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

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Elevated LDL cholesterol

Liver with dysfunctional or no LDL receptors

Mutations in LDL receptor, apolipoproteinB or PCSK9

Atherosclerosis

Myocardial infarction

Coronary heart disease

Nordestgaard et al Eur Heart J 2013
Seven Issues with FH

1. Under-recognised prevalence
2. Under-detected
3. Under-diagnosed
4. Under-treated
5. Lack of awareness
6. Suboptimal therapies
7. Lack of co-ordinated care
Anatomy of Guidance

Detection of Index Cases

Organization of Care

Apheresis
New therapies

Diagnosis

Assessment

Management

Cascade Screening

Genetic Testing

Elements of Guidance
Detection of Index Cases: Screening Options

• Targeted screening
  • Adults with premature CVD, primarily CHD and a personal and/or family history of hypercholesterolaemia

• Opportunistic screening
  • Adults and children in primary care, based on age- and gender-specific plasma LDL cholesterol levels

• Universal screening
  • Based on age- and gender-specific plasma LDL cholesterol prior to age 20 years and ideally before puberty
Detection of Index Cases: Phenotypic Diagnosis

- Country-specific clinical tools for adults
  - Dutch Lipid Clinic Network Criteria
  - Simon Broome Criteria
  - MED-PED Criteria
  - Japanese FH Criteria
- Adjust for effect of acute illness and concurrent use of statins on LDL cholesterol levels
- All patients with suspected FH should be referred to a clinic specialising in lipidology and/or metabolic disorders for further assessment
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature coronary and/or vascular disease (men aged &lt;55 years, women aged &lt;60 years) OR with known LDL-cholesterol above the 95th percentile for age and gender</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged &lt;18 years with LDL-cholesterol above the 95th percentile for age and gender</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with premature coronary artery disease (men aged &lt;55 years, women aged &lt;60 years)</td>
<td>2</td>
</tr>
<tr>
<td>Patients with premature cerebral or peripheral vascular disease (men aged &lt;55 years, women aged &lt;60 years)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis before 45 years of age</td>
<td>4</td>
</tr>
<tr>
<td><strong>Blood Test</strong></td>
<td></td>
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<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>Score</td>
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<tr>
<td>LDL-C ≥8.5</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 6.5–8.4</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 5.0–6.4</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 4.0–4.9</td>
<td>1</td>
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**Diagnosis**

- **Definite FH**: >8
- **Probable FH**: 6-8
- **Possible FH**: 3-5
- **Unlikely FH**: <3
Adults: Diagnosis and Assessment

- Exclude secondary causes of hypercholesterolaemia
- Phenotypic and/or genetic testing
- Genetic testing increases diagnostic accuracy
- Assess additional CVD risk factors
  - Hypertension, diabetes, obesity, smoking
  - Lipoprotein(a)
  - Level and duration of untreated LDL cholesterol
  - Prematurity of the family & personal history of CVD
  - Framingham and other CVD risk equations should not be used
Adults: Diagnosis and Assessment

• Presence of additional CVD risk factors should guide the intensity of management

• Cardiovascular imaging may be useful for assessing asymptomatic patients
  • Cardiac computed tomography
  • Carotid ultrasonography
  • Clinical value of imaging not fully established
FH detection in Oxfordshire

Demonstrates significant under-diagnosis in young

Children: Screening and Diagnosis

- Children with xanthomata or other physical findings of homozygous FH should be screened as early as 2 years of age.
- Children with suspected heterozygous FH should be screened between the ages of 5 and 10 years.
- Children may be genetically tested for FH after a pathogenic variant has been identified in parent or first-degree relative.
Children: Screening and Diagnosis

- Use age-, gender- and country- specific plasma LDL cholesterol concentration thresholds for phenotypic diagnosis
  - LDL cholesterol > **5.0** mmol/L indicates high probability of FH in absence of available parental history of hypercholesterolaemia or premature CHD
  - LDL cholesterol > **4.0** mmol/L indicates high probability of FH in presence of parental history of hypercholesterolaemia or premature CHD
Family Cascade Screening

Systematic search for affected individuals in the family of index case

<table>
<thead>
<tr>
<th>Relation</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st degree</td>
<td>50%</td>
</tr>
<tr>
<td>2nd degree</td>
<td>25%</td>
</tr>
<tr>
<td>3rd degree</td>
<td>12.5%</td>
</tr>
<tr>
<td>General Population</td>
<td>0.2 % or 1 in 500</td>
</tr>
</tbody>
</table>

Screening principle
1 FH patient → >4 new FH
Cascade Screening: Risk Notification of Families

• Notification of relatives at risk of FH should generally not be carried out without the consent of the index case
  • Follow specific legislation on possible breach of confidentiality
  • Adopt a proactive approach that respects the principles of privacy, justice and autonomy
  • Offer pre-testing counselling to family members of index case prior to any form of testing
• Cascade screening should ideally be co-ordinated using a centralized system
Cascade Screening

