Identification and management of familial hypercholesterolaemia: what does it mean to primary care?

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ABSTRACT

Familial hypercholesterolaemia is one of the most common dominantly inherited disorders to be identified in primary care, leading to raised serum cholesterol evident from the first year of life. Around 1 in 500 people are affected by this condition, but less than 15% of these are currently attending lipid clinics, suggesting that the vast majority are unrecognised in general practice. The recently released National Institute for Health and Clinical Excellence evidence-based guideline on the identification and management of familial hypercholesterolaemia provides an opportunity to bridge this gap. Primary care has a role in systematic and opportunistic case finding, such as recognising the relevance of a family history of premature coronary heart disease and/or grossly elevated cholesterol. Although affected individuals need specialist care, GPs can reinforce the information provided by specialists and support cascade screening to other affected members of the extended family.

Keywords

family health; familial hypercholesteroaemia; family health; medical genetics; primary health care.

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INTRODUCTION

This review summarises the recommendations that have an impact on primary care from the National Institute for Health and Clinical Excellence (NICE) guideline on the identification and management of familial hypercholesterolaemia.[1] Familial hypercholesterolaemia is an inherited disorder leading to raised serum cholesterol evident from the first year of life. This may present with signs indicative of raised cholesterol levels such as tendon xanthomata, and, if untreated, the development of premature coronary heart disease (CHD). The disorder has an autosomal dominant mode of inheritance, so children and siblings of a person with familial hypercholesterolaemia have a 50% chance of inheriting the condition. Most individuals only inherit one 'defective' gene from their parents so are heterozygous for the disorder. Heterozygote familial hypercholesterolaemia occurs in approximately 1 in 500 people, and therefore a GP practice of 10 000 patients may have around 20 patients with familial hypercholesterolaemia, clustered in six to eight families. Currently around 17 of these patients (85%) are unlikely to have been identified.[2] If these heterozygote patients are left untreated, 50% of the men will develop a myocardial infarction before the age of 50 years, while 30% of the women will develop myocardial infarction before the age of 60 years.[3] Treatment with lipid-lowering drugs, most commonly statins, can substantially reduce CHD mortality and morbidity in patients with familial hypercholesterolaemia.[4,5] Despite this effective treatment, many people with the condition, particularly young individuals who would benefit most in terms of life years gained, fail to be identified.[6] Box 1 summarises key points about familial hypercholesteroaemia for primary healthcare practitioners derived from the 2008 NICE guideline.[7]

IDENTIFYING FAMILIAL HYPERCHOLESTEROLAEMIA

GPs should be alert to the possibility of familial hypercholesterolaemia in patients with a cholesterol >7.5 mmol/l; they should ascertain whether there is a

How this fits in

The National Institute for Health and Clinical Excellence (NICE) has recently completed an evidence-based guideline on the identification and management of familial hypercholesterolaemia. The guideline covers all aspects of the patient care pathway from initial diagnosis in primary and secondary care to more complex management in tertiary care, and makes over 100 recommendations for the identification and management of patients with familial hypercholesterolaemia. This article focuses only on the impact of this guidance, and the evidence that underpins it, for primary healthcare practitioners, including both GPs and practice nurses. NICE recommendations are based on systematic reviews of best available evidence. When minimal evidence is available, recommendations are based on the guideline development group's opinion of what constitutes good practice.

family or personal history of CHD, and measurement of fasting blood lipid profile should be organised to include high-density lipoprotein (HDL) and triglyceride, so that an estimation of low-density lipoprotein cholesterol (LDL-C) concentration can be made. Before considering a diagnosis of familial hypercholesterolaemia, secondary causes of hypercholesterolaemia should be excluded, such as hypothyroidism, diabetes, and current drug therapy.

Clinical examination should include documentation of possible tendon xanthomata that are pathognomonic of familial hypercholesterolaemia.[3] In people with heterozygote familial hypercholesterolaemia, they usually only develop in the third decade, and not all affected relatives within a family may have them. These cholesterol deposits lead to 'skin-coloured' firm non-tender nodules on tendons. They are present in the extensor tendons of the hand and the Achilles tendons, and rarely occur on the extensor hallicus longus and triceps tendons. In children with homozygous familial hypercholesterolaemia, these may be misdiagnosed as warts. Other less diagnostic stigmata include premature corneal arcus and xanthelasmata around the eyelids.

