Pediatric Familial Hypercholesterolemia

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The Life Course of FH

Fetal exposures

RF Exposures:
- Environmental
- Familial
- Lifestyle

NORMAL NEWBORN

GENETIC INPUT

CHILDREN AT RISK

INTERMEDIATE OUTCOMES:
- Atherosclerosis
- Subclinical atherosclerosis
- End organ injury

Lifestyle Interventions

Pharmacologic Interventions

ADULTS AT RISK

CLINICAL CARDIOVASCULAR DISEASE OUTCOMES:
- Morbidity
- Mortality
- Quality of Life
Atherosclerosis: A Progressive Process

Endothelial dysfunction and plaque progression due to risk factor exposure

Blood levels of inflammatory markers (e.g., CRP)

Clinically silent
10 20 30 40 50

Increasing age

Unstable Angina
MI
Coronary Death
Stroke
Critical Leg Ischemia

Effort Angina or Claudication

Plaque Rupture/Fissure & Thrombosis

Occlusive Atherosclerotic Plaque

Fibrous Plaque

Fatty Streak

Normal
Atherosclerosis Begins in Late Childhood in FH

Difference in mean carotid IMT and 95% confidence interval between FH children and unaffected siblings plotted versus age, adjusted for family relations.
## Diagnosing FH

<table>
<thead>
<tr>
<th>ICD-10, proposed</th>
<th>Clinical Diagnosis</th>
<th>Genotype diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHx of FH</td>
<td>Any LDL-C; 1° relative with FH</td>
<td>Not obtained</td>
</tr>
</tbody>
</table>
| HeFH             | Child: LDL-C ≥ 160 mg/dl  
Adult: > 190 mg/dl  
and 1° relative with FH or early MI  
or gene positive | Presence of one abnormal LDL-C raising (LDL receptor, apo B or PCSK9) gene defect  
*Lower LDL-C may be present in CASCADE setting; higher LDL-C than 400 mg/dl can occur* |
| HoFH             | LDL-C > 400 mg/dl; one or both parents  
a) having clinically diagnosed FH, b) + gene test for an LDL-C raising (LDL receptor, apo B or PCSK9) gene defect  
or c) ARH | Presence of two identical (true HoFH) or non-identical (compound HeFH) abnormal LDL-C raising (LDL receptor, apo B or PCSK9) gene defects; includes the rare autosomal recessive type (ARH)  
*HoFH can have LDL-C < 400 mg/dl; sitosterolemia, other causes excluded* |
| FH, unspecified  | Severely elevated LDL-C | Genotype data do not support above classifications (gene negative, LDL-C/genotype discordance) |

*Gidding et al, Circ, 2015*
Causes of Familial Hypercholesterolemia
Screening for FH

• Universal at age 9-11 years
  • School-based
  • Office measurement vs lab measurement
  • Trigger reverse cascade

• Cascade

• EMR/IT strategies
  • Labs flag elevated LDL-C as consistent with FH
  • Data mining
  • Find FH sponsored by FH Foundation
Universal versus selective screening: testing current NCEP guidelines

20266 Subjects (5th grade with LDL tested and reported Family History)

14468 Met NCEP Screening Guidelines (71.4%)

1204 LDL ≥ 130 (8.3%)

170 Warrant Pharmacologic Tx (LDL ≥ 160) (14.1%)

1034 Do Not Warrant Pharmacologic Tx (85.9%)

13264 LDL < 130 (91.7%)

5798 Did Not Meet NCEP Screening Guidelines (28.6%)

548 LDL ≥ 130 (9.5%)

98 Warrant Pharmacologic Tx (LDL > 160) (17.9%)

450 Do Not Warrant Pharmacologic Tx (82.1%)

5250 LDL < 130 (90.5%)

Ritchie S K et al. Pediatrics 2010;126:260-265
©2010 by American Academy of Pediatrics
FH Screening: modeling

Morris JK et al; Am J Med Genet 2011; 158A: 78
Childhood is the Best Age To Identify FH

Fig 1 Plots of detection rates against false positive rates for total and LDL cholesterol concentrations according to age in years.
Reverse CASCADE Screening by Genotyping

• Identify children with FH
  • LDL cholesterol can be used to discriminate those with FH and those without in childhood
• Identify first degree family members with high LDL cholesterol
• Genotype the parents
• Yield: 4/1000 children and 4/1000 first degree family members (Wald, NEJM, 2016)
Total Cholesterol Levels in Children with and Children without an FH48 Mutation.

