygous FH population.

Identified: 82 studies

Ordered: 7 studies

Included: 1 study

Excluded: 6 studies

5.2.8.2   Clinical evidence

Combined therapy (statins with bile acid sequestrants, nicotinic acid, fibrates, fish oils, bile acid sequestrants with nicotinic acid)

No evidence was identified which evaluated combination statin therapy with bile acid sequestrants, nicotinic acid, fibrates, fish oils and bile acid sequestrants with nicotinic acid in children.

Ezetimibe in combination with statins

There were no RCTs identified for the treatment of children alone with ezetimibe.

One study was identified which evaluated the efficacy and safety of ezetimibe in combination with atorvastatin or simvastatin in homozygous adults and children (at least 12 years old or body weight≥40kg) (Gagne et al, 2002)(Gagne, C., Gaudet, D., Bruckert, E. et al , 2002). Fifty individuals were randomised to ezetimibe 10mg plus 'statin-40' (simvastatin or atorvastatin 40mg) (n=16) or ezetimibe 10mg plus 'statin-80' (simvastatin or atorvastatin 80mg) (n=17) or to statin-80 (n=17). There were 7 participants less than 18 years old in this study (14%). The results were as follows:

changes in lipid concentrations from baseline (simva-40):

direct LDL-C absolute change 0.5mmol/l statin-80 and 1.7mmol/l in ezetimibe plus statin 40/80 (p=0.007);

TC absolute change 0.49mmol/l statin-80 and 1.9mmol/l in ezetimibe plus statin 40/80 (p<0.01).

There were no other significant differences between the two treatment groups. There were reductions of at least 14% to 20.5% in LDL-C when ezetimibe was coadministered with a moderate (40mg) or maximal (80mg) dose statin therapy compared with maximal therapy with statins alone. Ezetimibe plus statin 80mg reduced LDL-C by 26.6% compared to statin 80mg, a reduction of 5.6% from baseline of simvastatin 40mg.

Two individuals in the ezetimibe group discontinued treatment; one due to epigastric and chest pain and another due to increase liver enzymes. There were

no significant differences between treatment groups on another other measures of safety.

5.2.8.3 Health economic evidence

No studies were identified.

5.2.9 Evidence statements on the effectiveness of maximal cholesterol lowering in adults

Key clinical question:

What is the effectiveness of aggressive (maximal) cholesterol lowering in adults with FH?

Question 7 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
Increasing the dose of the statin increases LDL-C reduction [1+] There are differences in efficacy and potency between statins in their LDL-C lowering [1+] Adverse events associated with statins include headache, altered liver function, paraesthesia and gastrointestinal effects (including abdominal pain, flatulence, diarrhoea, nausea and vomiting). Rash and hypersensitivity reactions have been reported but are rare. Muscle effects (myalgia, myositis and myopathy) have also been reported with the use of statins. Severe muscle damage (rhabdomyolysis) is a very rare but significant side effect. Further adverse events are associated with individual statins. For full details of adverse effects, contraindications and interactions, see the Summaries of Product Characteristics. (Statins for the prevention of coronary events. NICE Technology Appraisal 94, 2006; 1++)(National Institute for Health and Clinical Excellence, 2006b) A two year study [1+] that compared simvastatin 80mg versus simvastatin 80mg and Ezetimibe 10mg, in people with FH who were pre-treated with lipid modifying therapy did not demonstrate significant differences in carotid IMT (simvastatin 0.0058±0.0037 mm, simvastatin+Ezetimibe 0.0111±0.0038 mm, P=0.29). A significant 16.5 % reduction in LDL-C (P<0.01) was demonstrated (secondary outcome). The incidence of adverse events and discontinuation was similar in both groups.	Evidence is clear on the effect of statins to reduce LDL-C and TG, but included studies are old, small, and short-term. Therefore, other evidence on the longer term safety and efficacy of statins (including evidence of the effect on clinical outcomes (National Institute for Health and Clinical Excellence, 2006b)) was considered. In addition, because of the high initial concentrations of cholesterol in people with FH, the need to lower concentrations is of prime importance, so higher intensity statins may be required to achieve the maximal degree of cholesterol lowering. The GDG considered that there was only one double blind randomized controlled trial that compared (intermediate) outcomes in patients receiving different statin treatments (Smilde, T. J., van Wissen, S., Wollersheim, H. et al , 2001), They noted that this study showed that there were significant reductions in carotid IMT in patients randomised to atorvastatin 80mg as compared to simvastatin 40mg.The GDG considered that this change in carotid IMT, was likely to be associated with an improvement in clinical outcome. No conclusion could be drawn around the effect of other possible interventions, such as simvastatin 80mg or rosuvastatin, in terms of lack of progression of atherosclerosis. Atorvastatin 80mg was therefore chosen as the intervention for maximum cholesterol lowering for the purpose of health economic modeling. A > 50% reduction in LDL-C was recommended on the basis of the ASAP study (Smilde, T. J., van Wissen, S., Wollersheim, H. et al , 2001) (this being the therapeutic response associated with lack of progression of atherosclerosis). However, clinicians should use their expert judgment when individualising treatment. The GDG reviewed the ENHANCE study (Kastelein, J. J., Akdim, F., Stroes, E. S. et al , 2008) and considered that pre-treatment with lipid modifying medication, likely to be high dose statin treatment, prior to randomisation into either treatment arm was an important consideration in interpreting the changes in carotid IMT. They considered that the number of prior 'statin years' treatment was relevant to interpreting the primary outcome and noted that

Evidence statements	Evidence into recommendations
	baseline carotid IMT thickness was considerably lower in the ENHANCE study than that in the ASAPS study.The GDG concluded that (i) no definitive conclusion could be drawn based on this surrogate measure (ii) a clinical outcome trial was required (iii) that a 50% reduction in LDL-C, the approximate mean reduction with high dose, high intensity statin treatment in the ASAP study, would remain the basis of the recommendation regarding the objective of treatment.

5.2.10 Evidence summary on the effectiveness of maximal therapy in adults

5.2.10.1 Methods of the clinical evidence review

For this review we included only randomised controlled trials conducted in the FH population. Numbers based on the searches for statins overall.

Identified: 1113 studies

Ordered: 166 studies

Included: 16 studies

Excluded: 109 studies

Studies relating to other questions: 41

5.2.10.2 Clinical evidence

High versus lower dose statin comparisons

The McDowell et al (1991)(Mcdowell, I. F. W., Smye, M., Trinick, T. et al , 1991) study, referred to in the review for question 8a, randomised individuals to placebo or 10mg simvastatin during the first month of treatment. The dose of simvastatin was increased monthly for the individuals in the active arm of the treatment and the effects of 10mg, 20mg and 40mg simvastatin on lipid concentrations were compared. Significant decreases in LDL-C, total cholesterol and Apo B occurred at all doses of simvastatin versus placebo. Most of the cholesterol lowering effect was achieved during the first month on a dose of 10mg daily. Mean LDL-C Concentration (±sem) dropped from 6.4±0.5 to 5.6±0.4mmol/l when the dose was increased to 20mg simvastatin (p-values not given). There were no changes in lipid concentrations from 20mg to 40mg. Total cholesterol concentrations changed from 8.3±0.5 to 7.7±0.4mmol/l (no p-value) in conjunction with the change in dosage from 10mg to 20mg. There was no difference between 20mg and 40mg concentrations.

Synvinolin (MK-733 or simvastatin) was studied by Mol et al (1986)(Mol, M. J., Erkelens, D. W., Leuven, J. A. et al , 1986) who randomised 43 individuals to different doses of synvinolin versus placebo. All doses (2.5mg daily to 80mg daily) produced significant ($p<0.05$) reductions in total and LDL cholesterol than placebo except for treatment with 2.5mg once a day. The 80mg dose was no more effective than 40mg or 20mg in the small treatment groups. However, plotting the log of the dose against the percentage change in LDL-C after 4 weeks gave a straight line with a highly significant correlation ($p<0.001$). From this curve the researchers calculated that in the range of 2.5mg to 80mg synvinolin, every two-fold increase in dose caused an additional reduction in LDL-C of 4 to 6%.

The efficacy of high dose fluvastatin was studied by Leitersdorf et al (1993)(Leitersdorf, E., Eisenberg, S., Eliav, O. et al , 1993) in a double blind parallel group trial. A control group taking 40mg fluvastatin was compared to a treatment groups taking fluvastatin in 40mg and 60mg doses. Overall, fluvastatin 40mg was associated with a 20-21% decrease in total plasma cholesterol, and a 25-27% decrease in LDL-C ($p<0.001$). There was a significant decrease in LDL-C when the dose was increased to 60mg ($p<0.01$). Total cholesterol was unaffected.

Raal et al (1997)(Raal, F. J., Pilcher, G. J., Illingworth, D. R. et al , 1997) randomised 12 homozygous people with FH to 80mg simvastatin (group 1) or 40mg (group 2) in three divided doses daily. After 9 weeks the dose in the 80mg group was doubled while the dose in group 2 remained constant. LDL-C Concentration fell by 14% at the 40mg/day dose but were reduced further at the higher doses (25% at the 80mg/day level and by 31% at the 160mg/day dosage ($p<0.0001$).

Comparisons between different statins
Six studies were reviewed which compared the lipid lowering effects of different statins in heterozygous people with FH.

The hypolipidaemic effects of lovastatin and simvastatin at doses of 10mg, 20mg, and 40mg were compared in a randomised crossover study of 23 people with FH (Illingworth et al, 1992)(Illingworth, D. R., Bacon, S., Pappu, A. S. et al , 1992). Concentrations of total cholesterol and LDL-C decreased significantly for both

drugs at all doses. Total cholesterol and LDL-C also decreased significantly as the dose of each drug was increased from 20 to 40 to 80mg/day. In this study, on a milligram per milligram basis the hypolipidaemic effect of simvastatin at a doses of 20mg and 40mg was equivalent to that seen with twice the dose of lovastatin (40 and 80mg).

Simvastatin and pravastatin were compared by Feillet et al (1995)(Feillet, C., Farnier, M., Monnier, L. H. et al , 1995) using a 20mg dose in a randomised sample of 26 individuals. Simvastatin was found to be significantly more effective (p<0.001) in reducing TC ,28%, and LDL-C, 35.6% than pravastatin (TC, 19.6%, LDL-C, 25.2%).

A study which compared the efficacy of simvastatin 80mg with atorvastatin 80mg (Wierzbicki et al, 1999)(Wierzbicki, A. S., Lumb, P. J., Chik, G. et al , 1999) in an open crossover trial found that both drugs reduced LDL-C by 47±13%[1] and 43±16%. Total cholesterol reductions did not differ. However, atorvastatin reduced HDL-C by 2±24% compared with 8±30% increase with simvastatin, which affected the LDL/HDL-C ratio achieved (p=0.001). Bo et al (2001)(Bo, M., Nicolello, M. T., Fiandra, U. et al , 2001) also evaluated atorvastatin versus simvastatin and found that although there were significant reductions in lipid concentrations with both drugs, atorvastatin caused greater reductions in total cholesterol (p<0.001) and LDL-C (p<0.01).

The ASAP study, conducted by Smilde et al(Smilde, T. J., van den Berkmortel, F. W., Wollersheim, H. et al , 2000) was a randomized, double blind clinical trial of 325 individuals with FH. Participants were given either atorvastatin 80mg or simvastatin 40mg and followed for 2 years. Although the primary outcome measure of this study was carotid IMT the reporting of comparative lipid concentrations in such a large number of FH patients aids the evaluation of high dose therapy in this population. Atorvastatin showed significantly greater reductions (mean [sd])in TC (5.73 [1.31] vs 6.71[1.38] mmol/l; p=0.0001) and LDL-C Concentration (3.88 [1.21] vs 4.81[1.38] mmol/l; p=0.0001) than did

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[1] Assumed to be sd, not reported in paper

simvastatin. There was also a significant difference in triglycerides (p=0.0023) and in apo B concentrations (p=0.0001). With regard to the primary outcome of carotid IMT, after treatment with atorvastatin for 2 years, IMT decreased (-0.031mm [95 %CI -0.007 to -0.055]; p=0.0017), whereas in the simvastatin group it increased (+0.036 [95% CI +0.01 to +-0.058]; p=0.0005). The change in thickness differed significantly between the two groups (p=0.0001).

Stein et al (2003)(Stein, E. A., Strutt, K., Southworth, H. et al , 2003) randomised 632 individuals to 20mg/day of atorvastatin or rosuvastatin with forced titration at 6 week intervals to 80mg/day. At 18 weeks, rosuvastatin therapy produced a significantly greater reduction in LDL cholesterol than atorvastatin (57.9% vs 50.4%; p<0.001) and a significantly greater increase in HDL-C (12.4% vs 2.9%; p<0.001).

5.2.10.3   Health economic evidence

No studies were found looking at high versus low dose statins from the literature search.

One cost utility analysis was found comparing fluvastatin 80mg versus simvastatin 40mg.

This study was done by PHARMAC(Metcalfe, S., 1997) a pharmaceutical management agency established by the New Zealand Public Health and Disability Act of 2000. The authors of the report used data from the Simon Broome register, other observational data and effectiveness data from the 4S trial. Most of the data was presented as graphs, but the sources of data and the methodology used were generally well reported, except for utility data.

The authors reported that simvastatin 40mg resulted in more QALYs gained compared to fluvastatin 80mg. The estimated ICERs were approximately $28,112 in men aged 55-59 years, to about $77,000 in children. The cost effectiveness improved with age.

The authors did not undertake a sensitivity analysis which weakens their study. In their base case model they assumed fluvastatin will cause a disutility of 0.01

(compared to a disutility of 0.00 for simvastatin), while in their discussion they acknowledge that published studies did not find any difference in utility between the two statins. The implications, which the authors acknowledge, are to exaggerate the QALY gains by simvastatin; hence making the ICERs more favourable. If this had been fully explored in sensitivity analysis or no difference assumed in the base model, the results may have been more useful.

In conclusion, simvastatin 40mg compared with fluvastatin 80mg used in individuals with FH appears to have value for money; this finding is weakened by a lack of sensitivity analysis and, especially, the assumptions about utility loss between the two statins.

