Familial Hypercholesterolaemia

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NICE guidelines for identifying FH

Simon Broome Criteria
• Diagnose a person with **definite FH** if they have:
  – cholesterol concentrations as defined below and tendon xanthomas, or evidence of these signs in a first- or second-degree relative.
  – or DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

• Diagnose a person with **possible FH** if they have cholesterol concentrations as defined in table below and at least one of the following:
  – Family history of myocardial infarction (MI): <50 years in second-degree relative or <60 years in first-degree relative.
  – Family history of raised total cholesterol in first- or second-degree relative as per table below.

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<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL cholesterol</th>
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<tr>
<td><strong>Under 16</strong></td>
<td>&gt; 6.7 mmol/L</td>
<td>&gt; 4.0 mmol/L</td>
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<tr>
<td><strong>Adults</strong></td>
<td>&gt; 7.5 mmol/L</td>
<td>&gt; 4.9 mmol/L</td>
</tr>
</tbody>
</table>
Familial hypercholesterolaemia

- 1 in 500 (possibly 1 in 250)
- Autosomal dominant
- LDL receptor defect (chromosome 19)

- Higher incidence in some populations
- Afrikaaners; Quebecois; Lebanese (1%)
FH: typical pedigree

MI age 45
TC = ?

MI @ 55
TC = 10 mM; LDL-C = 8 mM

MI age 45
TC = ?

Age = 10
TC = ?

Age = 11
TC = 7.0 mM
LDL-C = 4.7 mM

Age 11
TC = 7.0 mM
LDL-C = 4.7 mM

Age 35
TC = 7.5 mM
LDL-C = 5.0 mM

Changing epidemiology
• CVD ↓ 40% since 1980
• Population LDL-C falling
• Xanthomata disappearing

FH: typical pedigree

Age = 43
TC = 8.0 mM
LDL-C = 5.2 mM

Age 35
TC = 7.5 mM
LDL-C = 5.0 mM

Age 43
TC = 8.0 mM
LDL-C = 5.2 mM
Genetics of Familial Hypercholesterolemia

**Major Defect**
- Low density lipoprotein receptor (LDLR)
  - More than 1000 mutations known
    - 85% point mutation; 5% insertion-deletion; 10% splicing

**Minor defects**
- Familial defective apoB\textsubscript{100}
  - Defect of ligand not receptor
  - 1 in 20,000
  - Less severe phenotype
- PCSK-9 mutations
  - Controller of LDLR expression
  - Gain of function = FH phenocopy
  - 1 in 40,000
- Recessive FH (LRAP)
  - A variety of defects- best known in Sardinia
  - 1 in 10\textsuperscript{6}
  - Mild phenotype
Homozygous FH

- Rare: 1 in $10^6$
- TC > 16mmol/L
- Signs:
  - Tendon xanthomata, tuberose xanthomata, arcus
- Poor statin response (0-30% $\Delta$LDL)
  - As less residual LDLR function
- Life expectancy (untreated) = 33 years
  - CHD common by age 20
- Treatment
  - Drug therapy
  - Apheresis
  - Liver transplantation
Homozygous Familial Hypercholesterolaemia (FH)

Clinical characterisation:
- Childhood extreme LDL-C
- Premature atherosclerosis
- Increased risk of CHD
- Xanthomas
  - Tuberose xanthomata (skin)
  - Tendon xanthomata

Homozygous Familial Hypercholesterolaemia (FH)

Genetic Basis:
- Co-dominant trait with a gene dosage effect
- 10-40% “HoFH” patients have ‘no’ LDLR/APOB mutations
- Likely new loci on exome sequencing
- Role of miRNAs possible

Tendon xanthomas in homozygous FH - pathognomic = finger web xanthomata
Identifying Heterozygous FH:

- <25% cases identified.

- There are other causes of premature myocardial infarction / raised LDL-cholesterol.
  - 9p21 CHD locus
  - Post-menopause LDL-C rise
  - High CHO diets/ excess alcohol lead to raised LDL-C

- Overlap with ‘normal’ population.
  - 12% UK population have FHx CHD
    - 2-3% have CHD <65 years old.
    - 2-15% UK population have cholesterol >7.5 mmol/L.

