therapy, is recommended. [Recommended level I, evidence level B]
3. For the treatment of homozygous FH and drug therapy-resistant severe heterozygous FH, LDL apheresis therapy is recommended. [Recommended level I, evidence level B]

Other Types of Primary Hyperlipidemia

J Atheroscler Thromb, 2014; 21:82-85.

1. Patients with familial combined hyperlipidemia or familial type III hyperlipidemia are likely to develop CVD. As such patients respond well to dietary therapy, providing strict dietary therapy is essential. [Recommended level I, evidence level C]
2. Familial lipoprotein lipase deficiency and familial apoprotein C-II deficiency are only slightly related to atherosclerosis, although they are associated with a high risk of acute pancreatitis. Fat intake should be strictly restricted. [Recommended level I, evidence level C]

Coronary Artery Disease

J Atheroscler Thromb, 2014; 21:86-92.

1. In patients with acute coronary syndrome, strict LDL-C-lowering therapy is recommended from the initial stage of the disease. [Recommended level I, evidence level B]
2. In patients with CAD who are smokers or exhibit DM, CKD, non-cardiogenic cerebral infarction/PAD, metabolic syndrome or more than one major risk factor other than LDL-C, stricter LDL-C-lowering therapy is recommended together with management of risk factors other than LDL-C. [Recommended level IIa, evidence level B]

Diabetes Mellitus

J Atheroscler Thromb, 2014; 21:93-98.

1. Patients with DM require strict, comprehensive management of the lipid levels and blood pressure, as well as the blood glucose level, from the early stage of the disease. [Recommended level I, evidence level B]
2. In patients with DM complicated by microvascular complication such as retinopathy or nephropathy, non-cardiogenic cerebral infarction/PAD, smoking, metabolic syndrome, persistently poor glycemic control and more than one major risk factor stricter management of LDL-C is recommended together with management of risk factors other than LDL-C. [Recommended level IIa, evidence level B]

Chronic Kidney Disease

J Atheroscler Thromb, 2014; 21:173-174.

1. CKD is a high-risk condition. Comprehensive risk management, including reducing the LDL-C level to <120 mg/dL, is recommended. [Recommended level IIa, evidence level C]

Cerebrovascular Diseases

J Atheroscler Thromb, 2014; 21:175-179.

1. Statin therapy may prevent the development of cerebral infarction. [Recommended level I, evidence level A]

The Elderly

J Atheroscler Thromb, 2014; 21:180-185.

1. In the young-old (≥65 and <75 years of age), as well as adults, hyper-LDL cholesterolemia is an important risk factor for CAD.
2. Statin therapy for hyper-LDL cholesterolemia in the young-old may be effective for the secondary prevention of CAD. [Recommended level IIa, evidence level B]
3. Statin therapy for hyper-LDL cholesterolemia in the young-old may be effective for the primary prevention of CAD and cerebral infarction. [Recommended level IIa, evidence level B]
4. Statin therapy for hyper-LDL cholesterolemia in the old-old may be effective for the secondary prevention of CAD. [Recommended level IIa, evidence level B]
5. The significance of lipid-lowering therapy for hyper-LDL cholesterolemia in the old-old in the primary prevention of CAD is not clear at present. Patients should be individually treated at the discretion of their attending physician. [Evidence level C]

Women

J Atheroscler Thromb, 2014; 21:291-295.

1. Premenopausal women with dyslipidemia should be primarily treated with non-drug therapy, such as lifestyle modification. [Recommended level I, evidence level B]
2. Drug therapy should be considered in high-risk premenopausal women with familial hypercholesterolemia or those requiring secondary or primary prevention of CAD. [Recommended level I, evidence level C]
3. In postmenopausal women with dyslipidemia, lifestyle modification is given priority; however, drug therapy should also be considered, taking due account of the patient's risk factors. [Recommended level IIa, evidence level B]

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Review Articles

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

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These guidelines, with minor modifications, have also been published in the *International Journal of Cardiology*. Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.11.025.