5.2.11 Evidence statements on the effectiveness of maximal cholesterol lowering in children

Key clinical question:

What is the effectiveness of aggressive (maximal) cholesterol lowering in children with FH?

Question 7 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
No evidence was identified.	Recommendation was made to allow prescribing of higher doses, combinations, initiation at an earlier age for children at high risk, in exceptional circumstances only and only by specialists. This was to ensure that appropriate treatment is not denied or deferred inappropriately in the absence of evidence.

5.2.12 Evidence summary on the effectiveness of maximal therapy in children

5.2.12.1 Methods of the clinical evidence review

Inclusion criteria were randomised controlled trials conducted in the FH paediatric population . The paediatric population was included in the original search terms for statins (1113) and the searches for other cholesterol lowering drugs (789).

Identified: 1902 total

Ordered: 34 studies

Included: 0 studies

Excluded: 34 studies

5.2.12.2 Clinical evidence

No evidence was identified for this question in the paediatric FH population.

5.2.12.3 Health economic evidence

No studies were identified.

Return to recommendations

6 General treatment – information, lifestyle and assessment and review

6.1 Introduction

6.1.1 Information needs and support

As with any health condition, people with FH have information and support needs. However, due to the genetic nature of FH, and therefore the implications for the wider family, there may be specific needs for people given a diagnosis of FH. Such support and information is particularly key to the success of any cascade testing programme.

6.1.2 Lifestyle interventions, including dietary intervention

Pharmacological treatment is the preferred management strategy for FH. However, lifestyle interventions, including diet, physical activity, and smoking cessation, are important adjuncts to any drug therapy. The aim of such interventions is not to 'treat' FH, that is by lowering LDL-C, but to confer the cardioprotective effect associated with a 'healthy' diet or increased physical activity.

6.1.3 Key components of assessment and review

Assessment and review are key to the management of any long term condition. As with the information and support needs, we have focused on the components of assessment and review specifically related to FH. A key aim therefore of any assessment or review is to identify any new onset, or deteriorating, symptoms of CHD (see also Chapter 7 on CHD assessment and monitoring).

6.2 Information needs and support

6.2.1 Evidence statements on information needs and support

Key clinical question:

What information and support is required for:

- adults
- children and young people?

Question 6 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
No evidence that compared methods of delivery for information and support of individuals with FH was identified. One cross-sectional observational study(Hollman, G., Olsson, A. G., and Ek, A. C., 2006) did not find a significant association between knowledge of FH and adherence to medication [2-].	It should be noted that there is no direct comparative evidence in this population, so generic principles of communication of familial risk were agreed and specific recommendations made based on these. The GDG considered that familial risk communication, rather than genetic counselling per se, was the focus of information sharing and communication, as issues around termination of pregnancy rarely arose in relation to familial hypercholesterolemia. The recommendations reflect information (both information to be gathered and information to be given) for individuals newly identified/diagnosed and also for relatives. This may be therefore different to other risk communication, for example, familial breast cancer. The recommendations also reflect the different information needed at different times in the process of care, for example, where patients are seen in specialist clinics after having had a lipid test in primary care with a possible diagnosis of FH. Recommendations on the need to gather a family history and the ascertainment of key pieces of relevant information, both clinical data and lifestyle factors, were made based on the professional experience of the GDG. This should then be continually added to throughout the patient journey and cascade testing. Although family history may not be totally accurate(Bensen, J. T., Liese, A. D., Rushing, J. T. et al , 1999), there was a lack of evidence on the extent of this in FH. A recommendation was made that where possible, the patient should be encouraged to check any information with relatives. As with any confidential information, healthcare professionals should be aware of current guidelines on data protection and best practice for maintaining patient records. The communication of the possibility that a relative may have inherited FH can sometimes be difficult for families and the health professionals involved in their care. Recommendations on how communication could be facilitated and patients be supported were made, however, given the varied personal relationships and sensitivities, the term 'facilitate' was used and the GDG decided not to over-specifiy the actions that healthcare professionals might feel were appropriate in individual circumstances..

6.2.2 Evidence summary on information needs and support

6.2.2.1 Methods of the clinical evidence review

The searches for Question 6 were not restricted by study type or age of patients.

Identified: 935

Ordered: 17

Included: 1

Excluded: 16

6.2.2.2 Clinical evidence

Communication of familial risk

No studies were identified which addressed communication of familial risk for FH specifically.

The GDG considered that the general purpose and principles of communication of familial risk were covered in the NICE guidance for familial breast cancer(National Institute for Health and Clinical Excellence, 2006a) and in guidelines produced by Eurogentest, a European Network of Excellence aimed at harmonising genetic testing services. These reference documents were then reviewed by expert members of the GDG and recommendations agreed.

Information and support

Several observational and qualitative studies have explored the extent to which diagnostic testing and treatment of FH impacts on the psychosocial well-being of those affected. These studies will provide background information to inform the use of specific interventions.

Marteau et al(Marteau, T., Senior, V., Humphries, S. E. et al , 2004) studied the impact of genetic testing for FH within a known FH population. Three hundred and forty one families comprising 341 probands and 128 adults were randomized to either routine clinical diagnosis or to routine clinical diagnosis plus genetic testing.

A five item perceived control over FH scale and a six item fatalism about FH scale were administered. Finding a mutation to confirm a clinical diagnosis of FH did not reduce perceptions of control or adherence to risk-reducing behaviours in this population but there was a trend in the mutation positive individuals to believe less strongly in the efficacy of diet (p=0.02 at 6 months) and more strongly in the efficacy of cholesterol lowering medication (p=0.06 at 6 months).

Using qualitative analysis of 23 semi structured interviews, Agard et al(Agård, Anders, Bolmsjö, Ingrid Agren, Hermerén, Göran et al , 2005) found that in general, the interviewees viewed their diagnosis of FH pragmatically. Many did not look upon their diagnosis as a 'disease.' If cholesterol had been normalised and there were no other obvious signs and symptoms of coronary heart disease, they deemed themselves 'healthy.' Apart from a special concern about what to eat, the impact on the interviewees appeared to be minimal. Discussing the genetic implications of FH with family members with whom they had close contact was natural, but informing distant family members was not.

Psychosocial function in 86 boys and 66 girls treated for FH was compared with healthy peers using the Child Behaviour Checklist, Teacher's Report Form and Youth Self Report as well as semi-structured interviews(Tonstad, S., Nøvik, T. S., and Vandvik, I. H., 1996). Scores were similar in the children with FH and the population sample. Scores for family, mood and expression of anger were actually lower than in the population cohort.

Quality of life, anxiety and concerns among statin treated children with FH and their parents was assessed by de Jongh et al(de Jongh, S., Kerckhoffs, M. C., Grootenhuis, M. A. et al , 2003)using self report questionnaires. The study group consisted of 69 children and 87 parents. FH children and their parents reported no problems with regard to quality of life and anxiety. There were some FH related concerns. One third of the children thought FH could be cured; one third of children did not know what they were allowed to eat. Among parents, 79.3% suffered distress because their child had FH and 37.9% stated that FH as a genetic disease was a burden to the family.

In an attempt to facilitate family communication about FH written information packages were provided to Dutch probands(van den Nieuwenhoff, Hélène. W. P., Mesters, Ilse., Nellissen-Joyce, J. T. M. et al , 2006) Eight probands and eight relatives were interviewed to evaluate this method of communication. The data suggest that probands approved the family approach for case finding, although reluctantly. The packaged aided family disclosure by reducing hesitation. However, only first degree relatives were informed and only one discussion took place. For relatives the written materials served as a cue for action and a means to gain access to a diagnostic cholesterol test.

One of the social implications of an FH diagnosis may be difficulty in obtaining life assurance. Neil et al(Neil, H. A. W., Hammond, T., Mant, D. et al , 2004) sent the same questionnaire to twenty four companies in 1990 and 2002. The mean excess rating increased from 89% (SD52) in 1990 to 158% (SD40) in 2002 (p<0.000) but fell to 56% (DS43) on treatment which was 33% lower (p=0.022) than the original rating in 1990. It appears that in 2002 the underwriters assessed risk more realistically and this should encourage at risk individuals to be tested.

Interventions

There is very little literature on interventions to provide information and support for adults and children/young people being considered for a diagnosis of FH. One study which evaluated disease knowledge and adherence to treatment in individuals with FH was conducted by Hollman et al(Hollman, G., Olsson, A. G., and Ek, A. C., 2006) in Sweden. Sixty eight adult patients completed questionnaires (92% response rate). There were no significant differences in demographic data between the male and female respondents. More than 90% of individuals knew about cholesterol and the reasons for drug treatment. However, only 34% of participants had knowledge of the risk of genetic transmission of FH and just 21% had knowledge of their family history; 25% of participants lacked knowledge of CHD as a risk. There was no significant correlation between knowledge and adherence to medication in this study.

No further research was identified relating to education about FH using videos, leaflets, websites or other modalities. No research was identified regarding the

role of support groups, family contacts or charities to provide assistance to individuals with FH.

6.2.2.3   Health economic evidence

No published, relevant evidence was identified.

6.3 Lifestyle interventions including Diet
(see also Key components of assessment and review)

Return to recommendations

6.3.1 Evidence statements on the effectiveness of dietary interventions

Key clinical question:

What is the effectiveness of dietary interventions to improve outcome in adults and children with heterozygous or homozygous FH?

Question 13 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
There are no long-term studies that indicate a cholesterol lowering diet significantly lowers lipid concentrations in individuals with FH. There is evidence from short-term studies that foods containing plant sterols and stanols can reduce LDL-C cholesterol concentrations of both heterozygous adults and children with FH [1+].	There was limited evidence in the FH population and all trials were very short term. However, motivation and compliance levels may be high in the FH population, and therefore levels of persistence may be high, trials of longer term (i.e. over 12 months) may not be needed to demonstrate a sustained effect. To corroborate the effectiveness of these interventions, high level, robust evidence from the general population was used to derive recommendations. This is justified as there is evidence that cholesterol concentrations in individuals with FH and treated with statins are lowered to a similar relative degree by dietary interventions as those not taking statins. However, the absolute change in LDL concentrations may not be clinically significant in individuals with FH, so medication should not be delayed in order to fully assess the effect of dietary intervention. The GDG considered the possible effects of a cholesterol lowering diet in children with FH. An absence of evidence was noted in terms of LDL-C lowering or longer term outcomes. The psychological impact on children was also not known and the possibility of an adverse impact in a healthy child at a young age was acknowledged. The GDG therefore agreed that in the absence of trial evidence, advice should be given that was in accordance with the general population, and a cholesterol lowering diet initiated during early childhood was not supported. Other general recommendations on lifestyle from other NICE guidance were referenced and specific factors stressed as appropriate for individuals with FH. Evidence on the longer term use of stanols and sterols was very limited. This is an important clinical question, particularly the use of these supplements as an adjunct to pharmacological treatments or as the only treatment option for those who are intolerant of all pharmacological treatments. Further research is therefore needed. Evidence was not sufficient to draw definitive conclusions regarding their effectiveness and the GDG noted that as these were available as food products patients might wish to purchase them in which case it was important to emphasise they would need to be taken consistently for them to have any effect. No evidence was identified that demonstrated that the use of sterols or stanols in children was associated with vitamin deficiencies.

6.3.2 Evidence summary on the effectiveness of dietary interventions

6.3.2.1 Methods of the clinical evidence review

The searches for Question 13 were restricted to RCT level data.

Identified: 935

Ordered: 40

Included: 5

Excluded: 35 (13 included in systematic reviews)

6.3.2.2 Clinical evidence

Lipid-modifying diets

A Cochrane review entitled 'Dietary treatment for familial hypercholesterolaemia' was published in 2001(Poustie, V. J. and Rutherford, P., 2001). There were seven eligible trials randomised controlled cross over trials. All were short term trials with each arm of the trial lasting between one and three months. The results of the analysis of these studies was as follows:

- Cholesterol lowering diet compared with no dietary intervention:
  One trial with 19 participants. NS difference.
- Cholesterol-lowering diet compared with all other dietary interventions:
  5 trials with 80 participants. NS differences for ischaemic heart disease, death, TC, LDL-C, HDL-C, TG, Apo A and Apo B,
- Cholesterol-lowering diet compared with low fat diet:
  One trial with 16 participants. No significant difference.
- Cholesterol lowering diet compared with increase in plant stanols:
  One trial of 14 children with no significant difference.
- Cholesterol lowering diet compared with increase in plant sterols:
  Two trials but one (Neil) failed to provide data from FH subgroup and the other found NS difference. A review of the Neil trial(Neil, H. A., Meijer, G. W., and Roe, L. S., 2001) however revealed that an analysis of statin treated FH

individuals was provided in the text of the paper. Plant sterol therapy significantly reduced LDL-C concentration from 4.40 to 3.90mmol/l after 8 weeks (p<0.0001, 95% CI 0.28 to 0.72) . Placebo had no effect.

– Cholesterol lowering diet compared to high protein diet:
  Two trials were combined and a non-significant difference was found for ischaemic heart disease, death, TC, LDL-C, HDL-C, TG.

The authors of the review concluded that there was not sufficient data to reach a conclusion about the effectiveness of cholesterol lowering diets or other dietary interventions for FH, and that an RCT was needed to investigate dietary treatment for FH.

Because of the limited evidence for the effect of dietary intervention in patients with FH, high quality meta-analyses of dietary interventions in the general population were reviewed (see question 17 in Appendix B). A Cochrane review "Reduced or modified dietary fat for preventing cardiovascular disease"(Hooper, L., Summerbell, C. D., Higgins, J. P. T. et al , 2000) reviewed RCTs, lasting at least 6 months, which evaluated the effect of dietary advice, supplementation or a provided diet all of which were intended to reduce or modify dietary fat or cholesterol in adults regardless of their cardiovascular status (mixed population). The meta-analysis showed that the average initial total cholesterol concentration was 5.8mmol/l and there was an average reduction of 0.64 mmol/l (a fall of 11.1%) at 6-24 month follow up.

