EAS Consensus Paper

Familial Hypercholesterolaemia in Children and Adolescents: Identifying and Treating Early to Prevent Premature Heart Disease

Slide set adapted from:
http://dx.doi.org/10.1093/eurheartj/ehv157
Prevention

Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment

Key points about Familial Hypercholesterolaemia (FH)

- One of the most common genetic disorders, affecting 1:200 to 1:250 people
- Inherited in an autosomal dominant manner
- Disabling at a young age and shortens life expectancy.

- Consider Homozygous FH if:
  - LDL-C levels >13 mmol/L (500 mg/dL)
  - Tendon xanthomas in the hands and Achilles tendons
  - Evidence of premature cardiovascular disease, aortic valve disease

- A psychological challenge for families because of the inherited nature of the disorder, the lack of early symptoms in HeFH, and the need for long term lifestyle changes and pharmacologic therapy.
What is familial hypercholesterolaemia?
About FH

FH is an autosomal dominant disorder

- The most common FH-causing mutations are in the gene coding for the LDL receptor \((LDLR)\). There are >1500 documented mutations in the \(LDLR\) gene.
- Less common mutations involve \(APOB\) and \(PCSK9\)
- Rarely, mutations in \(LDLRAP1\) lead to recessive FH
FH and atherosclerosis

- FH is an asymptomatic condition. Accumulation of LDL-C in the plasma results in accelerated atherogenesis. If undiagnosed, this leads to premature coronary events, typically in early middle age.

- The relative risk for a fatal coronary event in a young adult with FH aged 20-39 years is 80-100 fold greater than age-matched controls.

- In general, the severity of atherosclerosis is proportional to the extent and duration of elevated LDL-C – the “Cholesterol -Year- Score”.

Schmidt HH et al. Am J Cardiol 1996;77:575-80
How common is familial hypercholesterolaemia?
FH Prevalence

- Heterozygous FH affects about 1 in 200-250 people
- World-wide nearly 35 million people have FH

FH Prevalence

- FH affects about 5 in every 1,000 births
- Worldwide one baby is born with FH each minute
Why we need to identify and treat FH early
Carotid IMT: A marker of early atherogenesis in FH children

Significant difference from 7.5 years

Difference in mean carotid IMT and 95% confidence interval between FH children and unaffected siblings

Early detection is critical

• Early detection of FH and early initiation of lifestyle and pharmacological treatment is imperative to reduce the life-long burden of elevated LDL-C levels
LDL-C burden in untreated FH children

Early statin treatment delays LDL-C burden

Impact of early statin treatment on event-free survival

Cumulative event-free survival (%)

Key
- FH children
- FH parents

p = 0.02

How to diagnose FH in children
Family History + Hypercholesterolemia = FH in Children*

- Cholesterol testing should be used to make a phenotypic diagnosis
  - 5 mmol/L (190 mg/dL), 2 successive occasions over 3 months
  - 4 mmol/L (160 mg/dL) AND family history of premature CVD ± baseline high cholesterol in one parent
  - 3.5 mmol/L (130 mgdL) AND positive genetic diagnosis in the family
- Rule out secondary causes (thyroid, liver or renal dysfunction, concomitant medication, obesity)
- Genetic testing confirms the diagnosis (after parental testing)

*FH Foundation
Diagnostic algorithm for FH in children & adolescents

High cholesterol in a child

- LDL-C >4 mmol/L via:
  - screening from age 5 years
  - premature CHD in parent
  - cascade screening

Parent with pathogenic FH mutation

- Test child on DNA and LDL-C
  - Child has mutation
    - Definite FH
      - Re-test LDL-C every 12 months
        - LDL-C >3.5 mmol/L
          - Clinical management (see Table 4)
        - LDL-C >5 mmol/L
          - Highly probable FH
            - Lifestyle management and re-testing if LDL-C >3 mmol/L
              - LDL-C >4 mmol/L and parent has premature CHD or high LDL-C
                - Re-test child on LDL-C
                  - Yes
                  - No
              - No
            - Yes
            - No
          - Yes
          - No
        - No
      - No
    - No
  - No
- Lifestyle management and re-testing if LDL-C >3 mmol/L
  - No