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KEYWORDS:
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Diagnosis;
Familial hypercholesterolemia;
International guidance;
Models of care;
Screening;
Treatment

Abstract: Familial hypercholesterolemia (FH) is a dominantly inherited disorder present from birth that markedly elevates plasma low-density lipoprotein 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 noncholesterol risk factors, and the safe and effective use of low-density lipoprotein–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 used to inform clinical judgment and be adjusted for country-specific and local healthcare needs and resources.

Endorsement

The recommendations contained in this document have been fully endorsed by The National Lipid Association, 6816 Southpoint Parkway (Suite 1000), Jacksonville, FL 32216, USA.

Conversion factors

mg/dL cholesterol = mmol/L × 38.7
mg/dL triglyceride = mmol/L × 88.6; mg/dL lipoprotein(a) = 0.0357 μmol/L.

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 also was determined by 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 used 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 hypercholesterolemia [**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 in patients younger than 20 years of age and ideally before puberty [**2C**].
1.5 In adults, country-specific clinical tools, such as the Dutch Lipid Clinic Network Criteria (DLCNC),

Simon Broome, Make Early Diagnosis Prevent Early Death (MEDPED), 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 hypercholesterolemia (FH) should not be carried out in patients who are acutely ill; LDL-cholesterol levels should be appropriately adjusted in people on statins, particularly if a reliable pretreatment 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 hypercholesterolemia should first be excluded [**1A**].

2.2 The most reliable diagnosis of FH can be made using both phenotypic (see summary point **1.5** and **4.8**) 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 hypercholesterolemia 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 (eg, 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 hypercholesterolemia 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 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, 2 fasting LDL-cholesterol values are recommended [**1B**].

3.5 A plasma LDL cholesterol of 5.0 mmol/L or greater indicates high probability of FH in the absence of a positive parental history of hypercholesterolemia or premature CHD; an LDL cholesterol of 4.0 mmol/L or greater indicates high probability of FH in the presence of a positive parental history of hypercholesterolemia 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 used to assess risk, but its value is not fully established; it should only be carried out in centers 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 Pretesting counseling 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 coordinated by a dedicated center and should not be carried out in primary care without central coordination, 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 DLCNC and Simon Broome criteria, should not be used to make the diagnosis of FH in relatives [**1A**].

4.9 DNA testing makes cascade screening more cost-effective and should be used 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 2 years of age [**2A**].

4.11 Children with suspected heterozygous FH should be screened between the ages of 5 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 (eg, by DLCNC), 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 with the use of 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 caused by 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 noncholesterol 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 (CK), glucose, and creatinine should be measured before starting drug therapy. All patients on statins should have hepatic aminotransferases monitored; CK 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 prepregnancy counseling, with appropriate advice given by the clinician 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 3 months before planned conception, as well as during pregnancy and breastfeeding [**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 (LA) is not available [**1C**].

6.10 Well-controlled and low-complexity patients should be followed-up in primary care, whereas greater-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 noncholesterol risk factors; primordial prevention (counseling 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 8 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 8 and 10 years with proven FH on a suitable diet and LDL-cholesterol >4.0 mmol/L on 2 occasions should be started on low-dose statin monotherapy, with an optimal LDL-cholesterol of <4.0 mmol/L targeted [**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 2 occasions should be started on statin monotherapy, with an optimal LDL cholesterol of <3.5 mmol/L targeted, 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, CK, glucose, and creatinine should be measured before starting drug therapy. All patients on statins should have hepatic aminotransferases monitored; CK should be measured and compared with pretreatment 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 prepregnancy counseling, with appropriate advice on contraception given, 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 greater-complexity patients will need regular review by a pediatrician. Opportunities should be created for integrated care between general practitioners and pediatricians. Family based and transitional care clinics should be considered by adult and pediatric services [**3B**].

7.13 Children with homozygous FH should be referred on diagnosis to a specialist center 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, via the use of 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. LA and related treatments

8.1 LA should be considered in all patients with homozygous or compound heterozygous FH (ie, homozygous FH phenotype) and carried out in a dedicated center by professionals 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 5 and no later than 8 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, pediatric, genetic, imaging, transfusion medicine, nursing, dietetic, psychology, pharmacy, and pathology laboratory services [**3A**].