Another Cochrane review on dietary advice "Dietary advice for reducing cardiovascular risk"(Brunner, E. J., Rees, K., Ward, K. et al , 2007) included RCTs lasting at least 3 months with mixed dietary advice given verbally and/or written to individuals and groups both in person and by telephone in a mixed adult population, including some trials which had screened patients for their risk and cardiovascular status. The review showed that if dietary advice was followed there was an average decrease in LDL cholesterol of 0.18 mmol/l over 3-24 months (difference in means -0.18, 95% CI -0.27 to -0.10).

A meta-analysis by Howell et al "Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis"(Howell, W. H., McNamara, D. J., Tosca, M.

A. et al , 1997) of single group or multiple-group repeated-measures comparisons of mixed dietary interventions in a mixed adult population supplements the two Cochrane reviews. The meta-analysis showed that, on average, if patients in the high-risk range for LDL cholesterol (>4.14mmol/l) reduced their intakes of saturated fatty acids and polyunsaturated fatty acids there was a 4.5-7.7% reduction in LDL cholesterol concentrations; this study has outcomes based on a typical American diet (described as 385mg of cholesterol per day and 37% of the total energy coming from fat, of which 7% are polyunsaturated fatty acids, 17% are monounsaturated fatty acids and 7% from saturated fatty acids) in 1994.

All 3 meta-analyses were of short term trials with mixed populations and diets; however they did suggest that cholesterol lowering diets can lead to a maximum lipid lowering of 5-10%.

Plant stanols and sterols

A systematic review with meta analysis was conducted by Moruisi et al(Moruisi, Kgomotso. G., Oosthuizen, Welma., and Opperman, Anna. M., 2006) to investigate the efficacy of phytosterols/stanols in lowering total cholesterol and LDL-C Concentration in FH patients. This review included only controlled, randomized, double blind studies with good compliance and sufficient statistical power. However there was heterogeneity with regard to concomitant drug use. Six trials from 1976 to 2004 qualified to be in the review. Four of these were included in the meta analysis. The results of the systematic review of 6 studies showed LDL-C reduction of 14-15% and TC reduction of 11% in children with the highest dosages of 2.3g/day plant sterol and 2.8g/day plant stanol enriched spreads. Intake of 1.6g/day plant sterol enriched spread by children resulted in reductions of 10.2% in LDL-C and 7.4% in TC concentrations. In the adult group, 2.5g/day plant sterol enriched spread caused a reduction of 10% in LDL-C and 8% in TC concentrations.

The results of the meta analysis of 124 participants on 2.3±0.5g phytosterols/stanols/day for 6.5±1.9 weeks were as follows: TC reduced by 0.65 mmol/l (95% CI -0.88 to -0.42mmol/l, p<0.00001) and LDL-C by 0.64mmol/l (95% CI -0.86 to -0.43mmol/l, p<0.00001). I^2 was 0%.

The efficacy of plant stanols and sterols was compared in a study by O'Neill et al(O'Neill, F. H., Patel, D. D., Knight, B. L. et al , 2001). One hundred and thirty nine individuals with FH (most of whom were taking statins) from two medical centres in west London and healthy controls were divided into three treatment groups and randomised to receive plant sterol (Flora Pro Activ) or plant stanol (Benecol spread or Benecol cereal bar). There was no statistical differences in the response to plant sterols or stanols between FH participants taking statins and those who were unaffected. Decreases in LDL-C ranged from 4.8% to 6.6%. Changes in total cholesterol ranged from 3% to 7.5%. Decreases in both concentrations were more marked in the plant sterol group at 1 month and in the plant stanol group at 2 months. In the plant sterol group the decrease at 2 months was only half as great as at 1 month and was no longer significantly different from baseline. Changes in HDL-C were slight but there was a tendency for values to decrease by about 3% in each of the groups.

With sterols there was an increase in serum plant sterols and a significant decrease in 7 alpha-hydroxy-4-cholesten-3-one, a marker of bile acid synthesis. Stanols lowered both LDL-C and plant sterol concentrations significantly and had no effect on bile acid synthesis.

According to the authors the findings suggested that absorption of dietary plant sterols down regulates bile acid synthesis which attenuates their cholesterol lowering efficacy. The authors concluded that plant stanols are preferable for the long term management of hypercholesterolemia.

Another RCT(Ketomäki, Anna, Gylling, Helena, and Miettinen, Tatu A., 2005) evaluated serum concentrations of lipids and plant sterols in 18 adults with FH taking statins. This double blinded randomised cross over study consisted of two consecutive 4 week intervention periods during which participants either consumed a sterol or stanol spread. The results were as follows (note, table adapted from published paper):

Table 1

Mean±sem (mmol/l)	Baseline	Stanols	Sterols
TC	6.30±0.24	5.65±0.22*	5.71±0.21*
LDL-C	4.50±0.21	3.81±0.18*	3.86±0.19*
HDL-C	1.26±0.05	1.32±0.04	1.37±0.04**

*Changes in TC and LDL-C were significant from baseline $p < 0.05$

**Changes in HDL-C were significant from baseline $p < 0.01$ for sterols.

Plant sterols were decreased in serum, lipoproteins and red cells by about 25% with stanols and increased by 37-80% with sterols, especially in those on high statin doses.

In this study stanols and sterols both reduced LDL-C but sterols increased serum lipoprotein and red cell plant sterol concentrations in statin treated FH individuals while all the respective values were decreased with stanols.

A study by Jakulj et al(Jakulj, Lily, Vissers, Maud N., Rodenburg, Jessica et al , 2006) examined the effect of plant stanols on lipids and endothelial function in pre-pubertal children with FH. Forty one children between the ages of 7-12 years were randomised to either a low fat plant stanol containing yogurt (2g of stanol) or a low fat yogurt without plant stanol. LDL-C, HDL-C, TC and TG and flow mediated dilation for endothelial function were measured and the results were as follows:

Table 2

Mean±sd	Stanol	Placebo	Mean change (95% CI)	% change
TC (mmol/l)	6.47±1.35	7.00±1.49	-0.53* (-0.79 to +0.28)	7.5%
LDL-C (mmol/l)	4.77±1.32	5.24±1.45	-0.48* (-0.69 to +0.27)	9.2%
HDL-C (mmol/l)	1.35±0.24	1.38±0.27	-0.03 (-0.13 to +0.06)	Not reported
TG (mmol/l)	0.61±0.51	0.57±0.51	-0.05 (-0.18 to +0.08)	Not reported
FMD %	10.5±5.1	10.5±5.1	+0.05 (-2.40 to +2.51)	Not reported

Adapted from published paper(Jakulj, Lily, Vissers, Maud N., Rodenburg, Jessica et al , 2006)

Changes in TC and LDL-C were significant compared to placebo p<0.001

In this study plant stanols reduced LDL-C Concentration in children with FH but without improving endothelial function.

6.3.2.3 Health economic evidence

No published, relevant evidence was identified.

6.4 Key components for assessment and review

6.4.1 Evidence statements on key components for assessment and review

Key clinical question:

What are the key components of assessment and review for individuals (adults and children) with homozygous or heterozygous FH including the information and support required for individuals (adults and children) with FH regarding

- diet,
- exercise and/or regular physical activity
- smoking cessation?

Question 16 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
Components of ongoing assessment and review – see question 12 Diet – see question 13 No studies on exercise and/or physical activity in FH were identified. No studies on smoking cessation were identified. No studies on information content and support for individuals and carers were identified.	No evidence to recommendations documented.

7 General treatment – Coronary heart disease assessment and monitoring (including referral)

7.1 Introduction

7.1.1 Ongoing clinical assessment of CHD

Individuals with FH are at a greater risk of developing CHD than individuals without FH. Assessment of new onset symptoms of CHD and monitoring of any CHD progression is therefore fundamental to any management strategy. Such assessment and monitoring requires clinical judgment and should be undertaken as appropriate for the individual.

7.1.2 Evidence statements on ongoing clinical assessment

Key clinical question:

What is the effectiveness of investigations to assess the degree of atherosclerosis to improve outcomes in individuals with heterozygous FH?

- Exercise ECG
- Carotid IMT
- Coronary calcium
- Cardiac catheterisation

Question 12 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
No studies were identified that reported clinical outcomes as a result of routine investigative procedures including the exercise ECG, carotid IMT, coronary calcium, cardiac catheterization.	There was no robust evidence for this question (lack of comparators, lack of good diagnostic studies, lack of clinical outcomes). Therefore, recommendations were made based on the experience of the GDG on: • differences in non invasive assessment of coronary heart disease or symptomatic vs asymptomatic adults • differences in monitoring for adults with FH vs people without FH • how should results from performance tests be used with other data (such as history, clinical assessment and other factors etc) • referral criteria. Any monitoring should aim to identify those people at medium risk (see also the discussion of risk in Chapter 4 on diagnosis), as people at high risk should be identifiable from diagnosis (i.e. homozygous FH or other clinical data, such as signs and symptoms of CHD). However, concern was expressed that asymptomatic coronary disease may not be detected without routine investigation. It was considered that in individual instances, an ECG should be considered as a baseline investigation for adults with FH. A baseline ECG was considered not to be indicated in healthy children. The GDG considered that a fasting sample was reasonable given that the patient may only have an annual review and that elevated LDL-C concentrations are the basis of this condition. The evidence did not allow the making of specific recommendations (such as frequency of investigations) and it was the view that clinical judgment should be used based on the individual's signs, symptoms, diagnosis, history etc. Due to clinical heterogeneity no specific age-related cut-off for referral was possible or felt appropriate.The term 'early adulthood' was used within the possible referral criteria for futher evaluation. This term was deliberately not specified numerically, as it was felt that clinical heterogeneity precluded arbitrary age cut offs and judgements would need to be made in individual instances. The GDG decided not to include diabetes as a specific risk factor because the risk factors described in the recommendation were examples and diabetes was relatively uncommon in the FH population (expert GDG advice). Children with homozygous FH were considered to be at high risk and therefore monitoring would identify different issues to that for children with heterozygous FH. Children with homozygous FH should be referred for investigations as

| | incident CHD should be strongly assumed in those cases.

Any recommendations on monitoring have assumed, as in the recommendations, that all people with homozygous FH are evaluated fully at diagnosis. |
| --- | --- |

7.1.3 Evidence summary on ongoing clinical assessment

7.1.3.1 Methods of the clinical evidence review

The searches for this question were not restricted by study type or age of individuals.

Identified: 633

Ordered: 47

Included: 3 studies extracted; 16 descriptive studies in table for background information

Excluded: 28

7.1.3.2 Clinical evidence

This question aimed to identify evidence about ongoing monitoring of coronary heart disease (CHD) risk in individuals with heterozygous FH, and the effectiveness of various modalities used to assess risk.

The literature search did not identify any papers which provided evidence for routine investigations to be used when monitoring CHD risk in individuals with heterozygous FH. A number of papers were identified which described the usefulness of particular tests to assess CHD risk. Three of these papers(Aggoun, Y., Bonnet, D., Sidi, D. et al , 2000; Hoffmann, U., Dirisamer, A., Heher, S. et al , 2002; Jensen, J. M., Gerdes, L. U., Jensen, H. K. et al , 2000) compared various methods of assessment. It is important to note that measures of endothelial function are surrogate markers of vascular function and not used clinically for managing individual patients. No recommendations were made regarding the use of these methods to assess risk over time except in a research setting.

Aggoun et al(Aggoun, Y., Bonnet, D., Sidi, D. et al , 2000) compared measures of endothelial dysfunction with coronary artery calcium in individuals with FH and

healthy controls. Baseline vessel diameter was significantly smaller in individuals with FH compared to controls (3.2±0.3mm[1], range 2.7 to 3.6 vs 3.5±0.4mm, range 3.0 to 4.3; p<0.02, respectively). Flow mediated dilation was significantly reduced in individuals with FH compared with controls (10.7±5.3%, range 4.5% to 17.2% vs 17.3±4.6%, range 7.7% to 25.0%; p=0.002). None of the individuals with FH or controls showed calcification of the aortic root or the proximal coronary arteries, resulting in an Agatston score of 0 in every patient. For the whole group (n=26) total cholesterol and LDL-C were inversely correlated with flow mediated dilation (FMD), p=0.0003 and p=0.003 respectively. This study showed that peripheral FMD, a precursor of atherosclerosis, was altered in young heterozygous individuals with FH. This alteration occurred before coronary arterial or aortic root calcium was detected by CT scan and was independently related to hypercholesterolemia.

Another study(Hoffmann, U., Dirisamer, A., Heher, S. et al , 2002) compared arterial properties in individuals with FH and healthy controls with IMT results. Non invasive ultrasonic measurements were performed of the CCA luminal systolic and diastolic diameters and IMT. Brachial artery diameters were measured after reactive hyperemia and nitroglycerine treatment. In individuals with FH there was significant reduction of systo-diastolic variations in diameter of the CCA (by 20%, p<0.001) without a significant difference in IMT. The wall stiffness was greater in FH subjects than in controls (by 27%, p=0.003). The flow mediated dilation of the brachial artery was smaller in the FH subjects (4.2±2.9%) than in controls (9.0±3.1%, p<0.001). No correlation was evident between the carotid incremental modulus and either IMT or LDL-C.

Four CHD diagnostic models were compared by Jensen et al(Jensen, J. M., Gerdes, L. U., Jensen, H. K. et al , 2000). These included

- Model A - traditional risk factors including age, sex, cholesterol, hypertension, smoking and BMI;
- Model B-cholesterol year score and

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[1] Assumed to be mean±sd, not reported in paper

– Models C,D -aortic & coronary calcium measured by spiral computed tomography (CT).

The following variables from models A and B were significantly associated with CHD in individuals with FH:

- age, $p < 0.001$
- treated cholesterol, $p < 0.05$
- BMI borderline, $p < 0.06$
- smoking, $p < 0.02$.
- Models C and D were highly significant:
- coronary calcium, $p < 0.001$
- aortic calcium, $p < 0.001$.

The age adjusted ROC curves for coronary calcium score were significantly greater than those for traditional risk factors ($p < 0.002$) cholesterol year score ($p < 0.0001$) and age adjusted aortic calcium score ($p < 0.0004$).

Table below lists papers which describe the various modalities used to assess coronary heart risk in 14 research studies. No direct comparisons are made in these papers.