- Carried out initially in first-degree relatives
  - LDL cholesterol and/or genetic testing
  - Use age-, gender- and country- specific LDL cholesterol levels
  - Extend to second- and third- degree relatives
- Genetic testing makes cascade screening more cost-effective
  - Employ to screen family members after mutation identified in the index case
- Diagnostic tools for index cases should not be used
Genetics of FH

Genes:
- LDLRAP1
- PCSK9
- APOB
- LDLR

Chromosomes:
- Chr 1
- Chr 2
- Chr 19
Genetic Testing

- Offer ideally to all index cases who have a phenotypic diagnosis of FH
- Genetic testing must be carried out in an accredited laboratory
- If genetic testing detects a variant, its pathogenic significance needs to be assessed
- If genetic testing does not detect a variant, FH cannot be excluded, particularly if clinical phenotype is strongly suggestive of FH
Treatment Options

- Heart healthy diet
- **Drugs**: Statins, Ezetimibe
- Lipoprotein Apheresis
- **New therapies**: Biologics, MTPIs
Cumulative LDL-C (mmol)

Homozygous FH

Heterozygous FH

Threshold for CHD

Without FH

Adults: Management

• All adult patients should receive advice on lifestyle modifications and on correcting all non-cholesterol risk factors

• Therapy should ideally aim for at least 50% reduction in plasma LDL cholesterol, followed by
  • LDL cholesterol < 2.5 mmol/L (no CVD or other risk factors)
  • LDL cholesterol < 1.8 mmol/L (with CVD or other risk factors)
Adults: Management

- Achieving targets requires a fat-modified, heart-healthy diet, and statin therapy with or without ezetimibe.
- Drug combinations, including bile acid sequestrants, niacin, probucol or fibrates, may be required with more intensive strategies to further reduce LDL cholesterol.
- Monitor hepatic aminotransferases, creatine kinase, glucose and creatinine.
Adults: Management

• All women of child-bearing age should receive pre-pregnancy counselling
  • Appropriate advice on contraception before starting a statin
• Statins and other systemically absorbed lipid regulating drugs should be discontinued 3 months before conception, as well as during pregnancy and lactation
• Menopausal hormone therapy should be avoided in women
Why new therapies?

• LDL-cholesterol targets not achieved with standard therapies
• High residual risk on statins
• Statin intolerance (myopathy)
• Radical therapies impracticable
New Therapies for LDL-C

- ApoB Antisense Oligos
- MTT Protein Inhibitors
- PCSK Type 9 Inhibitors
PCSK9 monoclonal antibody ALIROCUMAB: LDL-C reduction on top of STATIN

LDL-C mean (±SE) % change from baseline

Baseline  Week 2  Week 4  Week 6  Week 8  Week 10  Week 12

-80  -70  -60  -50  -40  -30  -20  -10  0

Δ -5.1%

Δ -72.4%

Δ -43.2%

Baseline Week 2 Week 4 Week 6 Week 8 Week 10 Week 12

McKenney JM et al. J Am Coll Cardiol 2012;59:2344
Lomitapide and Mipomersen should be considered as adjunctive treatments to diet and cholesterol lowering drugs in adults with homozygous FH.

Experience with these agents in patients on lipoprotein apheresis is limited.
Children: Management

- Fat-modified, heart-healthy diet
- Consider statins at age 8 to 10 years, ideally before age of 18 years
- Boys and girls should generally be treated at similar ages
- Age 8 to 10 years:
  - Proven FH and LDL cholesterol > 4.0 mmol/l on two occasions
  - Aim for LDL cholesterol < 4.0 mmol/L with low-dose monotherapy
- After age 10 years:
  - Proven FH and LDL cholesterol > 3.5 mmol/l on two occasions
  - Aim for LDL cholesterol < 3.5 mmol/L, with the addition of ezetimibe or a bile acid sequestrant if required
Children: Management

• Statin employed should be:
  • Licensed for clinical use in this age group in specific countries
  • Prescribed according to clinical requirements
• Higher doses of potent statins may be required in homozygotes
• Monitor weight, growth, physical and sexual development, and well-being
• Monitor hepatic aminotransferases, creatine kinase, glucose and creatinine
• All adolescent girls should receive pre-pregnancy counselling, with appropriate advice on contraception before starting a statin
Lipoprotein Apheresis
**Lipoprotein Apheresis**

- Lipoprotein apheresis (LA) should be considered in all patients with homozygous or compound heterozygous FH.
- LA should be considered in patients with heterozygous FH with CHD who cannot achieve LDL cholesterol targets despite maximal drug therapy.
- LA should be considered in children with homozygous FH by the age of 5 and no later than 8 years.
Lipoprotein Apheresis

- Diet and drug therapy to lower LDL cholesterol should be continued during treatment with LA
- Efficacy, tolerability and safety must be regularly reviewed
- Atherosclerosis should be monitored with echocardiography, carotid ultrasonography and exercise stress testing
Liver Transplantation