- Prevalence of tendon xanthoma / CHD falling.
Heterozygous Familial Hypercholesterolaemia

• Presentation
  – TC > 7.5 mmol/L LDL > 4.7 mmol/L

• Physical signs
  – tendon xanthomata (30%)
  – arcus

• CHD age range 20-75 (highly variable)
  – Clinical diagnostic criterion :
    • CHD < age 60yrs
Clinical signs of FH
FH: tendon xanthomata & risk

Study
Schrott (1972) x
Heath (1989) x
Bertolino (2000) x
Garcés (2000) x
Neil (2003) x
Dedoussis (2004) x
Civeira (2005) x
Humphries (2006) x
van Aalst-Cohen (2006) x
Firth (2006) x

Mean in patients with x:
Mean in patients without x:
FH screening by lipid cut-offs

Population lipid distribution

FH detection by cohorts

Futema M et al; Athero 2015; 239: 295
LDL-C distributions in FH and the general population

A

Proportion of cohort

LDL-C (mmol/L)

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10 10.5

B

Proportion of cohort

LDL-C (mmol/L)

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10 10.5

### Inputs for FAMCAT

- Highest TC or LDL-C
- Age
- TG
- Drug therapies
  - Type; class, dose
- Family history
  - FH
  - MI
  - Lipids
- DM
- CKD

### ROC curves for FH tools

Area Under ROC (c-statistic)

- Model 1: 0.56
- Model 2: 0.75
- Model 3: 0.74
- Model 4: 0.86

TC > 7.5
SB
Dutch
FAMCAT
FH: additional stratifying markers

- Presence of tendon xanthomata
- Absolute LDL-C level
  - Best definition with TC > 9.3 (LDL-C > 7mmol/L)
- Severity of family history of CHD
- GP database screening
  - FAMCAT risk scoring*
- Lipoprotein (a) > 50mg/dL
  - Familial Atherosclerosis Trial
- Imaging atherosclerosis
  - Carotid intima-media thickness
  - Coronary artery calcium score

*Weng SF et al; Atherosclerosis 2015; 238; 336
What Is Carotid Intima Media Thickness (CIMT)?

Mean CIMT 1.174 mm
cIMT in FH and controls
## FH: CACS and medical history of CHD

### Coronary heart disease

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<tr>
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<th>Yes</th>
<th>No</th>
<th>P &lt;</th>
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<tr>
<td>Numbers</td>
<td>24</td>
<td>56</td>
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<tr>
<td>Age (years)</td>
<td>55.3 (11.7)</td>
<td>38.8 (10.6)</td>
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<tr>
<td>U-cholesterol (mmol L^{-1})</td>
<td>10.2 (2.2)</td>
<td>9.7 (2.1)</td>
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<td>T-cholesterol (mmol L^{-1})</td>
<td>7.3 (2.1)</td>
<td>8.3 (1.8)</td>
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<td>BMI (kg m^{-2})</td>
<td>25.6 (3.3)</td>
<td>24.5 (5.7)</td>
<td>0.06</td>
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<td>CC (mm^3 year^{-1})</td>
<td>50.3 (101.1)</td>
<td>3.1 (6.2)</td>
<td>0.001</td>
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<td>AC (mm^3 year^{-1})</td>
<td>46.2 (46.3)</td>
<td>11.7 (22.9)</td>
<td>0.001</td>
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<td>Sex (% male)</td>
<td>62.5</td>
<td>44.6</td>
<td>0.15</td>
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<td>Hypertension (%)</td>
<td>12.5</td>
<td>5.4</td>
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<td>Smoking (%)</td>
<td>83.3</td>
<td>53.5</td>
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### Diagram

- **Coronary calcification (log transformed)** vs **Age (years)**

- Correlation observed between coronary calcification and age.

- Linear trend indicated, suggesting age is a significant factor in coronary calcification.
Changing mortality of CHD in the last century

Based on Stallones RA; Sci Am 243; (11) 43
Sijbrands EJG et al; BMJ 2001; 322: 1019
FH Treatment

• Statin
  – Regression of carotid IMT at TC < 6mmol/L (ASAP study)