Adult patients who meet the Simon Broome criteria,[3] that is, they have at least two confirmed measurements of fasting total cholesterol >7.5 mmol/l and/or LDL >4.9 mmol/l, combined with signs of tendon xanthomata and/or family history of premature heart disease, should be referred to a specialist with expertise in familial hypercholesterolaemia, to confirm diagnosis, management, and coordination of the testing of relatives (50% of whom on average will also have familial hypercholesterolaemia). The specialist will also document, when possible, at least a three-generation pedigree using standardised pedigree terminology. This will identify a dominant pattern of inheritance by evidence of elevated cholesterol levels or premature CHD in all generations, irrespective of sex and relatives' lifestyle. Although GP computer systems do not have the facility to collate family history information as pedigrees, a practice record can also be kept using a series of Read classification codes for family history or by scanning copies of pedigree into the GP computer system. The pedigrees can be derived from specialist software, or motivated patients can access free pedigree-drawing software on the web.[8] GPs should encourage patients to check details directly with other members of the family and regularly update the family history to identify any emerging familial risk.

Currently, 85% of patients with familial hypercholesterolaemia are not identified,[2] but some patients with possible familial hypercholesterolaemia can be identified by a simple audit of medical records for patients with any previous cholesterol >7.5 mmol/l or premature CHD (diagnosed before the age of 55 years).[9] Also, current GP computer records will identify patients with a family history of CHD recorded. For all such patients it would be appropriate to take a detailed family history and to examine patients for relevant signs. Exploring the family history may identify relatives with premature heart disease, raised cholesterol, or signs of raised cholesterol. When such relatives are identified, the doctor or nurse should enquire about their exact relationship to the patient, age of diagnosis, their cholesterol level, and other lifestyle risk factors (for example, smoking). Under current Simon Broome diagnostic criteria,[3] family history of premature CHD is defined as myocardial infarction aged <60 years in a first-degree relative, or <50 years in a second-degree relative.

MANAGING FAMILIAL HYPERCHOLESTEROLAEMIA

In general practice, patients with familial hypercholesterolaemia may appear as only having a single cardiovascular risk factor (that is, raised cholesterol or family history), and standard cardiovascular risk-assessment tools (for example, Framingham, QRISK®2) substantially underestimate their risk and must not be used. This is because these individuals are hypercholesterolaemic from infancy with a higher cholesterol-years burden,[10] leading to a greatly increased risk of atherosclerosis, thus benefiting from early and aggressive lipid-lowering treatment to prevent premature CHD.

Despite being provided with thorough information and advice from specialists, patients may still not be clear about their condition and are likely to consult the GP and practice nurse. A recent survey suggested that although 90% of patients with familial hypercholesterolaemia knew about cholesterol and

Box 1. Summary of NICE Guideline CG71 relevant to primary care.[7]

Key facts about familial hypercholesterolaemia

- Familial hypercholesterolaemia leads to high plasma LDL-cholesterol levels, and, if untreated, many people will develop early coronary heart disease.
- Familial hypercholesterolaemia is a common genetic disorder (~1 in 500 are affected, so a general practice with 10 000 patients will have around 20 patients but currently only three patients are identified).
- Familial hypercholesterolaemia is inherited in an autosomal dominant manner, so children and siblings of a person with the disorder have a 50% chance of inheriting the condition.
- An underlying genetic cause of familial hypercholesterolaemia can be identified in around 80% of cases.
- Patients with familial hypercholesterolaemia usually require potent statins to achieve adequate LDL-cholesterol lowering.
- Cardiovascular disease risk-assessment tools, such as Framingham, are not appropriate for use in patients with familial hypercholesterolaemia as these tools significantly underestimate the cardiovascular disease risk in patients with familial hypercholesterolaemia.

Identifying familial hypercholesterolaemia

- Suspect diagnosis in adults with raised total cholesterol (typically >7.5 mmol/l), especially when there is a personal or a family history of premature coronary heart disease.
- Repeat fasting lipid profile to include total cholesterol, triglycerides, and HDL (to estimate LDL).
- If cholesterol is raised pre-treatment or suspicious personal or family history (see below):
  - exclude secondary causes of hypercholesterolaemia;
  - take detailed family history and regularly update; and
  - examine patient for signs of raised cholesterol (particularly tendon xanthomata[a]).

Referral criteria for diagnosis: abridged Simon Broome diagnostic criteria

- In adults, total cholesterol >7.5mmol/l and LDL >4.9 mmol/l.
- For children (<16 years of age) 6.7 mmol/l together with an LDL >4.0 mmol/l.

  Plus for a diagnosis of definite familial hypercholesterolaemia, tendon xanthomata in patient or in first- or second-degree relative.