- Orthotopic liver transplantation should be considered for younger patients with homozygous FH who cannot tolerate lipoprotein apheresis and drug treatment
Organization of Care for FH

Specialist & Primary Care Physicians, Physicians-in-training.
Training, Credentialing, Professional development

Structured Clinical Management Program
Shared between specialist clinics and primary care

Audit & Research Program
Registry, Clinical & basic Science, Clinical trials, Epidemiology & Health Economics

Structured Education Program
For community and health providers, multidisciplinary case conferences, journal clubs, accreditation

Patient & Family Support Group
Consultation, Education, Advocacy

Cardiac & Imaging Facilities
Stress testing, Ultrasonography, Echocardiography, Cardiac CT Scanning

Clinical Liaison
Cardiology, Cardiac Rehabilitation, Cardiothoracic Surgery, Stroke unit, Vascular Surgery

Medical Laboratory Services
Routine and Specialising in lipids and lipoproteins

Specialised Laboratory for Genetic Testing
Service and research

Specialist Nurses & Allied Health Support
Pharmacy / Medication support, Nutrition, Psychology, Exercise, Lay counselling, Training & Professional Development

Administrative, Secretarial & Information Technology Services
Support for Clinics, Outreach services and FH Registry

Influencers & Stakeholders
Department of Health, Policy Makers, Health Networks, Atherosclerosis Association, Family Support Group, National Heart Foundation

Specialised Adult-Paediatric Service
Family Clinics

Clinical Genetics, Family & Genetic Counselling
Defined clinical pathways
Organization of Care

• Care pathways should be developed for country-specific and local needs

• Specialist services should be multidisciplinary based and integrated with primary care:
  
  • Cardiology
  • Paediatric
  • Genetics
  • Imaging
  • Transfusion Medicine
  • Nursing
  • Dietetics
  • Psychology
  • Pharmacy
  • Pathology
Cascade screening should ideally be centrally co-ordinated

Low complexity patients should be managed in primary care, with the option of annual specialist review

Higher complexity patients should be managed principally in specialist centres

Medical, nursing and allied health staff should be accredited in cardiovascular prevention
Organization of Care

- Services should establish **partnerships** with academic and professional organisations to enhance teaching, training and research.
- A **registry** of patients and families should be established for clinical, research and audit purposes.
- A **support group** of patients and families should be established in all countries as a major priority for enhancing public, government and health care provider awareness, as well as for improving the total quality of care.
Conclusion

• The guidance needs to be complemented by judicious clinical judgment and adjusted for national and local needs
• Clinical trials are needed to close evidence gaps
• Future developments need to evolve within the framework of the Chronic Care Model
• This will entail effective establishment of partnerships with a wide spectrum of stakeholders:
  • Patient support groups
  • Public participants
  • Heart foundations and related non-Government organizations
  • Universities and academic centres
  • Health economists
  • Policy makers
  • Government ministers
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Process

• Workshops at the International Atherosclerosis Society (Sydney 2012).

• Workshop moderators identified and collated consensus, based on published research, clinical experience, common themes, expert opinion and other international guidelines.

• Questionnaire on contentious issues in FH completed by all members of the group and a selected group of 26 international experts.

• Satellite workshops, arranged by IFH Foundation, at the European Atherosclerosis Society (Milan, 2012; Lyon, 2013) and the World Congress of Clinical Lipidology (Budapest, 2012).

• Levels of evidence and gradings for recommendations based on previous consensus, published literature and expert opinion.

• Writing committee reached full consensus on recommendations, which were then approved by all contributors.

• Guidance endorsed by the National Lipid Association (August 2013).
Familial Hypercholesterolaemia

• The most common dominantly inherited disorder
• Low-density lipoprotein (LDL) cholesterol levels are markedly elevated from birth
• FH is most frequently due to mutations in genes affecting the LDL receptor that clears LDL particles from plasma
Familial Hypercholesterolaemia

- FH accelerates atherosclerotic cardiovascular disease, especially coronary heart disease
- Clinical manifestations often occurring after one to four decades of life
- There are probably more than 20 million people with FH worldwide
# Typical Features of FH

<table>
<thead>
<tr>
<th>Heterozygous FH</th>
<th>Homozygous FH</th>
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<tbody>
<tr>
<td>Cholesterol 7.0-14 mmol/L</td>
<td>Cholesterol 10-28 mmol/L</td>
</tr>
<tr>
<td>One major genetic defect in LDL metabolism</td>
<td>Two major genetic defects in LDL metabolism</td>
</tr>
<tr>
<td>Arcus cornealis and Achilles tendon xanthomas often present</td>
<td>Tendon and cutaneous xanthomas often before age 10 years</td>
</tr>
<tr>
<td>CHD onset 30-60 years</td>
<td>CHD onset in childhood</td>
</tr>
<tr>
<td>Most respond to drugs, but individual response variable</td>
<td>Poorly responsive to drugs; apheresis often indicated</td>
</tr>
</tbody>
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