High cholesterol in a parent

- Reasons for testing parent:
  - physical signs/symptoms
  - premature CHD in relative
  - cascade screening

Parent with pathogenic FH mutation

- Test child on DNA and LDL-C
  - Child has mutation
    - Definite FH
      - Re-test LDL-C every 12 months
        - LDL-C >3.5 mmol/L
          - Clinical management (see Table 4)
        - LDL-C >5 mmol/L
          - Highly probable FH
            - Lifestyle management and re-testing if LDL-C >3 mmol/L
              - LDL-C >4 mmol/L and parent has premature CHD or high LDL-C
                - Re-test child on LDL-C
                  - Yes
                  - No
              - No
            - Yes
            - No
          - Yes
          - No
        - No
      - No
    - No
  - No
- Lifestyle management and re-testing if LDL-C >3 mmol/L
  - No

Wiegman A et al. Eur Heart J 2015 Epub ahead of print
Consider Homozygous FH

Clinical evidence of:

- Premature cardiovascular disease
- Corneal Arcus
- Xanthelasma
- Tendon xanthomas in the hands and Achilles tendons
The importance of FH screening
Screening for FH in children and adolescents

- Despite the importance of early detection, FH remains under-diagnosed.

- Cascade screening of families is the most cost-effective strategy to increase FH diagnosis and treatment.

- A genotypic strategy is recommended if DNA testing is available.

- If DNA testing is not available, a phenotypic strategy based on country, age and gender-specific low-density lipoprotein cholesterol (LDL-C) levels should be used.
Screening for FH in children & adolescents

• Suspected heterozygous FH: Screen from age 5 years

• Suspected homozygous FH: Screen if clinically suspected (both parents affected or xanthoma present) as early as possible

• Age at screening should be similar for boys and girls
Treating FH children
Diet and risk factor control

- Assess cardiovascular risk factors including lipoprotein (a)
- No smoking
- Encourage exercise
- Diet
  - <30% of calories from fat
  - <7% of calories from saturated fat
  - <200mg cholesterol/day
  - Appropriate energy for normal growth and sufficient in micronutrients

Early initiation of lifestyle is essential for ensuring long-term adherence.
Risk factors: What is lipoprotein(a)?

- An LDL-like plasma lipoprotein BUT with an additional protein, apolipoprotein(a)
- Apo(a) comprises a series of loop structures called kringles. Kringle IV type 2 has from 2 to >40 copies
- Elevated Lp(a) ->50 mg/dL (80th percentile) is a cardiovascular risk factor
- FH is associated with elevated Lp(a)

KIV-2 copy Number variant: 2 to >40 repeats

When to start a statin?

Heterozygous FH:
• Generally, at age 8-10 years (depending on local prescribing information)
• Earlier if considered at very high risk
  - family history of very premature coronary artery disease (30s-40s)
  - diabetes
  - organ transplantation
  - multiple coronary risk factors
• Stronger statins may need to be introduced after puberty in the case of severe mutations

Homozygous FH: At diagnosis
LDL-C Targets in children with FH

8-10 years:
Aim for 50% reduction in LDL-C from pre-treatment level

≥10 years:
<3.5 mmol/L (130 mg/dL) especially if there are additional cardiovascular risk factors, including elevated lipoprotein(a)

Adding ezetimibe or a bile-acid sequestrant may be needed to attain LDL-C goal
Homozygous FH

- Children with homozygous FH should be referred to and cared for at a specialised centre
Monitoring FH children
Monitoring treatment in FH children & adolescents

- Monitor weight, growth, physical and sexual development, and well-being
- Measure hepatic aminotransferases at least every 3 months if there is a history of liver disease. Monitor more frequently if levels increase >3-fold x ULN.
- Measure plasma CK levels if musculoskeletal symptoms are reported.
- Measure fasting plasma glucose and/or random HbA1c every 6 months in children on higher doses of statins who are obese or have impaired glucose tolerance.
Safety: liver & muscle