9.4 Cascade screening should ideally be centrally coordinated by a dedicated center [**1A**].

9.5 Low-complexity patients should be managed in primary care, with the option of annual specialist review [**3A**].

9.6 Greater-complexity patients should be managed principally in specialist centers [**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**].

Introduction

Familial hypercholesterolaemia (FH) is the most common dominantly inherited disorder in humans.[1] FH is most frequently the result of dominant, loss-of-function mutations in genes affecting the low-density lipoprotein (LDL) receptor that clears LDL particles from plasma,[2] and therefore LDL cholesterol levels are markedly elevated from birth. FH accelerates the development of atherosclerotic cardiovascular disease (CVD), especially coronary heart disease (CHD), with clinical manifestations often occurring after 1 to 4 decades of life.[3,4] Screening allows early detection of individuals,[5–9] thereby allowing the use of preventive interventions, including lifestyle measures, cholesterol-lowering medications, and management of other CVD risk factors.[6–16] There are probably more than 15 million people with FH worldwide, but less than 10% have been detected and only 5% adequately treated.[3,4,17,18]

To address this major gap in coronary prevention, the International FH Foundation facilitated a series of discussions with experts to develop harmonized guidance for the care of FH. Formal presentations and informal discussions took place at the XVI International Symposium on Atherosclerosis (Sydney, 2012) in workshops that addressed evidence for treatment, screening and DNA testing, pediatric management, novel therapies, health economics, regional diversity in management, and models of care. Workshop moderators identified and collated consensus on the basis of published research, clinical experience, common themes, expert opinion, and other international guidelines on FH.[6–9,19–22] To supplement this process, a brief questionnaire on potentially contentious issues in FH (screening options, DNA testing, risk stratification, testing and treatment of children, use of imaging, and therapeutic targets) was then completed by a selected group of international experts, with the majority view used to inform further consensus. This international guidance presents a standard of care for patients with FH within in a framework that can be adjusted for country-specific, regional, and local requirements and within which future evidence and consensus may be developed.[23]

Detection of index cases: screening for FH

A systematic strategy for detecting index cases (ie, first individuals diagnosed in families) of FH is essential.[6–9] The index case is the trigger for cascade screening, whereby new cases can be efficiently discovered.[3,8,9] Both screening methods need to be well integrated in models of care.[8] Universal screening before 20 years of age and ideally before puberty, on the basis of on age- and gender-specific plasma LDL cholesterol levels, should also be considered if feasible.[9,21] However, experience concerning its use and implementation is very limited. From a population perspective, universal and cascade screening methods for FH should be closely integrated.[24] The success of all detection strategies will depend on adequately addressing several barriers, including population awareness of FH and family, physician, and societal concerns of the value of screening for FH.

Potential index cases of FH should be sought among patients younger than 60 years with CVD presenting to coronary care, stroke, cardiothoracic, and vascular units,[8,25] as well as among similar patients attending cardiac rehabilitation programs. The greatest yield will be from screening younger adult patients with CHD.[25,26] A coronary event in a family member can increase the perception of risk and the willingness of relatives to be subsequently tested for FH. Screening in primary care should use an initial nonfasting lipid profile,[8] which should be undertaken opportunistically, based on family history of hypercholesterolemia and premature CVD (age <60 years).[27,28] FH screening also should be offered to all patients with tendon xanthomata and premature arcus cornealis.[6–9,22] All forms of opportunistic screening should account for the effect of any acute illness in lowering plasma total and LDL cholesterol,[29] in which case lipid testing should be delayed or repeated at least 8 weeks after recovery. There is a role for community laboratories alerting primary care physicians about FH on the basis of a high plasma LDL-cholesterol (eg, >5 mmol/L) or high total cholesterol (eg, >7 mmol/L).[30] When feasible, all patients with suspected FH should be referred to a specialist with expertise in FH for confirmation of the diagnosis.[26,28,31] All patients with homozygous FH (untreated LDL cholesterol >13 mmol/L; treated LDL-cholesterol >7.5 mmol/L)[32] must be referred to the nearest specialist center for management.[8,31,33]

