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Executive Summary of Practice Guidelines

Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation

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Abstract

Familial hypercholesterolaemia (FH) is a dominantly inherited disorder present from birth that markedly elevates plasma low-density lipoprotein (LDL) cholesterol and causes premature coronary heart disease. There are at least 20 million people with FH worldwide, but the majority remains undetected and current treatment is often suboptimal.

To address this major gap in coronary prevention we present, from an international perspective, consensus-based guidance on the care of FH. The guidance was generated from seminars and workshops held at an international symposium. The recommendations focus on the detection, diagnosis, assessment and management of FH in adults and children, and set guidelines for clinical purposes. They also refer to best practice for cascade screening and risk notifying and testing families for FH, including use of genetic testing. Guidance on treatment is based on risk stratification, management of non-cholesterol risk factors and safe and effective use of LDL lowering therapies. Recommendations are given on lipoprotein apheresis. The use of emerging therapies for FH is also foreshadowed.

This international guidance acknowledges evidence gaps, but aims to make the best use of contemporary practice and technology to achieve the best outcomes for the care of FH. It should accordingly be employed to inform clinical judgment and be adjusted for country-specific and local healthcare needs and resources.

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Levels of evidence and grades of recommendation

Levels of evidence

1 = systematic review/meta-analysis/at least one randomized control trial/good quality diagnostic tests.
2 = good quality clinical or observational studies.
3 = expert opinion or clinical experience/argument from first principles.

(The evidence for therapeutic interventions was considered principally in respect of effects on plasma low-density lipoprotein (LDL)-cholesterol concentrations, but where available was also based on data on subclinical atherosclerosis or cardiovascular outcomes.)

Grades of recommendation

A = can be trusted to guide practice.
B = can be trusted to guide practice in most situations.
C = can be used to guide practice, but care should be taken in application.

Summary of recommendations

1. Detection of index cases: screening and phenotypic diagnosis

1.1 Targeted, opportunistic and universal screening strategies should be employed to detect index cases (2B).
1.2 Index cases should be sought by targeted screening of adults with premature cardiovascular disease (CVD), primarily coronary heart disease (CHD) and a personal and/or family history of hypercholesterolaemia. (1A)
1.3 Opportunistic screening of adults and children in primary care, based on age- and gender-specific plasma LDL-cholesterol levels, should be routinely adopted. (2B)
1.4 Universal screening based on age- and gender-specific plasma LDL-cholesterol levels should be considered prior to age 20 years and ideally before puberty. (2C)
1.5 In adults, country-specific clinical tools, such as the Dutch Lipid Clinic Network, Simon Broome, MED-PED or Japanese FH criteria, may be used to make a phenotypic diagnosis. (1A)

1.6 The effect of acute illness and concurrent use of statins in lowering plasma LDL-cholesterol must be considered: testing for familial hypercholesterolaemia (FH) should not be carried out during acute illness; LDL-cholesterol level should be appropriately adjusted in people on statins, particularly if a reliable pre-treatment value is not available. (2A)
1.7 All patients with suspected FH should be referred to a clinic specializing in lipidology and/or metabolic disorders for further assessment, if such a service is available. (3A)

2. Diagnosis and assessment of adults

2.1 Secondary causes of hypercholesterolaemia should first be excluded. (1A)
2.2 The most reliable diagnosis of FH can be made using both phenotypic (see 1.5 above and 4.8 below) criteria and genetic testing, but when genetic testing is not available the diagnosis can be made phenotypically. (1A)
2.3 DNA testing increases the accuracy of detecting FH and, if resources permit, should be considered to confirm the diagnosis, especially if cascade screening is planned; a fully accredited laboratory should be used. (1A)
2.4 Although FH is a life-time coronary risk equivalent, patients should be assessed for additional major cardiovascular risk factors, including lipoprotein(a) (Lp(a)), the level of hypercholesterolaemia at diagnosis and the prematurity of the family (especially first-degree relatives) or personal history of CVD. Framingham or other cardiovascular risk equations should not be used. (2A)
2.5 The presence of additional cardiovascular risk factors should guide the intensity of medical management. (2A)
2.6 Cardiovascular imaging (e.g. cardiac computed tomography (CT) and carotid ultrasonography) may be useful for assessing asymptomatic patients, but its value is not fully established. (2C)