The Rationale for Genetic Testing

• Provides a definitive molecular diagnosis of FH
• Provides prognostic and risk stratification information
• Facilitates family-based cascade testing
• Allows for precision during genetic counseling
• Has value to the pediatric patient population with FH
• Personal utility
• Minimal psychological impact
Who should genetic testing be offered to?

**TABLE 2 Recommendations and Considerations for Genetic Testing for FH**

A. Proband (index case)

Genetic testing should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following:

1. Children with persistent* LDL-C levels ≥160 mg/dl or adults with persistent* LDL-C levels ≥190 mg/dl without an apparent secondary cause of hypercholesterolemia† and with at least 1 first-degree relative similarly affected or with premature CAD‡ or where family history is not available (e.g., adoption)

2. Children with persistent* LDL-C levels ≥190 mg/dl or adults with persistent* LDL-C levels ≥250 mg/dl without an apparent secondary cause of hypercholesterolemia,† even in the absence of a positive family history

Evidence Grade: Class of Recommendation IIa, Strength of Evidence B-NR

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Sturm A, JACC, 2018

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*Persistent elevated levels for ≥1 year
†At least 1 first-degree relative similarly affected
‡Premature CAD before age 55 years
BARRIERS TO IMPLEMENTING CHOLESTEROL SCREENING

- FH awareness
- MD
  - Belief in preventing early atherogenesis
  - Time/skill/reimbursement
- Family
  - Competing health issues
  - Education
  - Financial resources
  - Privacy concerns
- Society
  - Cost, relative importance, publicity, guideline support
MENDELIAN RANDOMIZATION: IMPLICATIONS FOR CHOLESTEROL

- Genetic variation identifies risk status
  - Low frequency, high impact
  - High frequency, small effect
- Provides rationale for benefit of lifelong low LDL cholesterol levels
  - 50% risk reduction per mmol/DL (40 mg/dl) of LDL-C
- Overcomes limitations of observational studies providing more precise risk estimates (measurement variability, confounding from social variables)
- Consistent with clinical trial data suggesting greater effect with longer LDL lowering interventions
- NNT of 2 for pediatric treatment and LDL-c > 5.0 mmol/L
Plot of PCSK9 scores and individual PCSK9 polymorphisms on LDL-C and CHD risk

From Brian Ference with permission
Treatment: 150 cholesterol-years

Nordestgaard BG et al. EHJ 2013; in press
FH Outcomes Improved with Statins
Younger people benefit the most

Fig 2 Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

Versmissen J, BMJ, 2008
Significant reductions in coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study.

Neil et al Eur Heart J 2008

<table>
<thead>
<tr>
<th>Attained age (years)</th>
<th>Person-years observation</th>
<th>1 January 1980 to 31 December 1991</th>
<th>1 January 1992 to 31 December 2006</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>SMR</td>
</tr>
<tr>
<td>Primary prevention</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>2031</td>
<td>3</td>
<td>0.08</td>
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<tr>
<td>40–59</td>
<td>2181</td>
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<td>20–79</td>
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<td>6.05</td>
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<tr>
<td>Secondary prevention</td>
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<tr>
<td>20–39</td>
<td>178</td>
<td>5</td>
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<tr>
<td>40–59</td>
<td>1016</td>
<td>9</td>
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<tr>
<td>60–79</td>
<td>539</td>
<td>11</td>
<td>3.24</td>
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<tr>
<td>20–79</td>
<td>1733</td>
<td>25</td>
<td>4.83</td>
</tr>
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</table>
Ultimate Modifier of FH – Early Lifelong Treatment
Natural History of FH
Additional Findings