Diagnosis and assessment of adults

A number of criteria exist for diagnosing FH phenotypically in adults, but none are internationally agreed.[6–9,22] The Dutch Lipid Clinic Network Criteria (DLCNC) are used to calculate a numerical score predicting the probability of the diagnosis of FH.[34] These criteria are increasingly accepted as simple and comprehensive[8,13,34]; the numerical score is not highly dependent on the plasma level of LDL cholesterol and can be more sensitive in detecting index cases, with a score >5 making the diagnosis highly probable. The Simon Broome system is comparable with the DLCNC in predicting an FH mutation but does not use arcus cornealis and may also overlook patients with true FH who are not overtly hypercholesterolemic. The MEDPED System, which relies on plasma total and LDL cholesterol and strictly requires that cholesterol measurements be first known in other family members,[35] may also be less specific in predicting mutations than other methods. The Japanese criteria, which are comparable with the Simon Broome system, use a population-specific LDL cholesterol >4.7 mmol/L and allow for a radiographic diagnosis of Achilles tendon xanthomata.[22] More international research is required to establish simple and harmonized criteria for the clinical diagnosis of FH.

The diagnosis of FH should be based on at least 2 fasting measures of plasma LDL cholesterol.[8,10,13] Obtaining the patient's family history of CHD and hypercholesterolemia is important to enhance the phenotypic diagnosis,[6,26,34–36] but often this information is neglected or may not be available in practice.[25,37] The presence of tendon xanthomata in early life with marked elevation in plasma LDL cholesterol establishes the diagnosis of severe FH,[32] but Sitosterolemia should also be excluded with plasma phytosterol and DNA testing[38]; in adults, tendon xanthomata with normal plasma cholesterol may be seen in Sitosterolemia and cerebrotendinous xanthomatosis. Secondary causes of hypercholesterolemia (eg, hypothyroidism, proteinuria, medications) must be excluded,[8,13,22] but the clinical stigmata of FH do not occur in these conditions. LDL cholesterol is underestimated by the Friedewald equation if the plasma triglyceride level is >4.5 mmol/L,[28] when a direct LDL-cholesterol assay should be used. The levels of apolipoprotein B-100 (apoB) and non–high-density lipoprotein (HDL) cholesterol (ie, total cholesterol minus HDL cholesterol) for diagnosing FH have not been defined. FH must be distinguished from familial combined hyperlipidemia,[22,39] a multigenic disorder with a variable lipid phenotype that coexpresses with insulin resistance and does not exhibit tendon xanthomata. Significant hypertriglyceridemia makes the diagnosis of FH less likely but may rarely be seen with coexisting genetic defects in lipoprotein metabolism.[40,41] For patients on cholesterol-lowering medication, pretreatment LDL cholesterol values must be obtained or interpolated from the drug type and regimen used.[42]

All patients diagnosed with FH should be investigated for other CVD risk factors[8,22,43,44] and the presence of symptomatic or subclinical atherosclerosis.[7,8,45] Assessment must take account of the psychological, intellectual, social, and ethnic status of the patient.[46,47] A detailed and culturally appropriate exploration of the individual's family history of CVD, particularly among first-degree relatives, is essential. Risk of CVD among patients with FH can vary widely.[43,44] This may relate to the pretreatment plasma level of cholesterol, genetic causes affecting lipid metabolism or arterial biology, and the presence of other major risk factors, in particular smoking, obesity, low HDL cholesterol, hypertension, and diabetes.[43,44] Mutations that very markedly elevate plasma LDL-cholesterol[48] and independently increase plasma Lp(a) concentrations also enhance the risk of CVD in FH.[49] Elevated Lp(a) also may contribute to the development of aortic stenosis.[50] Framingham Risk Scores, or scores derived from other cardiovascular risk engines, are not reliable to guide management in FH and should not be used,[8,10,11,51] particularly in younger patients, in whom a measure of long-term risk based on imaging of subclinical atherosclerosis may be more appropriate.[14,52,53] An assessment of cholesterol-life years, or cumulative cholesterol burden, may also be useful in risk assessment,[54] but its value in managing individual patients requires evaluation.