  Plus for a diagnosis of possible familial hypercholesterolaemia, family history of myocardial infarction aged <60 years in first-degree relative[b], aged <50 years in second-degree relative[c], or a family history of raised cholesterol levels.

  Patients with 'definite' or 'possible' familial hypercholesterolaemia should be referred to a specialist with expertise in familial hypercholesterolaemia, to confirm the diagnosis, management and coordination of the testing of relatives.

Managing familial hypercholesterolaemia

- Monitor and support adherence to lipid-lowering treatment and lifestyle advice (smoking cessation, exercise and dietary improvement).
- At least annually, monitor full lipid profile, drug side-effects, and symptoms/signs of cardiovascular risk or disease (performed by GPs if not under specialist care).
- Identify patients to refer back to specialist:
  - patients that have developed further coronary heart disease risk factors;
  - side-effects noted with lipid-lowering treatment that compromise treatment adherence;
  - LDL cholesterol not controlled by maximal standard therapy;
  - to instigate cascade screening of other family members;
  - those that develop symptoms or signs of coronary heart disease or being diagnosed with coronary heart disease;
  - pregnancy and pre-pregnancy care; and
  - all children with suspected familial hypercholesterolaemia referred (back) by the age of 10 years or the earliest opportunity thereafter.

[a]Tendon xanthomatas are firm, non-tender nodules on tendons, particularly extensor tendons of the hands and Achilles tendons. Absence does not exclude familial hypercholesterolaemia. [b]First-degree relatives are: parents, siblings, children. [c]Second-degree relatives are: grandparents, aunts/uncles, nieces/nephews, half-siblings, grandchildren. HDL = high density lipoprotein. LDL = low density lipoprotein.

the reasons for treatment, only three-quarters knew that they were at risk of a cardiac event, with one-third knowing the mode of inheritance of familial hypercholesterolaemia and one-fifth being aware of their own family histories.[11]

Even while under specialist care, opportunistic contact with the primary care practitioner can provide an opportunity to monitor drug adherence, reinforce lifestyle advice (for example, smoking cessation), identify the presence of any new risk factors (for example, hypertension, and recent family history), investigate symptoms of coronary heart disease, and enquire about drug side-effects. If the patient has been discharged from specialist care, this assessment should be offered in general practice at least on an annual basis, with fasting lipid profile, renal function, and glucose testing arranged. Since there is a small possibility of fetal abnormality associated with statin use in early pregnancy,[12] it is recommended that contraception should be discussed at the commencement of statin treatment in women of child-bearing age, and that this discussion is revisited regularly. Standard effective contraceptive methods, including the combined oral contraceptive, are not contraindicated for women with familial hypercholesterolaemia. However, because there is a potential small increased risk of cardiovascular events with the use of combined oral contraceptives, healthcare professionals should consider other forms of contraception. The evidence for safety of the combined oral contraceptives was derived from its use in women with non-familial hypercholesterolaemia, and indicates that primary and secondary generation combined oral contraceptives have a slightly higher myocardial infarction risk than third-generation oral contraceptives, for which myocardial infarction risk is negligible.[13,14] Further, women planning to start a family should stop lipid-lowering treatment 3 months before attempting to conceive.

Referral back to a specialist with expertise in familial hypercholesterolaemia should be considered if the patient develops new CHD risk factors or drug side-effects, to instigate drug modification as part of pre-pregnancy planning, or in patients who do not achieve their target reduction in LDL, that is, a ≥50% reduction from baseline levels.[15]

It is not recommended that GPs should be responsible for cascade screening, but members of the extended family who are in the same practice should be referred to the specialist service, where screening will be coordinated. GPs should encourage index cases with familial hypercholesterolaemia to discuss screening with relatives, while relatives directly contacting clinicians should be offered referral. The Simon Broome criteria should not be used to make a diagnosis of familial hypercholesterolaemia in these relatives, as the LDL cut-offs in these criteria will miss relatives at risk of familial hypercholesterolaemia.[9]

GPs should have a low threshold for urgent cardiological referral if patients develop symptoms and/or signs of CHD. Further, all pregnant women with familial hypercholesterolaemia should be referred early to a shared care team comprising an experienced obstetrician and a cardiologist. Those women who do conceive while on statins should stop treatment immediately and be referred urgently to an obstetrician for fetal assessment. In pregnancy, routine serum cholesterol measurements are not recommended, as there are marked changes in lipids and lipoproteins in pregnancy.[16] Breast feeding should be encouraged in familial hypercholesterolaemia as for the general population, but systemically absorbed lipid-lowering treatments (such as statins) should not be used until after weaning.