<table>
<thead>
<tr>
<th></th>
<th>FH n=194</th>
<th>Sibling n=83</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspartate aminotransferase – IU/I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>25.0 (22.0-30.0)</td>
<td>26.0 (22.0-30.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>&gt; 3x ULN – no. (%)</td>
<td>1 (0.5%)</td>
<td>1 (1.1%)</td>
<td>0.55</td>
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<tr>
<td><strong>Alanine aminotransferase – IU/I</strong></td>
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<tr>
<td>Median (IQR)</td>
<td>18.0 (13.0-25.0)</td>
<td>17.0 (13.0-24.0)</td>
<td>0.63</td>
</tr>
<tr>
<td>&gt; 3x ULN – no. (%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0.51</td>
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<tr>
<td><strong>Creatine kinase – IU/I</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (IQR)</td>
<td>101.0 (72-150)</td>
<td>101.0 (82.0-161.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>&gt; 10x ULN – no. (%)</td>
<td>0 (0.0%)</td>
<td>2 (2.1%)</td>
<td>0.03</td>
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Safety: growth/development

• Growth

<table>
<thead>
<tr>
<th></th>
<th>FH n=194</th>
<th>Sibling n=83</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height – m</td>
<td>1.74 ± 0.1</td>
<td>1.76 ± 0.09</td>
<td>0.27</td>
</tr>
<tr>
<td>Weight – kg</td>
<td>74.2 ± 14.8</td>
<td>73.8 ± 12.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>24.4 ± 4.8</td>
<td>23.9 ± 3.9</td>
<td>0.36</td>
</tr>
</tbody>
</table>

• Menarche: 13.1 vs 13.2 years, P=0.72
Special issues: adherence

• Check adherence if heterozygous FH children fail to achieve LDL-C targets with combination lipid-lowering treatment.

• Consider referral of non-adherent patients to a dedicated, multidisciplinary clinic
Special issues in adolescent girls with FH

Contraception
• Preferred contraceptive measures: low oestrogen oral agents, intra-uterine devices and barrier methods
• Monitor lipids after starting oral contraceptives

Pregnancy
• Counselling is recommended for all women considering pregnancy due to the risk for FH
• Statins should be discontinued: Bile-acid resins are the only safe agents for use in pregnancy and breast-feeding
Better education about FH a priority

Norwegian Registry data
• 118 FH patients, treated with statin from age 8-10 years in trials
• 72% (48 of 67 consented) continued on statin
• Only 9% participants had LDL-C ≤ 2.5 mmol/L

Implications
• Statins are severely underused in young adult FH patients.
• Better education of patients and frequent (yearly) consultations therefore seem warranted.
Conclusions

• World-wide, one baby is born with FH every minute

• Identifying and treating children with FH is the key to gaining decades of healthy normal life and making premature coronary heart disease history

• Better awareness and education are essential to achieving this
About lipoprotein(a)
What is lipoprotein(a)?

• An LDL-like cholesterol-rich particle which differs from LDL as it contains an additional protein, apolipoprotein(a).
• Apo(a) comprises a series of loop structures called kringles. Kringle IV type 2 has from 2 to >40 copies
Plasma Lp(a) levels in general population

20% have plasma Lp(a) levels >50 mg/dL

Nordestgaard BG et al. Eur Heart J 2010;31:2844-53
Lp(a) and cardiovascular risk: Epidemiological evidence

- Copenhagen General Population Study:
- people with Lp(a) > 50 mg/dL had 2-3-fold increased risk for MI

<table>
<thead>
<tr>
<th>Percentile</th>
<th>mg/dL</th>
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<tbody>
<tr>
<td>&gt;95th</td>
<td>&gt;117</td>
</tr>
<tr>
<td>90th-95th</td>
<td>77-117</td>
</tr>
<tr>
<td>67th-89th</td>
<td>30-76</td>
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<tr>
<td>22nd-66th</td>
<td>5-29</td>
</tr>
<tr>
<td>&lt;22nd [Reference]</td>
<td>&lt;5</td>
</tr>
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</table>