3. Diagnosis and assessment of children and adolescents

3.1 Secondary causes of hypercholesterolaemia should first be excluded. (1A)
3.2 With the exceptions noted in 3.3, children should be genetically tested for FH only after a pathogenic

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Conversion factor: mg/dl cholesterol = mmol/l × 38.7; mg/dl

variant (mutation) has been identified in a parent or first degree relative. (1A)

3.3 Children may initially be genetically tested for FH when parents or first degree relatives are unknown or deceased, or as an accepted screening practice in certain countries, such as the Netherlands. (3B)

3.4 Age-, gender- and country-specific plasma LDL-cholesterol concentration thresholds should be used to make the phenotypic diagnosis; because of biological variation, two fasting LDL-cholesterol values are recommended. (1B)

3.5 A plasma LDL-cholesterol of 5.0 mmol/l or above indicates high probability of FH in the absence of a positive parental history of hypercholesterolaemia or premature CHD; an LDL-cholesterol of 4.0 mmol/l or above indicates high probability of FH in the presence of a positive parental history of hypercholesterolaemia or premature CHD. (1B)

3.6 Patients should be risk stratified according to age, presence of other cardiovascular risk factors, family history of early onset CVD (especially in first-degree relatives) and the level of LDL-cholesterol at diagnosis. (2A)

3.7 The presence of additional cardiovascular risk factors, and hence risk stratification, should guide the intensity of medical management. (3A)

3.8 Carotid ultrasonography may be employed to assess risk, but its value is not fully established; it should only be carried out in centres with specific expertise. (2C)

3.9 Cardiac CT should not be used routinely to assess patients with heterozygous FH. (3A)

4. Cascade screening: testing and risk notification of families

4.1 Notification of relatives at risk of FH should generally not be carried out without the consent of the index case. (3A)

4.2 Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for breach of confidentiality in the relevant jurisdiction. (3C)

4.3 A proactive approach that respects the principles of privacy, justice and autonomy is required. (3A)

4.4 Pre-testing counselling should be offered to at risk family members of an index case prior to any form of testing. (1A)

4.5 Systematic cascade screening should ideally be co-ordinated by a dedicated centre and should not be carried out in primary care without central co-ordination, particularly if employing DNA testing. (1B)

4.6 Cascade screening of families should be carried out using both a phenotypic and genotypic strategy, but if DNA testing is not available a phenotypic strategy alone should be used. (1A)

4.7 Cascade screening should initially be carried out as a priority in first-degree relatives and then extended to second- and third-degree relatives. (1A)

4.8 In the absence of genetic testing, the diagnosis of FH should be made in close relatives using age-, gender- and country-specific plasma LDL-cholesterol levels. Diagnostic clinical tools for index cases, such as the Dutch Lipid Clinic Network and Simon Broome criteria, should not be employed to make the diagnosis of FH in relatives. (1A)

4.9 DNA testing makes cascade screening more cost-effective and should be employed to screen family members after the mutation is identified in the index case. (1A)

4.10 Children with xanthomata or other physical findings of homozygous FH, or at risk of homozygous FH should be screened as early as possible and definitely by two years of age. (2A)

4.11 Children with suspected heterozygous FH should be screened between the ages of five and 10 years; age at screening should be similar in boys and girls. (2B)

5. Genetic testing

5.1 Genetic testing for FH should ideally be offered to all 'index cases' who have a phenotypic diagnosis of FH. (3A)

5.2 When the phenotypic diagnosis of FH is unlikely (e.g. by Dutch Lipid Clinic Network Criteria), genetic testing of the 'index case' need not be carried out. (1C)

5.3 Genetic testing for FH must be carried out in an accredited laboratory using standardized methods that target specific mutations and/or by exon-by-exon sequencing. (1A)