Table 1 Assessment of CHD risk

Author	Population	Intervention	Results
Beppu et al(Beppu, S., Minura, Y., Sakakibara, H. et al , 1983)	25 heterozygotes 6 homozygotes 30 controls	Two dimensional echocardiography of aortic root	In the short axis view plaques were seen in all homozygotes and 5 heterozygotes.
Celermajer et al(Celermajer, D. S., Sorensen, K. E., Gooch, V. M. et al , 1992)	10 children with FH 20 smokers 20 adults with CAD 50 controls	Ultrasound detection of endothelial dysfunction	In smokers, FH children and adults with CAD flow mediated dilatation was much reduced or absent ($p < 0.001$) in comparison with each relevant control group. Endothelial dysfunction is present before anatomical evidence of plaque formation in the arteries and may be an important early event in atherogenesis.

Author	Population	Intervention	Results
Cuomo et al(Cuomo, S., Guarini, P., Gaeta, G. et al , 2002)	114 subjects (5-30 years) with parental history of premature MI and 114 age and sex matched controls	Ultrasound evaluation of common carotid artery intima media thickness	Individuals with a parental history of premature MI had significantly increased carotid IMT – ages 5-18 (p=0.008) and ages 19-30 p=0.007.
Genda et al(Genda, A., Nakayama, A., Shimizu, M. et al , 1987)	51 consecutive individuals with heterozygous FH and 279 consecutive individuals without FH	Coronary angiography	The coronary stenosis index, and the proportion of subjects with > 75% stenosis vessel subset were almost three times higher in the FH group.
Herrera et al(Herrera, C. J., Frazin, L. J., Dau, P. C. et al , 1994)	8 Individuals with FH - 3 on 'standard therapy' (control) and 5 on apheresis	Transesophageal echocardiography	Baseline and follow up at 12 months with TEE were performed. TEE detected plaques and changes after intervention. Changes over time in the control group were not significant. Changes in the apheresis group were showed significant improvement in total arterial area (p<0.05) and plaque to wall ratio (p<0.05).
Hoffmann et al(Hoffmann, U., Bodlaj, G., Derfler, K. et al , 2001)	10 heterozygous Individuals with FH receiving LDL apheresis; 10 men with confirmed CAD; 10 men with no history of CAD	Coronary imaging by EBCT scanner and calculation of a calcium score for each calcium deposit noted on the scan.	The individuals with FH displayed median calcification features that were almost three times higher than the medians of CAD individuals (p<0.0001). Quantification of coronary calcium provides independent and incremental information compared to clinical risk assessment or angiography and may be an important, noninvasive screening tool for early diagnosis of CAD in individuals with FH.

Author	Population	Intervention	Results
Hopkins et al(Hopkins, P. N., Stephenson, S., Wu, L. L. et al , 2001)	68 FH-CAD individuals and 194 FH controls with no history of CAD.	Comprehensive examination of risk factors for CAD among individuals with FH	Significant risk factors were as follows: 1. Age ($p<0.0001$) 2. Gender with men having 5.64 times the risk of women ($p<0.0001$) 3. Cigarette smoking (OR 2.71, $p=0.026$) 4. Smaller LDL as determined by the LDL-C/LDL apolipoprotein B ratio (OR 2.60, $p=0.014$) and 5. High WBC, $p=0.014$ Lipoprotein(a) and xanthoma were associated with risk only in very early coronary cases. After correction for age, carotid intima thickness was not associated with CAD risk. There were no other significant risk factors. The authors conclude that there is little justification for extensive investigation of risk factors in individuals with FH. Treatment of LDL-C should be the focus.
Lavrencic et al(Lavrencic, A., Kosmina, B., Keber, I. et al , 1996)	28 individuals with FH (one homozygous and 27 heterozygous); 28 sex and age matched healthy controls	Use of carotid IMT to assess the extent of early atherosclerotic changes of carotid arteries	The mean carotid IMT was significantly greater in individuals with FH than in controls ($p<0.001$). In all subjects, the mean IMT was significantly correlated with TC, LDL, TG and systolic blood pressure. Thus B mode ultrasonography could provide a useful tool to identify those who are more likely to develop premature atherosclerotic disease.

Author	Population	Intervention	Results
Mabuchi et al(Mabuchi, H., Koizumi, J., Shimizu, M. et al , 1989)	5 homozygous and 105 male and 56 female heterozygous individuals	Use of coronary angiographic study to predict CV risk.	A coronary stenosis index score (CSI) was calculated based on angiographic results and age. The results were as follows: Mean age mortality: • homozygotes 25.9 years • male heterozygotes 56 years • female heterozygotes 69.2 correlated with coronary stenosis score of 20, calculated at angiogram.
Michaelides et al(Michaelides, A. P., Fourlas, C. A., Pitsavos, C. et al , 2004)	194 heterozygous individuals	Exercise testing in asymptomatic individuals	22 % (42) of the 194 asymptomatic individuals had a positive ET. A multivariate analysis adjusted for sex, BMI, smoking, diabetes, family history of CAD, presence of xanthomas and lipid concentrations showed that only high fibrinogen concentrations were significantly and independently associated with a positive ET. The adverse effects of FH on the CV system may be partly mediated by coagulability factors.
Riberio et al(Ribeiro, P., Shapiro, L. M., Gonzalez, A. et al , 1983)	3 homozygotes and 32 heterozygotes. 32 age matched healthy normolipidaemic controls were included for comparison.	Use of cross-sectional echocardiography for identifying aortic root lesions and coronary artery ostial stenosis	All three homozygotes showed CV disease on echo and cardiac catheterization confirmed this. Echo of aortic root in 32 heterozygotes was similar to control but 10 individuals showed abnormal bright echoes within the aortic cusps and four had supravalvular changes similar to but less severe than the homozygotes. Serial cross sectional echo may be useful for monitoring the progress of CV disease and the effect of treatment.

Author	Population	Intervention	Results
Tato et al(Tato, F., Keller, C., Schewe, S. et al , 1991)	59 heterozygous and 6 homozygous individuals with FH	Use of cardiac echocardiography to assess for CAD	Pathological echo changes were found in 59% of heterozygotes and in all homozygotes. In heterozygotes, aortic root sclerosis usually appeared after the age of 30; in homozygotes severe changes were present before the age of 10. A pathological echo correlated strongly with the presence of overt CAD. Echo proved to be a useful non-invasive method for evaluation of individual coronary risk.
Tonstad et al(Tonstad, S., Joakimsen, O., Stensland-Bugge, E. et al , 1996)	90 FH children and 30 controls	Assessment of CV risk factors in relation to carotid IMT	Mean carotid IMT was greater in FH than in controls (p=0.03). Mean intima-media thickness in the far wall of the carotid bulb was positively associated with concentrations of apo B, homocysteine and fibrinogen after control for pubertal state. These associations were unchanged after multi-variate analysis. The authors suggest that B-mode ultrasonography may prove to be a useful tool in risk stratification of children with FH.
Wendelhag et al(Wendelhag, I., Wiklund, O., and Wikstrand, J., 1995)	53 individuals with FH and 53 controls with cholesterol below 6.5 mmol/l and matched on sex, age, height and weight	Three year follow up of the progression of intima media thickening in carotid and femoral arteries after therapy with pravastatin, cholestyramine or a combination	Using B-mode ultrasound it was possible to perform a non invasive study of the morphology of large, superficially located arteries, the carotid and femoral arteries , and to determine that there was a net difference in of -0.06 mm in mean carotid intima-media thickness (CI -0.22-0.01) and of -0.09 mm in maximum carotid intima-media thickness (p<0.05, CI -0.16-0.01).

Author	Population	Intervention	Results
Wittekoek et al(Wittekoek, M. E., de Groot, E., Prins, M. H. et al , 1999)	248 Individuals with FH; 106 had CHD with the remaining subjects had no clinical evidence of CHD	IMT measurements of 20 prespecified carotid and femoral arterial wall segments	All IMTs in both groups were severely thickened. In individuals with CHD the distributions of IMT within tertiles for both arterial segments were opposite to those found in those without CHD (p<0.05 for both segments). The largest absolute differences were found in the femoral artery. The OR for clinically manifest atherosclerotic disease for the IMT measurement of the common femoral artery was approximately 3 and highly significant (p=0.007) while for the common carotid artery this was only 1.6 (p value non-significant).

Due to the paucity of evidence to support recommendations for ongoing monitoring in this group of high risk patients, the GDG referred to the National Service Framework (NSF) for Coronary Heart Disease (2000)[2], and specifically the recommendations on effective policies for both primary and secondary prevention of CHD. Individuals with heterozygous FH clearly meet the NSF criteria for 'high risk' which includes those with multiple risk factors for heart disease who are typically three to five times more likely to die, suffer a heart attack or other major coronary event than people without such conditions or risk factors.

7.1.3.3   Health economic evidence

No published, relevant evidence was identified.

[Return to recommendations](#)

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[2]

www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4094275

8 Specific treatment

8.1 Introduction

8.1.1 Specialist interventions – LDL Apheresis and transplantation

Individuals with homozygous FH and, in exceptional circumstances, those with heterozygous FH may need additional, specialist treatments if drug treatment is not able to achieve the necessary LDL-C lowering.

LDL Apheresis is a mechanical method of removing LDL-C from the blood, similar to that used for kidney dialysis. It is a process that needs to be undertaken approximately every two weeks and requires specialist administration and monitoring.

Liver transplantation (with or without the heart) is a surgical treatment option; again, this is generally only an option for people with homozygous FH, and rarely for those with heterozygous FH. Functioning liver cells that are able to process the LDL-C in the blood are transplanted and this is effectively a cure for FH. However, as with any transplant, there are considerable risks attached.

8.1.2 Contraception and obstetric issues (specifically related to drug treatment)

Girls and women being treated for FH need relevant and up-to-date information on the risks of drug treatment on any pregnancy. This will become increasingly important as girls and women are being treated earlier. Women and their partners should be reassured that with appropriate planning and counselling, most pregnancies are successful (see recommendations for details).

8.2 Specialist interventions

8.2.1 Evidence statements on LDL Apheresis

Key clinical question:

What is the clinical and cost effectiveness of the following interventions to reduce LDL cholesterol and improve outcome in individuals with either heterozygous FH or homozygous FH:

- LDL Apheresis alone versus no intervention/ usual care?
- LDL Apheresis and drug therapy versus drug therapy alone?
- plasmapheresis & drug therapy versus drug therapy alone?
- ileal bypass versus no intervention (heterozygote)?
- LDL Apheresis versus plasmapheresis?

Question 10 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
There are no randomized controlled trials for treatment of FH homozygous individuals. However observational studies of FH homozygous individuals show treatment with LDL Apheresis lowered LDL concentrations by 72% compared to use of multiple lipid-modifying maximal drug therapy. Controlled before and after studies showed that LDL LDL Apheresis treatment of individuals with FH who were primarily heterozygous and receiving lipid lowering drugs demonstrated a total percent decrease in LDL-C ranging from 34-81% [2+] In two small studies of individuals with heterozygous FH receiving LDL Apheresis and lipid modifying drug treatment, coronary artery disease regressed in 4 individuals (16%) and in 3 individuals (13%).(Donner, M. G., Richter, W. O., and Schwandt, P., 1997; Nishimura, S., Sekiguchi, M., Kano, T. et al , 1999) [2-] A study(Richter, W. O., Donner, M. G., and Schwandt, P., 1999) which followed subjects receiving LDL Apheresis for up to six years demonstrated a 1.8% incidence of adverse clinical events which included hypotension and a moderate decrease in haemoglobin and ferritin concentrations. [3] Fluctuations in plasma iron and ferritin concentrations were also noted in a case report of two homozygous individuals.(Berger, G. M., Firth, J. C., Jacobs, P. et al , 1990) [3] There are no trials comparing effectiveness of plasmapheresis & drug therapy versus drug therapy alone. Since the advent of statins there have been no studies comparing ileal bypass versus no intervention. There are no trials comparing effectiveness of LDL Apheresis versus plasmapheresis. Although the cost-effectiveness of LDL Apheresis remains as yet unproven and no published evidence was identified, a simple analysis indicates that it is likely to be deemed cost-effective for a treatment with orphan status.	Specific issues considered by the GDG included • initiation and discontinuation of treatment • timing of the lipid measurements and changes over time • frequency of LDL Apheresis • the measurement of progression of coronary heart disease, specifically in children (see Chapter 7 on assessment and monitoring) LDL Apheresis for patients with homozygous FH Although RCTs were identified, lower level studies were used to corroborate and provide longer term safety/effectiveness data as potentially, individuals may require this treatment on a long term basis. The evidence statements therefore reflect the lack of robust RCT evidence and recommendations have been made on the observational studies. Clinical experience also supports the effectiveness of LDL Apheresis in the reduction of xanthomatosis. A major criticism of the evidence was that most older studies used less well-tolerated drugs or sub-optimal doses, whereas current practice is that all patients undergoing LDL Apheresis are on maximal treatment (high dose statins plus nicotinic acid plus another lipid lowering drug plus omega 3 supplements). Generalisability was a concern as there are many factors that differ across countries, for example different criteria for treatment, different marketing/industry, and different financial structures for healthcare. As in most areas, there was minimal evidence for children, but clinical experience is that earlier treatment is better and that progression of coronary heart disease may be slowed, noting as above however that evidence for monitoring in children is also very limited. There is no direct clinical evidence on the optimal frequency of treatment, and the patient view was that factors such as time (recovery, travelling etc) and the impact on the family were important. Frequency therefore would be affected by clinical

	factors and patient acceptability.
	<u>LDL Apheresis for patients with heterozygous FH</u>
	Current practice is that some individuals with heterozygous FH have access to LDL Apheresis., . LDL Apheresis should only be carried out in individuals already on maximum tolerated drug therapy who have symptomatically deteriorating CHD, for whom the additional reduction of LDL by the mechanical means of LDL Apheresis can reduce CHD.
	The identified evidence did not directly support definitive entry criteria for this treatment. There were concerns over the low level of evidence, extrapolating from trials in individuals with homozygous FH, and the arbitrary nature of any cut-offs. LDL Apheresis is only therefore recommended in exceptional cases for this population.
	A formal cost-effectiveness analysis was not undertaken to evaluate the cost-effectiveness of LDL-apheresis for people with homozygous FH because of the lack of evidence to support modelling and the consequent unreliability of cost-effectiveness outcomes. Because of the small numbers of patients involved, LDL Apheresis was recommended as a treatment option for the estimated 50 or so patients who would benefit from treatment.