Familial hypercholesterolemia is a relatively common inherited condition of abnormal lipid metabolism that is associated with significant morbidity and mortality. This is effectively treated by the statin class of lipid-lowering drugs. Possible familial hypercholesterolaemia can be identified in general practice using routine patient information and investigations, and patients with confirmed familial hypercholesterolaemia warrant treatment with potent statins.

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REFERENCES

1. DeMott K, Nherera L, Humphries SE, *et al. Clinical guidelines and evidence review for familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia.* London: National Collaborating Centre for Primary Care and Royal College of General Practitioners, 2008.
2. Marks D, Thorogood M, Farrer M, Humphries SE. Census of clinics providing specialist lipid services in the United Kingdom. *J Public Health Med* 2004; **26(4):** 353–354.
3. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial

COMMENTARY

What's so special about familial hypercholesterolaemia?

Last year the National Institute for Health and Clinical Excellence (NICE) issued clinical guidance on the diagnosis and management of familial hypercholesterolaemia.[1] The implications of this guidance for general practice are discussed by Qureshi *et al* in this issue of the *BJGP*.[2] But why do we need such guidance? We know already that we should treat high-cholesterol patients with a statin to reduce the risk of vascular disease, so what's so special about familial hypercholesterolaemia? Isn't familial hypercholesterolaemia simply the tail-end of the cholesterol distribution in a population? Epidemiologists have been telling us for years that focusing on the treatment of tail-ends is a poor preventive strategy because most events (in this case strokes and myocardial infarctions) occur to people in the middle of the population distribution simply because there are so many of them.[3] Wouldn't it be better for the NICE guidance to focus on shifting the whole population distribution of cholesterol rather than chopping off the tail?

The rationale for treating familial hypercholesterolaemia differently is the disproportionately high mortality risk, particularly in young adults, which is higher than would be predicted by the same cholesterol level in people without familial hypercholesterolaemia. Without treatment, over 50% of men and 30% of women with familial hypercholesterolaemia will have a heart attack before age 60 years.[4] This not because the atherogenic effect of high blood concentrations of low-density lipoprotein (LDL) cholesterol is any different in familial hypercholesterolaemia, but because people with familial hypercholesterolaemia are exposed to very high concentrations of LDL cholesterol from birth.[5] Most patients identified with high cholesterol in middle age, but without an LDL-receptor mutation which characterises familial hypercholesterolaemia, will have built up to their high levels over time through a combination of age, poor diet, obesity, and other risk factors. In contrast, by the time the heterozygous familial hypercholesterolaemia sufferer enters early adulthood they will have accumulated ≥20 years of continuous atherogenic exposure and are at a hundred-fold greater risk of a heart attack than other young people. Patients with homozygous familial hypercholesterolaemia (which occurs with a frequency of about 1 in a million rather than 1 in 500) are at such high risk that they may not live beyond childhood into early adulthood.

The NICE guidance is to refer all cases of suspected familial hypercholesterolaemia to a hospital specialist. GPs will wonder whether this is necessary. The suggested clinical criteria for diagnosis in sporadic adult cases are straightforward (total cholesterol >7.5mmol/l, tendon xanthomata, and family history), and so is the treatment (statin at high dose to reduce LDL-cholesterol by ≥50%). Why bother to refer patients who respond readily to treatment? The answer is twofold: the need for effective cascade screening of first-degree relatives of index cases, and the much reduced diagnostic value of the clinical criteria in these first-degree relatives[6] (reflecting the fact that their starting probability of familial hypercholesterolaemia is 50%).

Simply telling patients to advise their relatives to contact their own doctor doesn't seem to work well.[7] Direct contact from a specialist nurse (who can draw up a family tree with the help of the index case and then contact relatives directly to offer testing) is much more effective.[8,9] To make the diagnosis once the first-degree relatives have been traced, DNA testing is necessary to achieve diagnostic precision.[9]

You can't prevent death in young adulthood if you don't detect familial hypercholesterolaemia until routine cholesterol testing in middle age. So although everything that is done in the hospital lipid clinic for most index cases could be done in general practice, referral to hospital lipid clinics to initiate cascade screening is the strategy most likely to lead to identification and treatment of the estimated 85% of patients with familial hypercholesterolaemia who have not yet been identified, particularly the children who may suffer cardiac death in early adulthood if untreated. Referral may also have two other advantages: stressing the seriousness of the condition to patients and improving the treatment of those with more complex lipid abnormalities.