Multivariable Adjusted

HR (95% CI)

Lp(a) and cardiovascular risk: Epidemiological evidence

- Emerging Risk Factors Collaboration:
  Each 1 standard deviation increase in Lp(a) increased CHD risk by 13%
Lp(a) and cardiovascular risk: Genetic evidence

- Decreasing quartiles of kringle IV type 2 repeats were associated with increasing plasma Lp(a) levels and increased MI risk

![Graph showing the relationship between Lipoprotein(a) levels and KIV-2 quartile with hazard ratios and 95% CIs.](image)

Kamstrup PR et al. JAMA 2009;301:2331-9
Lp(a) and cardiovascular risk: Genetic evidence

- Plasma Lp(a) levels and CHD risk increases with ≥1 variant alleles of the LPA gene

Risk increases with ≥1 alleles for an LPA genotype

Clarke R et al. NEJM 2009; 361:2518-28
Lp(a) and FH

- CHD more prevalent in heterozygous FH patients with Lp(a) >40 mg/dL
- Frequency of variant LPA allele ~2.5-fold higher in FH patients with CHD than in those without

CHD more prevalent in heterozygous FH patients with Lp(a) >40 mg/dL

Seed M et al NEJM 1990;322:1494-9
Lp(a) and FH

- Retrospective cohort study of 2400 patients with heterozygous FH
- Lp(a) >30 mg/dL was associated with 1.5-fold increase in CVD risk

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate (n = 1956)</th>
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<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>P value</td>
<td>RR</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.95</td>
<td>2.54–3.43</td>
<td>&lt;0.00001</td>
<td>2.82</td>
</tr>
<tr>
<td>Smoking (time dependent</td>
<td>1.79</td>
<td>1.55–2.08</td>
<td>&lt;0.00001</td>
<td>1.67</td>
</tr>
<tr>
<td>Hypertension (time</td>
<td>1.42</td>
<td>1.15–1.75</td>
<td>0.001</td>
<td>1.36</td>
</tr>
<tr>
<td>Diabetes (time dependent)</td>
<td>1.96</td>
<td>1.28–3.01</td>
<td>0.002</td>
<td>2.19</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.01</td>
<td>–</td>
</tr>
<tr>
<td>HDL risk (males &lt;0.9</td>
<td>1.36</td>
<td>1.15–1.62</td>
<td>0.00004</td>
<td>1.37</td>
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<tr>
<td>Triglycerides (mmol L⁻¹)</td>
<td>1.12</td>
<td>1.05–1.20</td>
<td>0.001</td>
<td>–</td>
</tr>
<tr>
<td>Lp(a) risk (&gt;300 mg L⁻¹)</td>
<td>1.46</td>
<td>1.23–1.73</td>
<td>&lt;0.00001</td>
<td>1.50</td>
</tr>
<tr>
<td>Homocysteine risk (&gt;15</td>
<td>1.57</td>
<td>1.24–1.99</td>
<td>0.0002</td>
<td>–</td>
</tr>
</tbody>
</table>

* n = 1698.
Lipoprotein(a) as a cardiovascular risk factor: current status

Børge G. Nordestgaard¹*, M. John Chapman², Kausik Ray³, Jan Borén⁴, Felicita Andreotti⁵, Gerald F. Watts⁶, Henry Ginsberg⁷, Pierre Amarenco⁸, Alberico Catapano⁹, Olivier S. Descamps¹⁰, Edward Fisher¹¹, Petri T. Kovanen¹², Jan Albert Kuivenhoven¹³, Philippe Lesnik², Luis Masana¹⁴, Zeljko Reiner¹⁵, Marja-Riitta Taskinen¹⁶, Lale Tokgözoglù¹⁷, and Anne Tybjærg-Hansen¹⁸, for the European Atherosclerosis Society Consensus Panel¹

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