- Achieved LDL-c (4.16, FH vs 3.15, siblings)
- Mortality (0/203 FH patients vs. 11/156 parents)
- No major adverse events or side effects
- DM: 1/184 patients vs 2/77 siblings
- CIMT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow Up</th>
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<tbody>
<tr>
<td>Patients</td>
<td>0.446</td>
<td>0.555 (0.532 if at goal)</td>
</tr>
<tr>
<td>Siblings</td>
<td>0.439</td>
<td>0.551</td>
</tr>
</tbody>
</table>

Luirink et al, NEJM
FH in the 2018 AHA/ACC Lipid Guideline

- Treat severe primary hypercholesterolemia LDL-C ≥ 190 mg/dl with a high intensity statin (no risk calculation, begin at 8-10 years of age); for adults goal < 100 mg/dl, for children goal not specified
  - Use ezetimibe to get to goal, can add PCSK9 in certain settings
- Measure Lp(a) for further risk stratification
  (elevated > 50 mg/dl or 125 nmol/L)
- FH is a high risk condition in those with prior ASCVD and severe elevation of LDL-C is a risk enhancing factor
- Universal lipid screening at age 9-11 years; high risk screening beginning at age 2 years (low evidence grade)
Diet, Exercise, and other Risk Factors

• Diet/lifestyle management are important
  • Reduce saturated fat, < 7%
    • About 25-30% of calories from fat
    • Avoid trans fat
  • High soluble fiber: 10-20g/day
• Dietician referral
• Regular exercise
• Aggressively treat other risk factors
  • Hypertension, Diabetes, Metabolic Syndrome, Overweight/Obesity, Smoking, Inactivity, Lp(a)
CHOLESTEROL INTAKE

[Graph showing cholesterol intake over time with usual care and intervention groups.]
DIET
ADDITIONAL FACTORS

- 2 servings of fatty fish/week
- Increase dietary fiber through fruit, vegetable, legume, and whole grain consumption
- Plant sterols/stanols
- Reduce salt intake
- Moderate exercise 1 hour/day
SELECTING PATIENTS FOR DRUG THERAPY: CLINICAL FACTORS

- LDL cholesterol ≥ 190 mg/dl (or ≥ 160 mg/dl with multiple risk)
- Age/gender
- Family’s prior experience
- Safety
- Compliance
- Goal of therapy
Fig. 14. Rationale for the use of a bile acid–binding resin and an inhibitor of HMG CoA reductase in the treatment of FH heterozygotes.
- Lower cholesterol at least 20%
- Safe, well tolerated; risk associated with age (> 60) and use of multiple medications
- Work by inhibiting intrahepatic cholesterol synthesis
- Starting dose 10 mg/day
- Monitor liver function
AVAILABLE STATINS
TREATMENT GOAL
50% REDUCTION IN LDL OR TARGET OF 130 MG/DL

- Lovastatin
- Pravastatin
- Simvastatin
- Atorvastatin
- Fluvastatin
- Rosuvastatin
- Pitavastatin
MONITORING STATIN THERAPY

- Follow cholesterol levels
- Liver function tests
- History of muscle pain
- Discontinue during pregnancy
EZETIMIBE
BILE ACID METABOLISM INHIBITORS

- Lower cholesterol 40 mg/dl/dose
- Resins have GI side effects, poorly tolerated
- Resins safe, not systemically absorbed
- Bile acid reabsorption inhibitors have been used in children but limited trial data
- Main role: achieve LDL-c reduction in severely affected or statin intolerant patients
**Figure 2.** Mean IMT Changes From Baseline for the Different Carotid Arterial Wall Segments in the Pravastatin and Placebo Groups

<table>
<thead>
<tr>
<th>Segment</th>
<th>Pravastatin (n=104)</th>
<th>Placebo (n=107)</th>
</tr>
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<tbody>
<tr>
<td>Common Carotid Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid Bulb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Carotid Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Combined Carotid IMT</td>
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</tbody>
</table>

IMT indicates intima-media thickness. Error bars indicate SE. P values for the difference between the 2 groups in change from baseline were calculated using analysis of covariance adjusted for baseline values.
The Goal of FH Care