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Familial hypercholesterolaemia is one of the few conditions where a preventive intervention has a substantial impact on every individual receiving it, prolonging life on average by about 10 years.[10] A practice with a registered population of 10 000 may have 20 patients with heterozygous familial hypercholesterolaemia (similar to type 1 diabetes) but the problem will not have been managed as assiduously as diabetes: on average only three patients will have been detected and treated. We need to do better than this. We also have a duty to ensure that our local primary care trusts understand the number of life years that can be cost-effectively saved by cascade screening for familial hypercholesterolaemia[11] and therefore fund the screening and DNA-based diagnosis of the first-degree relatives of the index cases we identify.

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REFERENCES

1. National Institute for Health and Clinical Excellence. *Identification and management of familial hypercholesterolaemia: NICE clinical guideline 71*. London: NICE, 2008. www.nice.org.uk/CG71 (accessed 28 Aug 2009).
2. Qureshi N, Humphries SE, Seed M, *et al*. Identification and management of familial hypercholesterolaemia: what does it mean to primary care? *Br J Gen Pract* 2009; **59:** 773–778. Advance online publication. DOI: 10.3399/bjgp09X472674.
3. Rose G. *The strategy of preventive medicine*. Oxford: Oxford University Press, Oxford. 1992: 23–25.
4. Stone NJ, Levy RI, Frederickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hypercholesterolaemia. *Circulation* 1974; **49:** 476–488
5. Humphries SE, Hadfield G. Identifying patients with familial hypercholesterolaemia in primary care. *Heart* 2008; **94(6):** 695–696.
6. Starr B, Hadfield SG, Hutten BA, *et al*. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clin Chem Lab Med* 2008; **46(6):** 791–803.
7. Marks D, Thorogood M, Neil SM, Humphries SE, Neil HAW. Cascade screening for familial hypercholesterolaemia: implications of a pilot study for national screening programmes. *J Med Screen* 2006; **13(3):** 156–159.
8. Bhatnagar D, Morgan J, Sidiq S, *et al*. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. *BMJ* 2000; **321(7275):** 1497–1500.
9. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, *et al*. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* 2001; **357(9251):** 165–168.
10. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. *Atherosclerosis* 1999; **142(1):** 105–112.
11. Marks D, Wonderling D, Thorogood M, *et al*. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ* 2002; **324(7349):** 1303–1308.

DOI: 10.3399/bjgp09X472683

hypercholesterolaemia. *Atherosclerosis* 2003; **168(1):** 1–14.
4. Betteridge DJ, Broome K, Durrington PN, *et al*. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis* 1999; **142(1):** 105–112.
5. Neil A, Cooper J, Betteridge J, *et al*. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J* 2008; **29(21):** 2625–2633.
6. Neil HA, Hammond T, Huxley R, *et al*. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 2000; **321(7254):** 148.
7 National Institute for Health and Clinical Excellence. *Familial hypercholesterolaemia. Identification and management of familial hypercholesterolaemia.* London: NICE, 2009. http://www.nice.org.uk/CG71 (accessed 3 Sep 2009).
8. Qureshi N, Wilson B, Santaguida P, *et al*. Appendix B: Forms/guides and internet family history tools. Family history tools available on the internet. In: Qureshi N, Wilson B, Santaguida P, *et al*. *Collection and use of cancer family history in primary care.* http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistory/famhist.pdf (accessed 16 Jun 2009).
9. Gray J, Jaiyeola A, Whiting M, *et al.* Identifying patients with familial hypercholesterolaemia in primary care: an informatics-based approach in one primary care centre. *Heart* 2008; **94(6):** 754–758.
10. Starr B, Hadfield SG, Hutten BA, *et al*. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clin Chem Lab Med* 2008; **46(6):** 791–803.
11. Hollman G, Olsson AG, Ek AC. Disease knowledge and adherence to treatment in patients with familial hypercholesterolemia. *J Cardiovasc Nurs* 2006; **21(2):** 103–108.
12. Edison R, Muenke M. Congenital anomalies following gestational statin exposure. *Am J Hum Genet* 2003; **73:** 212.
13. Baillargeon JP, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90(7):** 3863–3870.
14. Khader YS, Rice J, John L, Abueita O. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception* 2003; **68(1):** 11–17.
15. LaRosa JC, Grundy SM, Waters DD, *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352(14):** 1425–1435.
16. Amundsen AL, Khoury J, Iversen PO, *et al*. Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. *Atherosclerosis* 2006; **189(2):** 451–457.