5.4 If genetic testing detects a variant, its significance as a pathogenic mutation, a previously reported variant of uncertain significance, a novel variant of uncertain significance or a benign (normal) variant needs to be assessed and recorded. (1A)

5.5 If genetic testing does not detect a variant, FH due to undetected mutations or mutations in untested genes cannot be excluded, particularly if the clinical phenotype is strongly suggestive of FH. (1A)

6. Management of adults

6.1 All adult patients with FH must receive advice on lifestyle modifications and advice to correct all non-cholesterol risk factors should be provided according to expert recommendations. (2A)

6.2 Therapy should ideally aim for at least a 50% reduction in plasma LDL-cholesterol, followed by an LDL-cholesterol <2.5 mmol/l (absence of CHD or other major risk factors) and <1.8 mmol/l (presence of CHD or other major risk factors). (2C)

6.3 Achieving these targets will require a fat-modified, heart-healthy diet and statin therapy with or without ezetimibe. (1A)

6.4 Drug combinations including bile acid sequestrants, niacin, probucol or fibrates, may be required with more intensive strategies to further reduce LDL-cholesterol. (1B)

6.5 Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting drug therapy. All patients on statins should have hepatic aminotransferases monitored; creatine kinase should be measured when musculoskeletal symptoms are reported; glucose should be monitored when there are risk factors for diabetes. (2A)

6.6 All women of child-bearing age should receive pre-pregnancy counselling, with appropriate advice on contraception, before starting a statin and this should be reinforced at annual review. (2A)

6.7 Statins and other systemically absorbed lipid regulating drugs should be discontinued three months before planned conception, as well as during pregnancy and breast feeding. (2A)

6.8 Although carotid ultrasonography has been used in clinical trials, its role in monitoring therapy as part of the clinical care for FH has not been established and it should therefore not be used at present for this purpose. (3C)

6.9 Lomitapide and mipomersen should be considered as adjunctive treatments to diet and cholesterol lowering drugs in adults with homozygous FH to further reduce plasma LDL-cholesterol, particularly if lipoprotein apheresis is not available. (1C)

6.10 Well controlled and low complexity patients should be followed up in primary care, whereas higher complexity patients will need regular review by a specialist, with the option of shared care. Review intervals should vary according to clinical context. Opportunities should be created for integrating the primary and specialist care of FH. (3B)

7. Management of children and adolescents

7.1 Patients must receive advice on lifestyle modifications and on correcting non-cholesterol risk factors; primordial prevention (counselling to inhibit the development of risk factors) is particularly important. (2A)

7.2 To lower elevated plasma LDL-cholesterol in this age group generally requires a fat-modified, heart-healthy diet and a statin, with the possible addition of ezetimibe or a bile acid sequestrant. (1A)

7.3 All patients should be treated with diet, with statins considered at age eight to 10 years and ideally started before age of 18 years; plasma LDL-cholesterol targets in this age group need not be as intense as for adults. (2B)

7.4 Boys and girls should generally be treated at similar ages, although with a particularly adverse family history of CHD and other major risk factors, boys with heterozygous FH could be considered for earlier treatment with statins. (2B)

7.5 Children, between the ages of eight and 10 years, with proven FH on a suitable diet and LDL-cholesterol >4.0 mmol/l on two occasions should be started on low-dose statin monotherapy, aiming for an LDL-cholesterol <4.0 mmol/l. (3C)

7.6 After the age of 10 years, children with proven FH on a suitable diet and LDL-cholesterol >3.5 mmol/l on two occasions should be started on statin monotherapy, aiming for an LDL-cholesterol <3.5 mmol/l, with the addition of ezetimibe or a bile acid sequestrant if required. (3C)

7.7 The preferred statins for initiating therapy are those that are licensed for clinical use in this age group in specific countries; other statins may be prescribed according to clinical indications, higher doses of potent statins being required in homozygotes. (1C)

7.8 Although statins can be safely used in children, weight, growth, physical and sexual development, and well-being should be monitored in this age group. (1A)

7.9 Plasma levels of hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting drug therapy. All patients on statins should have hepatic aminotransferases monitored; creatine kinase should be measured and compared with pre-treatment levels when musculoskeletal symptoms are reported; glucose should be monitored if there are risk factors for diabetes. (2A)