8.2.2 Evidence summary on the effectiveness of LDL Apheresis

8.2.2.1 Methods of the clinical evidence review

The searches for this review were not restricted by study type or age of individuals. Studies in languages other than English (specifically Japanese and German) were also scanned on advice from the GDG.

Identified: 639 English and 157 foreign language

Ordered: 94

Included: 21

Excluded: 73 (studies with less than 20 individuals excluded except where there was no other evidence available)

8.2.2.2 Clinical evidence

LDL Apheresis alone versus no care/usual care

In a before and after study of twenty five homozygous individuals with FH and heterozygous individuals with organ involvement, e.g. xanthomatosis, general atherosclerosis, CHD, were carefully screened and pretreated with diet and drugs for 6 months and then placed on LDL Apheresis(Borberg, H., 1999). No lipid lowering drugs were used during the trial. The effects on lipid concentrations were as follows:

Table 1

	Before treatment	After treatment
Mean TC (mmol/l)	8.35 (7.13-10.9)[1]	3.54 (2.72-5)
Mean LDL-C (mmol/l)	6.36 (4.77-9.51)	2.10 (1.13-3.31)
Mean HDL-C (mmol/l)	1.13 (0.67-1.92)	0.87 (0.51-1.41)

Table adapted from published paper(Borberg, H., 1999).

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[1] Assumed to be mean and range, not reported in paper

Quantitative measurement of 111 circumscribed coronary stenoses showed a mean stenosis degree of 45±26% at entry and 43±22% at final cineangiofilm demonstrating no significant change. Eight localized stenoses showed a regression of more than 10% and 11 had a progression of more than 10%. An expert panel consensus evaluation for overall coronary atherosclerosis determined that no individual had evidence of regression, there were no changes in 16 individuals, debatable progression in 3 individuals and undecided in one individual.

LDL Apheresis and drug treatment versus drug treatment alone

A systematic review of literature from 1998-2004 which evaluated LDL Apheresis and drug treatment versus drug treatment alone was conducted by Moga and Harstall(Moga, C. and Harstall, C., 2004). A thorough search of the literature was done and strict inclusion and exclusion criteria were applied. However, the quality assessment of the literature was not described. Also, only two LDL Apheresis systems were included and no studies with mixed heterozygous/homozygous populations were reviewed. A meta-analysis was not done as there was no RCT evidence. The reviewers concluded that there was weak evidence that the DSC Liposorber system in combination with lipid lowering drug therapy lowered LDL cholesterol concentrations in older individuals (>50 years of age) with severe FH when they were treated at least once every two weeks for a minimum of one year. The mean percent decrease in LDL-C ranged from 34%-81%. However, the use of a combined therapy meant that the contribution of LDL apheresis to the treatment effect was unclear.

As there is very little evidence in this area and no meta-analysis could be done in the Moga review(Moga, C. and Harstall, C., 2004) due to the variety of study designs, an assessment of the individual included studies which met the GDG inclusion criteria was undertaken.

The LAARS study(Kroon, A. A., Aengevaeren, W. R. M., vanderWerf, T. et al , 1996) randomised 42 Dutch men, aged between 30-67 years to treatment for two years with either biweekly LDL Apheresis plus simvastatin 40 mg/day or simvastatin 40mg/day alone. Sixteen individuals in each group were heterozygous

for FH (76% of study population). All individuals had severe coronary atherosclerosis.

A constant reduction of 63% of LDL-C was found in the LDL Apheresis group to an interval mean concentration of 2.95±1.13mmol/l. TC, LDL-C and Apo B showed the same course and were significantly lower in comparison to the medication group.

Table 2

Mean±sd	LDL Apheresis (n=21)	Medication alone (n=21)	p-value
TC (mmol/l)			
Basal	9.72±1.84	9.85±2.17	
Interval mean	4.63±1.18	5.95±1.60	
% change	-52.60±6.60	-39.50±7.70	0.005
LDL-C (mmol/l)			
Basal	7.78±1.86	7.85±2.34	
Interval mean	2.95±1.13	4.13±1.58	
% change	-62.90±8.3	-47.40±8.10	0.01

Table adapted from published paper(Kroon, A. A., Aengevaeren, W. R. M., vanderWerf, T. et al , 1996)

There was no significant difference in the number of clinical events. The mean change per patient in percent stenosis was not different for both groups. However in the LDL Apheresis group the total number of lesions was decreased as the result of the disappearance (<20%) of 40 minor stenoses versus 20 in the medication group (p=0.005) whereas 23 versus 32 new stenoses were found respectively (p=0.19). By categorical approach, 9 individuals in the LDL Apheresis group and 11 individuals in the medication group were classified as progressors. Two and 5 individuals were regressors respectively and the remaining men

showed stable disease. Exercise tolerance was significantly improved in the LDL Apheresis group by bicycle exercise tests (p<0.001 for time).

A controlled trial conducted in Japan(Nishimura, S., Sekiguchi, M., Kano, T. et al , 1999) assessed the difference in frequency of definite progression and regression coronary artery stenosis. Twenty five heterozygous individuals with FH were treated with LDL Apheresis and drugs and 11 individuals were treated with drugs alone. Three lipid lowering drugs, pravastatin, probucol and bile acid sequestrants were used in all individuals if tolerated. All underwent follow up angiography 2.3 years later. Mean minimum lumen diameter increased significantly in the LDL Apheresis group and decreased in the control group. Progression of coronary stenosis occurred in 64% of controls and 8% of LDL Apheresis group. Regression was found in 16% of the LDL Apheresis group and in no controls. There was a significant difference in frequency of individuals with progression of coronary artery stenosis, those unchanged and those with regression between the two groups (p<0.004). Three individuals in the LDL Apheresis group had clinical coronary events and four individuals in the control group had an event. Lipid concentrations were also reported. The mean (±sd) differences in lipid concentrations between the groups averaged over the follow up period were a lowering of both TC by 17% (5.07±0.92mmol/l versus 6.10±1.87mmol/l; p<0.05) and of LDL-C by 18% (3.59±0.78 mmol/l versus 4.36±1.49 mmol/l; p<0.05).

A small controlled trial(Koga, N., Watanabe, K., Kurashige, Y. et al , 1999) in Japan studied the long term effects of LDL Apheresis on carotid atherosclerosis in two groups of individuals. In the LDL Apheresis and drug group there were 2 homozygotes and 9 heterozygotes; the control group on drugs alone consisted of 10 heterozygotes. All LDL Apheresis individuals were taking a statin;10 were on probucol and one on cholestyramine. Eight of the control individuals were taking statins and 7 on probucol. The two groups were compared for changes in lipid concentrations and the development or progression of carotid atherosclerosis over 4 years time.

Table 3

	Mean baseline (±sd)	Time average value (±sd)	Change

Homozygous			
TC (mmol/l)	17.0±3.95	7.42±0.40	56.4%
LDL (mmol/l)	16.0±3.60	6.43±0.07	60.5%
Heterozygous			
TC (mmol/l)	12.9±2.47	5.63±1.26	56.5%
LDL (mmol/l)	11.5±2.46	4.32±1.20	56.8%
Control			
TC (mmol/l)	7.18±1.14	5.62±0.79	21.7%
LDL (mmol/l)	4.81±1.26	3.71±0.58	22.9%

Table adapted from published paper(Koga, N., Watanabe, K., Kurashige, Y. et al , 1999)

In the LDL Apheresis group, progression of plaques occurred in nine of the 11 individuals; one patient remained unchanged and one patient showed regression. In the control group all individuals showed progression. The difference between the two groups was not statistically significant. The annual progression rate of mean maximum IMT was a mean of 0.0002mm/year in the LDL Apheresis group. This was significantly lower than the mean of 0.0251 mm/year in the control group (p<0.005). In the LDL Apheresis group the mean maximum IMT in heterozygous individuals with FH was -0.0023mm/year. Although progression occurred in the homozygous individuals it was markedly slower than in the control group (p value not reported).

The long term effects of LDL Apheresis were studied in 29 individuals who participated in the follow-up phase of a controlled trial(Gordon, B. R., Kelsey, S. F., Dau, P. C. et al , 1998). In the original trial all homozygous individuals received apheresis but individuals with heterozygous FH were randomly assigned to diet, drug therapy (not described) and LDL Apheresis (n=45) or to diet and drug therapy alone (n=9). Results for individuals with data at the 4 year follow-up time point are presented below. Controls received LDL Apheresis only after the initial controlled phase of the study ended at 18 weeks.

Table 4

	Homozygotes (n=7)	Treated heterozygotes (n=19)	Control (n=3)
LDL-C baseline (mmol/l)	12.31	6.23	6.18
4 years	9.03	5.95	6.21
p-value	p=0.059	p=0.22	
HDL-C baseline (mmol/l)	0.46	0.49	1.54
4 years	0.55	0.48	0.58
p-value	p=0.33	p=0.82	

Table adapted from published paper(O'Neill, F. H., Patel, D. D., Knight, B. L. et al , 2001)

A total of 24 unique cardiovascular events occurred during the 5 years before initiation of LDL Apheresis whereas only 7 events occurred during the period of treatment with LDL Apheresis, a drop of 44% from 6.3 events per 1000 patient-months to 3.5 per 1000 patient-months.

There were no clinically important changes in laboratory values over time. Hypotension was the most common adverse event in 0.9% of procedures. One episode of blood loss with anaemia occurred.

A comparison of LDL Apheresis with bile acid sequestrants and statins in decreasing lipid concentrations was carried out in a multicentre study in Wales and London(Thompson, G. R., Maher, V. M., Matthews, S. et al , 1995). The study was a randomised angiographic trial of the effects on coronary atherosclerosis of fortnightly LDL Apheresis plus 40mg simvastatin daily or colestipol 20g plus simvastatin daily. Changes in lipid concentrations and in coronary stenosis were reported.

Table 5

	LDL Apheresis (n=20)		Drugs alone (n=19)		
	Mean baseline (sd)	Interval mean (sd)	Mean baseline (sd)	Interval mean (sd)	p-value
TC (mmol/l)	9.0 (2.0)	5.2 (0.7)	8.1 (1.7)	5.3 (1.0)	ns
HDL-C (mmol/l)	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	1.15 (0.3)	ns
LDL-C (mmol/l)	6.8 (2.2)	3.2 (0.8)	6.1 (1.8)	3.4 (1.1)	p=0.03

Table adapted from published paper(Thompson, G. R., Maher, V. M., Matthews, S. et al , 1995)

The interval means between LDL Apheresis procedures did not differ significantly from the mean values in the drug group for TC and HDL. The LDL value was significantly lower in the LDL Apheresis group (p=0.03).

Table 6

Diameter stenosis	LDL Apheresis (n=20)	Drugs alone (n=19)	p-value
Mean % per patient (sd)	-1.80 (4.00)	-2.25 (5.50)	ns
Mean % lesion change (sd)	-1.91 (9.38)	-2.06 (9.21)	ns

Table adapted from published paper(Thompson, G. R., Maher, V. M., Matthews, S. et al , 1995)

The mean changes in percent diameter stenosis after 2 years treatment did not differ significantly between the LDL Apheresis and drug groups on either a per patient basis or per lesion basis.

Several studies followed small cohorts of individuals who did not adequately respond to drug treatment and were subsequently treated with LDL Apheresis.

Thirty four heterozygous FH individuals in Germany with angiographically proven coronary heart disease who had not responded to maximum tolerated doses of simvastatin were treated with regular LDL Apheresis by differing systems for

(mean and SEM) 3.5±2.5 years(Donner, M. G., Richter, W. O., and Schwandt, P., 1997). Lipid concentrations changed as follows:

Table 7

	Immunoadsorption	**Dextran sulphate adsorption**	**HELP LDL Apheresis**
Mean TC (mmol/l) ±sd			
Baseline	7.69±3.07	7.79±1.82	9.43±1.84
Mean of final 5 treatments	5.02±0.87	4.95±1.12	5.33±0.53
Mean LDL-C (mmol/l) ±sd			
Baseline	6.63±1.41	5.92±2.02	6.51±1.43
Mean of final 5 treatments	3.17±0.58	3.25±0.68	3.56±0.51
Mean HDL-C (mmol/l) ±sd			
Baseline	1.05±0.31	1.05±0.12	0.99±0.15
Mean of final 5 treatments	1.28±0.25	1.18±0.18	1.23±0.21

Table adapted from published paper(Donner, M. G., Richter, W. O., and Schwandt, P., 1997)

In 23 individuals followed for more than 2 years, there was a regression of coronary atherosclerosis in 3 individuals and in all other cases there was a stop in progression of coronary lesions (that is, no change). Three individuals died of coronary complications after 6 and 9 months of therapy; one after 6 years. One patient suffered a non fatal MI.

Thirty four individuals with FH, of whom 31 were refractory to conventional drug therapy (three individuals could not tolerate lipid lowering drugs), were maintained on pharmacotherapy if tolerated and also treated with LDL Apheresis(Bambauer, R., Schiel, R., Latza, R. et al , 1999). A comparison of lipid concentrations before and after treatment and of four different LDL Apheresis systems was done.

The results of laboratory studies showed the following:

Table 8

	Baseline	**Under treatment**	**Mean % change**
Mean TC (mmol/l) ±sd[2]	10.5±1.92	5.42±1.52	-51.9%
Mean LDL-C (mmol/l) ±sd	7.42±1.95	3.70±1.72	-49.8%
Mean HDL-C (mmol/l) ±sd	1.05±0.19	1.10±0.33	+4.4%
Mean TG (mmol/l) ±sd	5.63 (sd not given)	3.26 (sd not given)	-57.8%

Table adapted from published paper(Bambauer, R., Schiel, R., Latza, R. et al , 1999)

Fibrinogen decreased by 73.3%.