FH is associated with early onset and increased burden of subclinical atherosclerosis.[53,54] Certain measures of subclinical atherosclerosis have been independently associated with the onset of CHD in the general population[55,56] but have been generally applied to FH in research settings alone and require additional evaluation. Increased carotid intima-medial thickness (CIMT) and the presence of plaques may be assessed by carotid ultrasonography.[53,55,57] Coronary artery calcification (CAC) and luminal obstruction can be assessed with cardiac computed tomography/angiography.[45,55,58] In asymptomatic individuals, CAC score may be superior to CT coronary angiography in risk prediction,[59] and more clinically useful than CIMT.[60] Noninvasive testing for atherosclerosis could be useful in the assessment and management of FH, but this is not established. Testing could be individualized to specific clinical situations[58,61] and can be particularly useful when the family history of CVD is unclear.[62] Subclinical atherosclerosis should be defined according to recognized criteria.[55] Reference intervals for common CIMT have recently been reported,[63] but have not been validated in FH. Echocardiography for aortic stenosis may be indicated for heterozygous individuals with marked elevation in plasma Lp(a) concentration,[49,50] and as a routine investigation in homozygous FH to diagnose both aortic and/or supra-aortic valve disease.[8,32,43–45,64]

Given that CVD risk and the clinical expression is variable in FH, it is reasonable to use some form of risk stratification. Subdivision into lesser, (absence of CHD, subclinical atherosclerosis and major risk factors) and greater (presence of CHD, subclinical alterations or major risk factors) risk can guide the intensity of medical management[7,8]; however, the cost-effectiveness of this therapeutic approach requires evaluation. Patients considered to have a homozygous FH phenotype should be classified at exceptionally high risk[32] and be referred to a specialist centre for consideration for LA[65] or trial of new therapies.[8]

Diagnosis and assessment of children and adolescents

FH should be identified in youth, certainly before 18 years of age and younger if indicated and feasible.[19–21,54,66,67] Identification is particularly important for those at risk for homozygous FH, where recognition at about 2 years or even earlier is considered optimal.[19–21,54,66,67] Sitosterolemia may masquerade as homozygous FH in childhood, and the diagnosis should be considered.[38] Boys and girls with potential heterozygous FH should also be screened before the age of 10 years, preferably between ages of 5 and 10 years. However, earlier screening may be justified with a family history of CHD before 55 years of age, especially in first-degree relatives,[64,68,69] or at the specific request of parents wishing to embed healthy lifestyle measures at a very early age. The detection of FH in childhood via the use of 3 strategies can be considered: cascade screening, universal screening, or selective screening based on family history.[21,27,67] In different

countries, clinicians will use different strategies on the basis of health care resources and recommendations by local expert groups. In several European countries and Australia, cascade screening based on genetic testing has been advocated,[5,6,8,19] whereas in the United States selective screening beginning at age 2 years and universal screening at age 9 to 11 years has been advocated.[9,20] Universal screening by age 20 years, and ideally before puberty, is recommended; universal screening has been practiced in Slovenia[21] and tested in some universities in Japan, but the yield and cost-effectiveness remain unclear. Universal screening of children, followed by child-parent testing, may be a more effective approach to detecting FH in the population than cascade screening alone.[24] Importantly, none of the aforementioned pediatric screening strategies for FH have hitherto been validated for efficacy, risk-benefit, and cost-effectiveness.[70]