7.10 All adolescent girls should receive pre-pregnancy counselling, with appropriate advice on contraception, before starting a statin and this should be reinforced at annual review. (3A)

7.11 Although carotid ultrasonography has been used in clinical trials, its role in monitoring therapy in patients with heterozygous FH has not been established and it should therefore not be used for this purpose. (3C)

7.12 Well controlled and lower complexity patients should be followed up in primary care, whereas higher complexity patients will need regular review by a paediatrician. Opportunities should be created for integrated care between GPs and paediatricians. Family based and transitional care clinics should be considered by adult and paediatric services. (3B)

7.13 Children with homozygous FH should be referred on diagnosis to a specialist centre and drug and/or apheresis treatment commenced as soon as possible. (2A)

7.14 In children with homozygous FH and rapidly progressive atherosclerosis, lomitapide and mipomersen, although not yet tested in children, should be considered, employing special access or compassionate use schemes, as adjunctive treatments to diet and conventional drugs to further reduce plasma LDL-cholesterol, particularly if apheresis is not available or declined by the patient/family. (3C)

8. Lipoprotein apheresis and related treatments

8.1 Lipoprotein apheresis (LA) should be considered in all patients with homozygous or compound heterozygous FH (i.e. homozygous FH phenotype) and carried out in a dedicated centre with the relevant expertise. (1A)

8.2 LA should be considered in patients with heterozygous FH with CHD who cannot achieve LDL-cholesterol targets despite maximal drug therapy or because they cannot tolerate statins. (2A)

8.3 LA should be considered in children with homozygous FH by the age of five and no later than eight years. (2A)

8.4 Diet and drug therapy to lower LDL-cholesterol should be continued during treatment with LA (2A).

8.5 The efficacy, tolerability and safety of LA must be regularly reviewed. (3A)

8.6 The effect of LA on progression of atherosclerosis should be monitored according to clinical indications in FH patients with echocardiography (aortic valve and root), carotid ultrasonography and exercise stress testing. (3B)

8.7 Lomitapide should be considered as an adjunctive to standard diet and drug therapy to further lower plasma LDL-cholesterol in adults with homozygous FH on LA. (1C)

8.8 Lomitapide should be considered, via a special access scheme, as an adjunctive treatment to further lower plasma LDL-cholesterol in children and adolescents with homozygous FH on LA with rapidly progressive atherosclerosis. (3C)

8.9 Mipomersen should be considered as an adjunctive to standard diet and drug therapy to further lower plasma LDL-cholesterol in adults, children and adolescents with homozygous FH on LA who cannot tolerate lomitapide. (3C)

8.10 If available, orthotopic liver transplantation should be considered for younger patients with homozygous FH who have rapid progression of atherosclerosis or aortic stenosis, cannot tolerate LA or when plasma LDL-cholesterol cannot be adequately lowered with LA, diet and drug treatment. (3B)

9. Organization and development of care

9.1 Care pathways for FH should be developed for country-specific and local needs. (3A)

9.2 Specialist services should be multidisciplinary based and integrated with primary care. (3B)

9.3 Specialist care of FH should ideally be supported by cardiology, paediatric, genetic, imaging, transfusion medicine, nursing, dietetic, psychology, pharmacy and pathology laboratory services. (3A)

9.4 Cascade screening should ideally be centrally co-ordinated by a dedicated centre. (1A)

9.5 Low complexity patients should be managed in primary care, with the option of annual specialist review. (3A)

9.6 Higher complexity patients should be managed principally in specialist centres. (3A)

9.7 Medical, nursing and allied health staff managing patients with FH should be accredited in cardiovascular prevention. (3A)

9.8 Services should establish partnerships with academic and professional organizations to enhance teaching, training and research. (3A)

9.9 A registry of patients and families should be established for clinical, research and audit purposes. (3A)

9.10 A support group of patients and families should be established as a major priority for enhancing public, government and health care provider awareness, as well as the total quality of care of FH. (3A)

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