In a study of the long term (6 years) efficacy of LDL –C apheresis on coronary heart disease(Mabuchi, H., Koizumi, J., Shimizu, M. et al , 1998) 87 individuals received intensive drug therapy and 43 individuals received medical therapy and LDL Apheresis. LDL Apheresis was compared with aggressive drug therapy which included 10-20mg/day pravastatin or 5-10mg/day simvastatin and then 500-1000mg/day of probucol and/or 4-12g/day of cholestyramine or 400mg/day of bezafibrate.

Using time averaged concentrations of LDL, because the rebound curves of TC and LDL after apheresis are not linear, it was shown that LDL –C significantly reduced LDL cholesterol from 7.42±1.73 to 3.13±0.80mmol/l (58%) compared with the group taking drug therapy (6.03±.32 to 4.32±1.53mmol/l (28%), p<0.0001). TC decreased by 53% from baseline concentrations (9.28±1.71mmol/l to 4.40±0.78mmol/l) with LDL Apheresis and by 25% (from 7.94±1.24 to 5.92±1.58mmol/l) with drug therapy (p<0.0001).

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[2] Assumed to be sd, not reported in paper

The proportion of individuals without any coronary events was significantly higher in the LDL Apheresis group (90%) than in the drug therapy group (64%) by 72% (p=0.0088).

Thirty individuals with FH resistant to diet and maximum lipid lowering drugs (not identified) were treated for up to 6 years with LDL Apheresis(Bambauer, R., Schiel, R., Latza, R. et al , 1996). Prior to treatment 23 of 30 individuals suffered from coronary heart disease. Twenty nine were heterozygous and 1 was homozygous.

Lipid concentrations changed as follows after treatment:

Table 9

	Baseline	Under treatment	% change	p-value
Mean TC (mmol/l) ±sd	10.4±1.9	5.5±1.5	-47.2%	p<0.0001
Mean LDL-C (mmol/l) ±sd	7.42±1.95	3.8±1.67	-48.7%	p<0.0001
Mean HDL-C (mmol/l) ±sd	1.05±0.02	1.16±0.29	+10.5%	p<0.0001
Mean TG (mmol/l) ±sd	5.63	3.4	-39.8%	p<0.0001

Table adapted from published paper(Bambauer, R., Schiel, R., Latza, R. et al , 1996)

Fibrinogen dropped by 25.6% (p<0.001). These results were confirmed in a second study published in 1997(Bambauer, R., Schiel, R., Latza, R. et al , 1997).

The K-LAS II study was carried out in Japan(Yamamoto, K., Nakashima, Y., Koga, N. et al , 1995) among 37 individuals who continued for a mean of 5 years on LDL-C LDL Apheresis. All individuals received concomitant treatment with lipid lowering drugs including daily doses of 10-20mg pravastatin, 1-2g probucol, 18-27g cholestyramine and/or 600-750mg nicotinic acid. In this study group there were no significant differences between mean pre-treatment concentrations of TC, HDL-C, LDL-C, TG from the end of the phase 1 study and the end of phase 2.

Table 10

	Phase 1	Phase 2	% change	p-value
TC (mmol/l)				
Mean pre-treatment ±sd	7.18±1.64	6.79±1.56	-5.4%	p=0.071
HDL-C (mmol/l)				
Mean pre-treatment ±sd	0.87±0.28	0.79±0.22	-8.8%	p=0.112
TG (mmol/l)				
Mean pre-treatment ±sd	1.43±0.87	1.40±0.92	-1.6%	p=0.255
LDL-C (mmol/l)				
Mean pre-treatment ±sd	5.4±1.5	5.13±1.38	-5.3%	p=0.156

Table adapted from published paper(Yamamoto, K., Nakashima, Y., Koga, N. et al , 1995)

Overall 7 (18%, 7/38) cardiovascular events were observed during a mean of 5 years of LDL Apheresis. One additional patient experienced new unstable angina.

Two studies describe the results of the HELP-LDL Apheresis multicentre study(Schuffwerner, P., Gohlke, H., Bartmann, U. et al , 1994; Seidel, D., Armstrong, V. W., and Schuff-Werner, P., 1991). Seidel et al(Seidel, D., Armstrong, V. W., and Schuff-Werner, P., 1991) reported on the evaluation of safety and cholesterol lowering effects of LDL Apheresis during the first 12 months. Ten German centres participated and 51 individuals aged between 28 and 65 years were recruited. Patients continued on a variety of lipid lowering drugs including bile acid sequestrants, fibrates, nicotinic acid and sitosterol. All individuals had severe CHD and type IIa hypercholesterolaemia. A distinction between individuals with heterozygous and homozygous FH was not made. Forty six individuals completed 12 months of regular treatment. At 12 months the following results were reported:

Table 11

	Baseline	12 months	p-value
Mean TC (mmol/l) ±sd			
Pre-apheresis	9.18±2.3	7.10±1.05	p<0.001
Post-apheresis	4.62±1.46	3.51±0.67	
Mean LDLC (mmol/l) ±sd			
Pre-apheresis	7.26±2.2	5.21±1.05	p<0.001
Post-apheresis	3.08±1.36	1.95±0.62	
Mean HDL-C (mmol/l) ±sd			
Pre-apheresis	1.04±0.28	1.24±0.28	p<0.001
Post-apheresis	0.94±0.36	1.06±0.31	
Mean TG (mmol/l) ±sd			
Pre-apheresis	2.07±1.46	1.66±0.01	p<0.05
Post-apheresis	1.69±0.64	1.38±0.39	

Fibrinogen concentrations fell 19-24% over the course of therapy and plasminogen concentrations were unchanged.

Schuff-Werner et al(Schuffwerner, P., Gohlke, H., Bartmann, U. et al , 1994) then published the final evaluation of the effect of regular treatment on LDL cholesterol and the course of coronary heart disease. The mean±sd pre/post LDL Apheresis LDL-C Concentration decreased from 7.33±2.26/3.10±1.41 mmol/l at first LDL Apheresis treatment to 5.21±1.03/1.97±0.62 mmol/l after 1 year to 5.26±1.1 /1.97±0.51 mmol/l after 2 years. The angiographies from 33 individuals obtained before and after 2 years of regular treatment were evaluated blindly and the mean degree of stenosis of all segments decreased from 32.5% (sd=16) to 30.6% (sd=16.8) over the 2 years. A regression >8% was observed in 50/187 (26.7%) segments whereas 29/187 (15.5%) segments showed progression. In 108/187 (57.8%) segments the lesions were stable (<8% deviation) over 2 years.

Thirty seven individuals were treated by 13 institutions registered as member of the Japan LARS group; the group consisted of 7 homozygous FH and 25 heterozygous FH 2 familial combined hyperlipidemia and 3 individuals with high cholesterol not confirmed as FH(Koga, N., Iwata, Y., and Yamamoto, A., 1992). Most of the individuals had been treated with cholesterol lowering drugs such as probucol, pravastatin and cholestyramine in combination with LDL Apheresis. Angiography was performed at intervals of 49 months for homozygotes and 32 months for heterozygotes to assess for changes in CHD. The evaluation of regression of no change and of progression in a lesion for each patient was defined as follows:

- individuals with at least one regressed segment and without any progressed segment were represented as regression;
- individuals with only unchanged segments were represented as no change; and
- individuals with at least one progressed segment and without any regressed segment were represented as progression.

Such representation led to the following results:

- regression occurred in 14 of 37 individuals (37.8%);
- no change, in 18 individuals (48.6%) and
- progression occurred in 5 individuals (13.5%).

Plasmapheresis & drug therapy versus drug therapy alone
No evidence was identified for this question.

Ileal bypass versus no intervention (heterozygote)
Two papers on this topic were identified: one case study(Issa, J. S., Garrido, A. J., Giannini, S. D. et al , 2000) and one observational study of 11 individuals(Ohri, S. K., Keane, P. F., Swift, I. et al , 1989) conducted without the use of statin therapy prior to surgery. The latter study was evaluated to provide background information only. Eleven individuals with heterozygous FH were treated by partial ileal bypass. Postoperatively, mean TC concentrations fell by 26% then rose to 20% below preoperative concentrations at 20-24 months (absolute values not provided). Five

individuals had refractory hypercholesterolemia and were then treated with lovastatin. One was treated with lovastatin and LDL Apheresis. All individuals experienced diarrhoea which improved with time but two individuals required reversal of their bypass for intractable gas bloat syndrome.

LDL Apheresis vs plasmapheresis

This case study of two South African females aged 17 years with homozygous familial hypercholesterolemia (Berger, G. M., Firth, J. C., Jacobs, P. et al , 1990) was included due to the paucity of evidence comparing LDL Apheresis to plasmapheresis. It is provided for background information only. Pre- and post-treatment lipid concentrations on three differing schedules of LDL Apheresis (twice per week, once per week and every two weeks) and after plasmapheresis (biweekly) were presented.

'Quasi steady state' values, i.e. the values just before every procedure representing the least favourable lipoprotein values in the course of therapy, were reported.

Absolute numbers were not provided. Graphs showed a profound reduction in the quasi steady state concentrations of plasma cholesterol, LDL and Apo B in schedules 1 and 2 of LDL Apheresis. In the first female the LDL/HDL ratio fell by 74% on schedule 1 (bi weekly treatment), 68% on schedule 2 (weekly) and 37% on schedule 3 (every two weeks) and 46% on plasmapheresis. A similar although less dramatic trend was noted in the second female but in neither was there a significant difference in these ratios comparing schedule 3 of LDL Apheresis with plasmapheresis (p-value not given).

Other laboratory parameters remained stable except for iron and haemoglobin concentrations which were reduced with both procedures.

LDL Apheresis alone versus LDL Apheresis and statin therapy

This small study of 9 Japanese homozygous individuals with FH(Yamamoto, A., Harada-Shiba, M., Kawaguchi, A. et al , 2000) undergoing LDL Apheresis was included because it is unique in studying the addition of statins in previously untreated individuals receiving LDL Apheresis. It is presented for background

information only. Five of the individuals were LDL receptor negative and four were receptor defective. Atorvastatin was given in escalating doses of 10, 20 and 40mg/day. The effect of atorvastatin-LDL Apheresis therapy in the two groups compared with regular treatment was as follows:

Table 12

	Regular treatment	**Combined treatment**	**p-value**
Mean TC (mmol/l) ±sd			
Negative	11.87±0.27	12.1±2.54	ns
Defective	7.49+2.06	6.54±2.31	p<0.05
Mean LDL-C (mmol/l) ±sd			
Negative	10.08±2.16	10.28±2.15	ns
Defective	6.38±1.91	5.44±2.22	ns
Mean HDL-C (mmol/l) ±sd			
Negative	1.00±0.11	1.08±0.13	ns
Defective	0.77±0.02	0.87±0.09	ns
Mean TG (mmol/l) ±sd			
Negative	1.76±1.03	3.49±2.42	ns
Defective	0.74±0.32	0.52±0.19	p<0.05

Table adapted from published paper(Yamamoto, A., Harada-Shiba, M., Kawaguchi, A. et al , 2000)

Five of the nine individuals responded well to atorvastatin (20.6% decrease in LDL-C); four of these individuals were receptor defective. Of the five receptor negative individuals only one showed a good response (14.9% decrease in LDL-C).

LDL Apheresis, statins and ezetimibe versus LDL Apheresis and statins alone

This case series of six Japanese homozygotes was included because it provided the only information on the treatment of homozygous individuals with FH on LDL

Apheresis with ezetimibe(Yamamoto, A., Harada-Shiba, M., Endo, M. et al , 2006).
It is useful for background information only. Receptor negative homozygous
individuals with FH on LDL Apheresis were included in this study. These
individuals were also being treated with a range of other cholesterol lowering
drugs including atorvastatin at varying doses and probucol 500mg or 1000mg/day.
Changes in lipid concentrations following treatment with ezetimibe were as follows:

Table 13

	LDL-C	TC	TG	HDL-C
Mean pre-treatment (mmol/l) ±sd	10.04±1.11	12.17±1.73	1.21±0.59	0.79±0.22
Mean post-treatment (mmol/l) ±sd	9.09±1.22	11.09±2.03	1.28±0.69	0.72±0.19
% change	-9.57%	-9.07%	+18.78%	-7.58%
95% CI (%)	-14.11 to -5.03	-17.43 to -0.72	-42.51 to +80.06	-18.96 to +3.82

Table adapted from published paper(Yamamoto, A., Harada-Shiba, M., Endo, M.
et al , 2006)

With the exception of one patient, significant decreases in LDL-C and TC at 2
weeks after each LDL Apheresis procedure were seen during the period from 4-12
weeks of treatment (p-values not given).

Safety

A retrospective analysis of laboratory and clinical safety data was reported by
Sachais et al(Sachais, B. S., Katz, J., Ross, J. et al , 2005). Data from 34
Americans receiving LDL Apheresis treated from 1996-2003 were collected. The
average length of treatment was 2.5 years. Adverse reactions were rare. The
most common reactions were light-headedness (1.5%), nausea/vomiting (1.2%),
hypotension (0.73%), and chest pain (0.58%). Examination of BUN, creatinine,
AST, ALT, total protein, albumin and PT, PTT revealed that all values were within
normal range and none were significantly altered by long term treatment. All
individuals had markedly decreased LDL-C and triglycerides after each treatment
without a significant change in HDL-C. All individuals had decreased time

averaged LDL-C (values not provided). After treatment with LDL-C LDL Apheresis for an average of 2.5 years, individuals had a 3.2 fold decrease in cardiovascular events and over a 20 fold decrease in cardiovascular interventions. Subjectively, individuals reported decreased episodes of angina symptoms and improved quality of life.

8.2.2.3 Health economic evidence

No relevant health economics evidence was found in the searched published literature for any relevant comparison. Also, the clinical evidence review indicates that there is a lack of robust clinical evidence of effectiveness, including epidemiological and prognostic data, which would be needed to populate an economic model. There is likely to be a high degree of uncertainty around the cost effectiveness estimates produced by such a model.

From the limited clinical evidence, based on small numbers in observational studies, LDL Apheresis appears to be an effective intervention for lowering LDL-C in patients with FH, specifically in those with homozygous FH. Homozygous FH is rare, with a prevalence of about 1 case per million population.