Age- and gender-specific plasma LDL cholesterol concentration thresholds should be used to make an initial diagnosis of FH.[68,71] Plasma LDL cholesterol level alone has excellent discrimination between those with and without FH who are younger than 10 years of age.[68,71,72] However, because of biological variation,[29,73] the average of at least 2 fasting LDL-cholesterol levels should be used to make the diagnosis of FH.[19,20,66] The effects of acute illness in lowering LDL cholesterol should be accounted for and tests repeated if necessary.[29,73] The diagnosis of heterozygous FH is highly likely in children who are older than 2 years of age if the LDL-cholesterol level is ≥5 mmol/L,[68,69] even in the absence of a family history of hyperlipidemia and premature CHD. Heterozygous FH is also probable at untreated LDL-cholesterol levels between 4 and 5 mmol/L, especially in the setting of a positive family history.[68] Homozygous FH should be considered if the untreated LDL cholesterol level is >13 mmol/L, especially if xanthomata are evident before the patient reaches 10 years of age.[19,20,32,66,74] Secondary causes of hypercholesterolemia, including nephrotic syndrome and hypothyroidism, should be excluded before diagnosing FH.[19,20,66]

As for adults, a complete CVD risk assessment, including determination of blood pressure, body mass index, tobacco use, glucose, and Lp(a) should be performed.[19,20,66] The presence of these additional risk factors, or other high-risk pediatric conditions, such as diabetes mellitus, Kawasaki disease with giant aneurysms, or chronic kidney disease, may be an indication for intensification of lipid-lowering treatment.[74] Eliciting a positive family of early CVD, especially among first-degree relatives,[64,68,69] is important for planning therapy.

Subclinical atherosclerosis imaging, using CIMT and assessment of CAC by CT scanning,[53,75] has been used in research settings to determine the presence of early atherosclerosis in children with FH; however, its practical value remains to be established. There are significant limitations to using subclinical atherosclerosis imaging to monitor treatment in clinical practice.[55] Measurement of CIMT requires special expertise.[76] The recently reported standardized reference intervals for common CIMT[63] excluded children.

There are also no accepted thresholds for defining the presence and progression of atherosclerosis in children by CIMT. CIMT measurements are highly age-dependent and poorly reproducible in young children, making assessment of change difficult.[75] Assessment of CAC is not recommended because it may be absent in early atherosclerosis due to cholesterol-rich plaques, does not regularly develop until mature adulthood, and repeat CT scans increase the exposure to radiation.[55]

Cascade screening: risk notification of families

The most cost-effective approach for detecting new cases of FH is family cascade screening of close relatives of a diagnosed index case via the use of a phenotypic or genotypic strategy.[5,6,8,77,78] Diagnostic testing based on a pathogenic mutation is more accurate, however, than using the phenotype alone.[79] If a DNA testing service is not available, cascade screening should be carried out using age-, gender-, and country-specific plasma LDL-cholesterol levels alone.[71] Because of higher pretest probability, clinical diagnostic tools for index cases should not be used for relatives. The drawing of a family pedigree can be valuable in planning the screening process.[6,8,33] Cascade screening should start with first-degree relatives (ie, parents, siblings, off-spring) and then be extended to second- and third-degree relatives.[6,8,33]

Risk notification

Risk notification underpins cascade screening.[6,8,80] Risk notification informs relatives of their risk of FH, the implications for their health, and the availability of clinical and/or genetic testing. Fundamental ethical precepts regarding autonomy, beneficence, and justice must be followed.

Contacting and informing families

Cascade screening should begin by contacting first- and then second-degree relatives, who then become probands for risk notification of their own relatives.[6,8,81] The index case should discuss family risk notification with the clinician or nurse, who will construct a family pedigree and identify relatives who should be offered testing for FH.[6,8,33] Relatives may be approached either by the index case, the clinical service, or by both.[6,8,80] Dual-risk notification may be the best option. Genetic counselors must be involved when sensitive family issues are identified.[6,8,33]

Index cases should be provided with written information that clearly explains the diagnostic testing process and implications and be encouraged to give this to their relatives.[6,8,33] Information sent to relatives should be written in general language to avoid alarm and concern while emphasizing the voluntary nature of testing[8,80] and the