• Cholesterol absorption inhibitor
  – ezetimibe

• Resin/bile acid sequestrant
  – cholestyramine

• Apheresis
NICE FH Guideline (CG71) - Treatment

- Potent Statin preferred
- Reduce LCL-C > 50% from baseline
  - non-FH: CVD (+)
    - atorvastatin 80mg (approx LDL-C 2mmol/L)
  - non-FH: CVD (-)
    - CVD risk > 10%/decade then atorvastatin 20mg
- Ezetimibe combination with Statin (TA 132)
- Intolerance/Contraindication to statins
  - consider any statin dose, ezetimibe or a fibrate
ASAP: cIMT in Familial Hypercholesterolaemia
Primary endpoint

LDL-C
-51%
P = 0.002

LDL-C
-41%

+0.036
P = 0.0005

p_d = 0.0001

Smilde TJ et al; Lancet 2001; 357: 577–81
Treatment of familial hypercholesterolaemia

Cumulative event-free survival (%) vs Follow-up (years)

- Statin treatment
- No statin treatment

N=2164

Vermissen J et al. BMJ 2008; 337 a2423
Effects of PSCK-9 inhibition on LDL-C & apoB

- PSCK-9 function
  - Down-regulate LDLR
- PSCK-9 inhibitors
  - Small molecule
  - Antibody
    - alirocumab; evolocumab; bococizumab:
      - LDL-C ↓ 17-65%
  - Antisense
    - ISIS-BMS PCSK-9; SPC-5001

Stein EA et al; Lancet 2012; 380 : 29
Family Screening

• Arrange to review all direct family members

• Screen for family mutation
  – Check LDL-C in relatives

• Enter second degree relatives into wider family screening programme
Cut-offs for FH screening in families

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<tr>
<th>Age</th>
<th>0 To 14</th>
<th>15 To 24</th>
<th>25 To 34</th>
<th>35 To 44</th>
<th>45 To 54</th>
<th>55 and Older</th>
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Starr BA et al; CCLM 2008; 46: 791-803
The phenotype matters: FH mutations and normocholesterolaemia

Huijgen R et al; Circ CV Genet 2011; 4: 413

<table>
<thead>
<tr>
<th></th>
<th>No-FH Group (n=145)</th>
<th>FH-Low Group (n=114)</th>
<th>FH-High Group (n=162)</th>
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</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>69 (48)</td>
<td>52 (46)</td>
<td>68 (42)</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.3±8.7</td>
<td>37.5±8.5</td>
<td>35.2±8.7</td>
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<tr>
<td>Hypertension</td>
<td>14 (10)</td>
<td>8 (7)</td>
<td>10 (6)</td>
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<tr>
<td>Diabetes</td>
<td>1 (1)</td>
<td>...</td>
<td>1 (1)</td>
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<tr>
<td>Smoker ever</td>
<td>73 (50)</td>
<td>51 (45)</td>
<td>66 (41)</td>
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<tr>
<td>Statin use§</td>
<td>5 (3)</td>
<td>25 (22)</td>
<td>111 (69)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>25.7±4.2</td>
<td>25.6±5.1</td>
<td>25.0±4.4</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128±14</td>
<td>124±12</td>
<td>124±13</td>
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<td>Lipid profile, mmol/L</td>
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<td>At molecular screening</td>
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<tr>
<td>LDL-C</td>
<td>3.2±1.0</td>
<td>2.9±0.7</td>
<td>5.2±1.0</td>
</tr>
<tr>
<td>pLDL</td>
<td>40 (21–68)</td>
<td>47 (21–64)</td>
<td>97 (95–98)</td>
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<tr>
<td>At study visit</td>
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<tr>
<td>TC</td>
<td>5.3±1.1</td>
<td>5.3±1.1</td>
<td>6.0±1.5</td>
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<tr>
<td>LDL-C</td>
<td>3.4±1.0</td>
<td>3.4±1.0</td>
<td>4.1±1.4</td>
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<tr>
<td>HDL-C</td>
<td>1.5±0.4</td>
<td>1.4±0.4</td>
<td>1.4±0.4</td>
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<tr>
<td>Triglycerides</td>
<td>0.9 (0.7–1.4)</td>
<td>0.7 (0.5–1.2)</td>
<td>0.7 (0.5–1.1)</td>
</tr>
</tbody>
</table>

![Image showing mean carotid IMT (95% CI) with p-values for comparison between groups.](image)
Conclusions

• Screening will find patients with genetic hyperlipidaemias
• FH is at least 1 in 500 UK population
• Family (cascade) screening required
• Statin treatment for FH irrespective of calculated CVD risk
• Combination therapy often needed to reduce LDL-C >50%.