Tonstad and Thompson(Tonstad, S. and Thompson, G. R., 2004) suggest a likely procedure cost of £523 in the UK although these figures are outdated. Current actual costs were obtained form 3 NHS centres that offer LDL apheresis (ranging from £1200-£1500) were obtained from Royal Brompton and Harefield NHS Trust, University Hospital of Wales and the Medical Research Council Clinical Sciences Centre. No single NHS tariff price was in place for this procedure and these costs were charged differently in the various centres. Assuming bi-monthly treatments the estimated annual cost is likely to (given rangex24). Assuming that LDL Apheresis is an effective treatment, then this cost is likely to be an over-estimate of the net incremental cost of treatment (excludes net savings from reduced need for other healthcare resource use likely to be consumed by FH patients not treated with LDL Apheresis).

8.2.3 Evidence statements on the appropriate indications for transplantation

Key clinical question:

What are the appropriate indications for

- i-combined heart and liver transplantation or
- ii- liver transplantation alone in homozygous FH?

Question 11 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
The evidence, based upon case studies only, suggest the benefit of intervention at an early age, before complications have occurred. [3] If successful liver transplantation will cure homozygous FH, although there may be problems in the long-term with immunosuppression. [3] There is no trial evidence to suggest benefit of combined heart and liver transplantation compared to liver transplantation alone.	Liver transplant can cure homozygous FH but because of the potential for long-term problems, the preferred sequence of treatment should be drug treatment, LDL Apheresis, then transplant but patient/carer preference should obviously be taken into account. Recommendations were made based on this preferred sequence of treatment.

8.2.4 Evidence summary on the appropriate indications for transplantations

8.2.4.1 Methods of the clinical evidence review

The searches for this review were not restricted by study type or age of individuals or language.

Identified: 108 English, 19 foreign language

Ordered: 18

Included: 15

Excluded: 3

8.2.4.2 Clinical evidence

Transplantation

The only literature available for the review of organ transplant in individuals with FH consisted of case studies, evidence grade 3. These studies were not quality assessed but were summarised in the table presented below.

Table 14 Liver and heart transplant case studies in individuals with FH

Author	Description	Indication	Outcome
Alkofer et al(Alkofer, B. J., Chiche, L., Khayat, A. et al , 2005)	39 year old male with heterozygous FH and terminal CHF	Double heterozygous mutation with only 20% LDL receptor function and history of CABG x 4 with new onset chest pain and severe coronary lesions and 3 closed by-pass grafts.	The heart lung transplant in this patient was difficult due to severe and prolonged hypercholesterolemia, immediate post op renal failure, an acute heart rejection episode and diabetes secondary to immunosuppressive therapy. The initial cholesterol concentrations were at first normal but 2 years after transplant statins were required to help lower the cholesterol to normal concentrations (5.13 mmol/l)

Author	Description	Indication	Outcome
Barbir et al(Barbir, M., Khaghani, A., Kehely, A. et al , 1992)	33 year old female with homozygous FH	Severe diffuse coronary artery disease and left ventricular outflow tract obstruction secondary to homozygous FH	2 months post liver-heart transplant TC decreased by 60.5%, LDL-C by 68.5%. 3 months post-op all lipoproteins were within normal range; xanthomata had marked regression and at 1 year there were no angiographic signs of accelerated coronary heart disease.
Bilheimer et al(Bilheimer, D. W., Goldstein, J. L., Grundy, S. M. et al , 1984)	6 year old homozygous female	Severe hypercholesterolemia secondary to homozygous FH with history of MI, CABAG x 2 and mitral valve replacement and continuing angina.	After liver-heart transplant, LDL-C declined by 81% and the fractional catabolic rate of I-LDL, a measure of functional LDL receptors in vivo, increased by 2.5 fold. Thus, the transplanted liver, with its normal complement of LDL receptors, was able to remove LDL-C from plasma at a nearly normal rate.
Castilla Cabezas et al(Castilla Cabezas, J. A., Lopez-Cillero, P., Jimenez, J. et al , 2000)	2 siblings, aged 14 years (male) and 6 years (female)	Diffuse coronary artery disease and severely elevated lipid concentrations.	Spanish study of two homozygous siblings with successful liver transplants. At two years post op TC was normal in both and no cholesterol lowering medication was required.
Cienfuegos et al(Cienfuegos, J. A., Pardo, F., Turrion, V. S. et al , 1988)	12 year old homozygous males	Homozygous FH with severely elevated lipid concentrations and history of aortic valve surgery at age 5; presented with 50% stenosis of left coronary artery and multiple diffuse lesions in the remaining coronary vessels.	Heart and liver transplant done in two stages. One year after the surgeries patient has a normal liver function and TC concentrations. Xanthomas have diminished and patient is on no special diet or hypolipidaemic drugs.

Author	Description	Indication	Outcome
Clinical Nutrition Classes(Heart-liver transplantation in a child with homozygous familial hypercholesterolemia, 1985)	6 year old female with homozygous FH	Homozygous FH with severely elevated lipid concentrations and acute MI and congestive heart failure.	Post-heart and liver transplant, TC fell to 6.93 mmol/l from 25.64 mmol/l and tendon xanthomata regressed dramatically. Fractional catabolic rate increased from 0.12 pools per day (non receptor level) to 0.31 pools per day (normal mean is 0.43 +0.06)
Hoeg et al(Hoeg, J. M., Starzl, T. E., and Brewer, H. B. J., 1987)	11 year old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations and history of bruits in carotid and femoral arteries, systolic ejection murmur at the cardiac base, a right parietal CVA.	After liver transplant, TC decreased by 76% and LDL-C by 83% and nearly total regression was seen in many xanthomata 5-6 months after transplantation.
Lopez-Santamaria et al(Lopez-Santamaria, M., Migliazza, L., Gamez, M. et al , 2000)	Brother and sister aged 18 and 16 years with previous ileal bypass and portacaval shunt	Homozygous FH with severely elevated lipid concentrations. Exercise tolerance test and echocardiograms were normal prior to surgery.	Since liver transplantation both individuals are alive, jaundice free with normal liver function at 13 months follow up for brother and 7 months for the sister. TC has decreased from 12.3 mmol/l to 3.31 mmol/l and LDL from 11.6 mmol/l to 2.51 mmol/l in the brother. The sister's values have decreased from TC of 18.46 mmol/l to 5.77 mmol/l and LDL of 17.8 mmol/l to 4.77 mmol/l.
Moyle and Tate(Moyle, M. and Tate, B., 2004)	3.5 year old homozygous FH female of Vietnamese descent	Homozygous FH with severely elevated lipid concentrations which continued to increase despite treatment with statins.	Serum cholesterol fell to normal and xanthomata regressed following liver transplantation and she remained well 17 months post-op.
Offstad et al(Offstad, J., Schrumpf, E., Geiran, O. et al , 2001)	FH homozygous woman born in 1950 (46 at time of surgery and followed for 4 years)	Homozygous FH with severely elevated lipid concentrations who was treated with plasma exchange but developed end stage calcific left ventricular outflow tract obstruction no amenable to standard valve reconstructive surgery	Heart-liver transplant resulted in immediate lowering of serum lipids; TC decreased from 7.3 mmol/l to 3.5 mmol/l; LDL-C decreased from 5.3 mmol/l to 1.7 mmol/l.

Author	Description	Indication	Outcome
Revell et al(Revell, S. P., Noble-Jamieson, G., Johnston, P. et al , 1995)	3 boys ages 10-15 years	Homozygous FH with severely elevated lipid concentrations in three boys who all also had angiographic evidence of coronary atheroma and two had exertional angina. One child had a CABG x 4 prior to liver transplant.	All received liver transplants and remained well with normal liver function from 12-45 months after transplantation. Lipid concentrations remained normal without need for any additional diet or lipid lowering drugs. Xanthomata disappeared within one year and one child had reversal of atheromatous coronary artery lesions. Average TC in these boys pre-op was 23.4 mmol/l which decreased to 5.6 mmol/l. Average LDL-C was 22.1 mmol/l which decreased to 4.8 mmol/l.
Shrotri et al(Shrotri, M., Fernando, B. S., Sudhindran, S. et al , 2003)	17 year old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations and an occluded right coronary artery with 70% stenosis of the left main stem marginal artery and left anterior descending artery. He underwent CABG and aortic valve replacement and then was listed for liver transplant.	11 years after liver transplant was alive and well. There is also a report of three other individuals, one of whom died 2 years after transplant of an MI and two others who are also alive and well after 9 and 4 years respectively. TC concentrations were described as 'normal' in all survivors.
Sokal et al(Sokal, E. M., Ulla, L., Harvengt, C. et al , 1993)	47 month old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations. His ECG was normal. Cardiac ultrasound was normal and ejection rate was 66%. No coronary lesions were seen on angiography.	After liver transplant liver enzymes and lipid concentrations were all within normal limits at 12 month follow up (TC 4.46 mmol/l and LDL-C 2.82 mmol/l). Author recommends that transplant be considered early in life before the onset of coronary complications.
Starzl et al(Starzl, T. E., Bilheimer, D. W., Bahnson, H. T. et al , 1984)	6 year 9month female with homozygous FH	Homozygous FH with severely elevated lipid concentrations and history of double CABG.	In first 10 weeks after transplantation TC fell to 6.92 mmol/l from over 25.64 mmol/l. Visible xanthomata regressed dramatically.

Author	Description	Indication	Outcome
Valdivielso et al(Valdivielso, P., Escolar, J. L., Cuervas-Mons, V. et al , 1988)	12 year old male with homozygous FH	Homozygous FH with severely elevated lipid concentrations. Cardiac history not provided.	Heart lung transplant was followed by 71% decrease in TC and 79% decrease in LDL-C. Six months post –op the patient leads a normal life.

8.2.4.3   Health economic evidence

No published, relevant evidence was identified.

8.3 Contraceptive and obstetric issues

8.3.1 Evidence statements for information/counselling on contraception for women and girls with FH

Key clinical question:

What information/counselling should be provided to girls/women of child bearing potential with FH with respect to contraception?

Question 14 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
There were no studies specific to girls/women with FH which identified appropriate information or counselling with regard to contraception. Observational studies of coronary risk in healthy women taking third generation OCs indicate that there is no significantly increased risk of MI in these women.[1-] One small study (Simonson, S. G., Martin, P. D., Warwick, M. J. et al , 2004) of concomitant use of rosuvastatin and a third generation OC showed no decrease in contraceptive efficacy and significant lowering of LDL-C. [2+]	See also question 15. Recommendations were made on the specific contraceptive choice issues for women and girls with FH. A range of factors were considered, including the lack of direct evidence, the mechanism of action of the different hormones, and the risks of an unplanned pregnancy. The recommendations aim to allow patient-prescriber discussion and informed choice. The GDG noted that observational studies did not demonstrate a significant increase in the the risk of MI in women taking tacking a 3rd generation OCP. They noted that the central estimate in each of these 3 studies was consistently greater than unity, and a plausible prior hypothesis was that oral contraceptives may increase the risk of MI in women at increased cardiovascular risk. A range of mechanism for any possible increased cardiovascular risk were considered including lipid mediated effects and the possibility of thrombo-embolic causes of death. If treated optimally, women with FH will have normalised lipid concentrations are likely to have a reduced cardiovascular risk, so combined oral contraception is not routinely contraindicated. The GDG were aware of forthcoming evidence from the Simon Broome register of the effect of statins on CHD mortality in women of reproductive age (personal communication, H A W Neil) that did not show any significant increase although the confidence interval was very wide. Due to potential interactions between statins (e.g rosuvastatin) and hormones within contraceptive pills, and interactions between lipid modifying medications and oral contraceptives in general, prescribers should refer to the SPC for individual drugs to guide their prescribing decisions.Combined oral contraception should therefore be available as an option (based on judgement and choice) after a full, informed discussion between the prescriber and the patient.

8.3.2 Evidence summary on contraception for women and girls with FH

8.3.2.1 Methods of the clinical evidence review

The searches for Question 14 included women with FH, women on statins and women at high coronary heart disease risk. The searches were not restricted by type of contraception.

Identified: 330

Ordered: 17

Included: 5

Excluded: 12

8.3.2.2 Clinical evidence and other information

There were no studies specific to girls/women with FH which identified appropriate information or counselling with regard to contraception. Five studies (Baillargeon, J. P., McClish, D. K., Essah, P. A. et al , 2005; Chasan-Taber, L. and Stampfer, M. J., 1998; Khader, Y. S., Rice, J., John, L. et al , 2003; Simonson, S. G., Martin, P. D., Warwick, M. J. et al , 2004; Spitzer, W. O., Faith, J. M., MacRae, K. D. et al , 2003) were identified which provide background information on coronary heart disease risk and the use of hormonal contraception in healthy women. One study(Simonson, S. G., Martin, P. D., Warwick, M. J. et al , 2004) was identified which describes the effect of combining a statin with an oral contraceptive (OC) in otherwise healthy women.

Four reviews(Baillargeon, J. P., McClish, D. K., Essah, P. A. et al , 2005; Chasan-Taber, L. and Stampfer, M. J., 1998; Khader, Y. S., Rice, J., John, L. et al , 2003; Spitzer, W. O., Faith, J. M., MacRae, K. D. et al , 2003) were identified which evaluated the association between OC use in healthy women and cardiovascular disease. High risk women were not evaluated. Three(Baillargeon, J. P., McClish, D. K., Essah, P. A. et al , 2005; Khader, Y. S., Rice, J., John, L. et al , 2003;

Spitzer, W. O., Faith, J. M., MacRae, K. D. et al , 2003) of these studies included a meta-analysis of observational data. The inherent bias of observational studies makes it difficult to combine studies and obtain a reliable summary statistic. However, the studies have been reported for background information.

Baillargeon et al(Baillargeon, J. P., McClish, D. K., Essah, P. A. et al , 2005) selected 14 case control studies and calculated summary risk estimates associated with current use of low dose OCs for MI events. The summary risk estimate for MI associated with current use of low dose OCs was odds ratio (OR) 1.84 (1.83 to 2.44). The results were also stratified by generation of OC. Second generation OCs were associated with a significant increased risk of MI, OR 1.85 (1.03 to 3.32);MI for third generation OC use was not significant, OR 1.28 (0.78 to 2.10).

Another meta-analysis of 19 case control studies and 4 cohort studies was carried out by Khader et al(Khader, Y. S., Rice, J., John, L. et al , 2003). Current OC users had an overall adjusted OR for MI of 2.48 (CI 1.91 to 3.22) compared to never users (p<0.0005). The risk of MI for past OC users was not significantly different from that for never users, overall OR 1.15 (0.98 to 1.35). Stratifying by generation of OCs showed that first and second generation OC users had a significantly higher risk of MI compared with nonusers and the overall ORs were 2.21 (1.30 to 3.76; p=0.004) and 2.17 (1.76 to 2.69; p<0.0005) respectively. Third generation OC users were not significantly different from nonusers in relation to the risk of MI, OR 1.27 (0.96 to 1.67; p=0.094). There was a dose response relationship to estrogen concentrations. Overall OR was 3.62 (2.22 to 5.90; p<0.0005), 1.97 (1.43 to 2.71; p<0.0005) and 0.92 (0.21 to 4.08; p=0.918) for oestrogen dose preparation greater than or equal to 50micrograms, 30-49micrograms and 20micrograms, respectively.

The findings of seven studies (6464 participants in total) on the risk of MI among users of second and third generation OCs were aggregated by Spitzer, Faith and Mac Rae(Spitzer, W. O., Faith, J. M., MacRae, K. D. et al , 2003). Compared with non users the aggregated OR for third generation OC was 1.13 (0.66 to 1.92) odds for MI and for second generation OC the odds for MI was 2.18 (1.62 to 2.94).

The association between combined oral contraceptives and cardiovascular disease was studied by Chasan-Taber & Stampfer(Chasan-Taber, L. and Stampfer, M. J., 1998). All English language human epidemiology studies of OCs that used cardiovascular disease as an end point were reviewed. Descriptive and analytic data was collected. Most of the excess risk for MI among OC users was found to be attributable to an interaction with cigarette smoking. Taken together, case control and cohort studies suggested that current users of OCs who were younger than 40 years of age and did not smoke had little or no increase in risk for MI (9 studies with no significant RRs). Most studies in the literature were too small to address the risk for MI from OCs according to coronary risk factors other than smoking and in many studies smokers and non smokers were not stratified.

Third-generation progestins from the gonane class were recently incorporated into oral contraceptive pill formulations to reduce the androgenic and metabolic side effects that occur with older agents. These new progestins include desogestrel, gestodene and norgestimate.

Oral contraceptive pills containing third-generation progestins reportedly have several benefits. Androgenicity associated with older progestins has been linked to adverse lipoprotein and carbohydrate changes, weight gain, acne, hirsutism, mood changes and anxiety. The third-generation progestins have minimal impact on blood glucose concentrations, plasma insulin concentrations and the lipid profile. Thus, they may be useful for women with lipid disorders or diabetes.

One final study by Simonson et al(Simonson, S. G., Martin, P. D., Warwick, M. J. et al , 2004) evaluated the effect of rosuvastatin on oestrogen & progestin concentrations in 18 healthy women taking a third generation OC (orthotricyclen). Co-administration of orthotricyclen and rosuvastatin did not result in lower exposures to the exogenous oestrogen or progestin components of the OC. LH and FSH were similar between cycles. There were no changes in the urinary excretion of cortisol. Rosuvastatin significantly decreased LDL-C (-55% [95% CI -59 to -51]), TC (95% CI -27% [-31 to -24), and TG (95% CI -12% [-22 to -3]) and there was a significant increase in HDL-C (11% [95% CI 5-17]).

8.3.2.3   *Health economic evidence*

No published, relevant evidence was identified.

8.3.3 Evidence statements on information for pregnant women with FH

[Return to recommendations](#)

Key clinical question:

What information or care should be provided to:

- pregnant women or women considering pregnancy with FH with respect to:
- lipid modifying treatment use or
- FH related complications around pregnancy/labour/delivery?
- lactating women with FH with respect to:
- lipid modifying treatment use?

Question 15 of the key clinical questions – please see Appendix B for details.

Evidence statements	Evidence into recommendations
There were no studies specific to pregnant or lactating women with FH which identified appropriate information or counselling with regard to lipid modifying treatment or complications in pregnancy, labour or delivery. Observational studies are inconclusive and there may be a small increased risk of a spectrum of congenital abnormalities associated with statin use in early pregnancy.	Recommendations were agreed to encourage and support women to breast feed. The evidence on the safety of statins in pregnancy was reviewed, but due the limited data (often case series or case studies) we were unable to quantify the exact level of risk. The evidence is limited with contradictory results, and is inconclusive. There may be a small increase in the rate of fetal malformations if mothers have taken statins in the first trimester. However the great majority of pregnancies have a normal outcome. There is no clear type or pattern of fetal malformation observed, and most of the fetal malformations would be detectable by ultrasound in utero. The balance and risks to both the woman and the fetus should be carefully considered. Recommendations were made to enable a detailed discussion between the woman and the prescriber leading to an informed choice. It should be stressed that there are no definitive estimates of the levels of risk or the patterns of expected fetal anomalies, so pragmatic recommendations on appropriate referral and monitoring of the pregnancy were agreed. Recommendations were made on shared care and CV assessment for women with established cardiovascular disease. A specific recommendation was also made for women with homozygous FH and other women with FH with defined pathologies. Serum cholesterol concentrations should not be monitored during pregnancy as there are physiological changes in LDL-C during pregnancy, and these cannot be treated pharmacologically. Routine monitoring of LDL-C concentration are therefore not recommended, but may be needed in specific instances.

8.3.3.1   Evidence summary on information for pregnant women with FH

8.3.3.2   Methods of the clinical evidence review

The searches for Question 15 specifically included women with FH. Studies identified for Question 15 were

Identified: 252

Ordered: 8

Included: 4

Excluded: 4

8.3.3.3   Clinical evidence

Information and counselling

There were no studies specific to pregnant or lactating women with FH which identified appropriate information or counselling with regard to lipid modifying treatment or complications in pregnancy, labour or delivery.

Pregnancy risk factors in women with FH

The Confidential Enquiry into Maternal Deaths 2000-2002(Lewis, G., 2004) listed cardiac deaths as the most common cause (excluding suicide) of indirect death in pregnancy (up to and including 42 days postpartum) in the UK. In fact, it was more common than any of the direct causes of death in pregnancy. The incidence has been rising in the past two decades reflecting an overall increased mortality from acquired heart disease. Further description of specific cardiac conditions which led to death was not provided. However according to the Confidential Enquiry, better care could have altered the course of 40% of the deaths from cardiac causes.

Amundesen et al (Amundsen, A. L., Khoury, J., Iversen, P. O. et al , 2006) documented changes in plasma lipids and lipoproteins during pregnancy in women with FH. In 22 pregnant women with FH, blood samples were collected at gestational weeks 17-20 (baseline), 24, 30 and 36 weeks and compared with a

reference group of 149 pregnant women who did not have FH. Total cholesterol and LDL-C (mean±sd) increased significantly between baseline and gestational week 36 by 29% to 11.6±1.9mmol/l in the first instance and by 30% to 8.6±2.0mmol/l in the case of LDL-C. Changes noted in the reference group were 25.4% increase in TC and 34.2% increase in LDL-C. The relative increases did not differ (p>0.05) but absolute values in FH women were markedly higher than in the reference group. Of note however is the relatively large number of pre-pregnancy smokers in the FH group (31% compared to 0% in the reference group). Pregnancy outcomes in the FH group did not differ significantly from those in the reference group.

In a further study of the same sample, Amundesen et al(Amundsen, A. L., Khoury, J., Sandset, P. M. et al , 2007) again compared risk markers for cardiovascular disease in pregnant women with and without FH. Absolute values of lipids were higher in pregnant women with FH than in healthy women. As pregnancy is also associated with activation of coagulation and possibly also of vascular endothelium, pregnancy might further increase the risk of cardiovascular disease in women with FH. In this study activation markers of hemostasis and endothelium activation were analyzed in a sample of 22 FH women and compared with 149 healthy women. The concentration of prothrombin fragments 1 + 2, a marker of thrombin generation was higher (p<0.05) in the FH group compared with the reference group. The baseline concentrations of the endothelial activation marker VCAM-1 were similar (p>0.05) in the FH and reference groups, VCAM-1 rose markedly (p<0.05) during pregnancy by 120% in the FH group, whereas it remained unaltered in the reference group. The results may be skewed by the large number of pre-pregnancy smokers in the FH group (31% compared to 0% in the reference group). Nonetheless, it is possible that enhanced endothelial activation as well as increased lipid concentrations may confer additional risks of cardiovascular disease among pregnant FH women.

Treatment of pregnant women with FH
Potential teratogenicity of statins in pregnancy has been reviewed and the results of six case series, case study and in vitro study reports are described in the table below.

There was one cohort study identified (Ofori, Benjamin, Rey, Evelyne, and Bérard, Anick, 2007), which included only pregnant women who had a live birth. The cohort was constructed retrospectively from routine data. There were three groups of women: Group A filled prescriptions for statins only before and during 1st trimester (n=153); Group B had filled prescriptions for fibrates or nicotinic acid only before and during 1st trimester (n=29) and group C used only statins between 1 year before and 1 month before pregnancy (n=106). The authors reported the outcome of an infant diagnosed with a congenital anomaly within the first year of life.

The crude OR using Group B as reference group were for Group A 0.18 (95% CI 0.03,1.01) and for Group C 0.43 (95% CI 0.10, 1.91). A multivariate analysis stratified by study group included maternal age, socioeconomic information and education, co-morbidities and health services utilisation. The adjusted OR for congenital anomalies for group A was 0.79 (95% CI 0.10, 6.02) and for group C 1.74 (95% CI 0.27, 11.27). In a second multivariate analysis which included only groups A and C, using group C as the reference group, the adjusted OR for group A was 0.36 (95% CI 0.06, 2.18). There were three anomalies in group A, an unspecified anomaly of the heart, a ventricular septal defect and an atrial septal defect. The statins prescribed in these three cases were lovastatin, atorvastatin and simvastatin. The absence of outcome data on non-live births and the small sample size meant that the study was underpowered, and could not detect small increases in overall risk among those taking statins during pregnancy.

Table 15

Authors	Study	Year	Design	Description	Summary of results
Edison & Muenke(Edison, R. and Muenke, M., 2003)	Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins	2004	Case series	170 cases from FDA Medical Products Reporting Program; two cases by literature review and 42 others following requests to manufacturers for clinical data. 70 cases met inclusion criteria.	There were 31 adverse outcomes with 4 cases of IUGR, and 5 cases of fetal demise. 22 infants had structural anomalies. Two major groups of recurrently reported anomalies were noted: 5 central nervous system malformations and 5 limb deficiencies. There were no adverse outcomes reported with use of pravastatin and fluvastatin.
Kenis et al(Kenis, I., Tartakover, Matalon, Cherepnin, N. et al , 2005)	Simvastatin has deleterious effects on human first trimester placental explants	2005	In vitro study of human explants	Laboratory data.	Simvastatin sharply inhibited migration of extravillous trophoblast cells from the villi to the mtrigel (p<0.05). Simvastatin also inhibited half of the proliferative events in the villi (p<0.05) and increased apoptosis of cytotrophoblast cells compared to control. Moreover, simvastatin significantly decreased secretion of progesterone from the placental explants (p<0.01). The conclusion is that simvastatin adversely affects human first trimester trophoblast.

Authors	Study	Year	Design	Description	Summary of results
Manson et al(Manson, J. M., Freyssinges, C., Ducrocq, M. B. et al , 1996)	Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy	1996	Case series	Spontaneous reports voluntarily submitted to Merck & Co, reports from clinical trials, postmarketing surveillance studies and regulatory agencies and reports in the literature.	Congenital anomalies were described in 9 reports, spontaneous abortions in 16 reports, fetal deaths/stillbirths in 2 reports, miscellaneous adverse outcomes in 4 reports and normal outcomes in 103 reports. The proportion of prospective reports with normal outcome was 85%. The proportions of prospective reports of spontaneous abortions (8%) and fetal deaths/stillbirths (1%) do not exceed what would be expected in the general population (15 and 3% respectively).
Petersen et al(Petersen, E. E., Rasmussen, S. A., Carey, J. C. et al , 2007)	Maternal exposure to statins and risk for birth defects	2007	Case Series	National Birth Defects Prevention Study and Slone Epidemiology Center Birth Defects, based on maternal report.	22 mothers of infants with birth defects reported statin use in pregnancy. 12 infants had cardiac defects, 4 infants had orofacial clefts and 2 infants had neural tube defects. Nineteen infants were classified as having isolated defects, 2 had multiple major defects and 1 had a syndrome. There were no limb defects.

Authors	Study	Year	Design	Description	Summary of results
Pollack et al(Pollack, P. S., Shields, K. E., Burnett, D. M. et al , 2005)	Pregnancy outcomes after maternal exposure to simvastatin and lovastatin	2005	Case series	Merck & Co pharmacovigilance database for reports of exposure to simvastatin or lovastatin.	225 prospective reports resulted in 6 congenital anomalies. The rate of congenital anomalies was 3.8% in the prospectively reported pregnancies and was slightly higher than the US background rate of 3.15% incidence of overall birth defects. Thirteen congenital anomalies (14%) were reported retrospectively. There was no specific pattern of congenital anomalies for either prospectively or retrospectively reported pregnancies. The authors concluded that due to the chronic nature of atherosclerosis the risks in pregnancy of taking a statin continue to outweigh the potential benefits.

Authors	Study	Year	Design	Description	Summary of results
Seguin and Samuels(Seguin, J. and Samuels, P., 1999)	Fluvastatin exposure during pregnancy	1999	Case report	Physician report.	28 year old woman s/p kidney transplant who continued on all medications during pregnancy including fluvastatin and delivered a healthy female infant. Fluvastatin differs from other statins in that it is entirely synthetic and has essentially no active metabolites, is highly protein bound and is 95% excreted in the liver.

8.3.3.4   Health economic evidence

No published, relevant evidence was identified.

Appendices A–G are available in a separate file

[Return to recommendations](#)

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