Distinguishing FH from non-FH: Right therapy, right patient, right time

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Disclosures

- Role as CMA of the *FH Foundation* is not compensated.
  - [www.thefhfoundation.org](http://www.thefhfoundation.org)

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- The FH Foundation receives support from many pharmaceutical and lab testing companies with an interest in FH
FH is caused by mutations in genes responsible for LDL-C metabolism and is common and devastating.

- Most common highly morbid genetic condition
  - Affects ~1:250
- Causes 2-4% of early onset MI
  - ~10,000/year
  - Untreated, 50% of men have MI by age 50
- Cost $100s of millions


Rodriguez and Knowles, Circulation 2016
Perak et al., Circulation, 2016
Gupta et al. JACC, 2014
Hopkins et al. J. Clinical Lipidology. 2011
Goldberg et al. J. Clinical Lipidology. 2011
A snapshot of FH in the US:
CASCADE FH™ Registry
FH disproportionately affects the risk of premature CAD

~40 lipid clinics in US
~4500 patients
* Avg untreated LDL-C ~ 230 mg/dl

Avg age FH diagnosis

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6040a1.htm

Current guidance from ACC/AHA focused on severe hypercholesterolemia (ie LDL-C > 190 mg/dl) to guide decision making.
CHD events in the FH “phenotype” (i.e. LDL-C > 190 mg/dl)

< 5% of adults with LDL-C > 190 mg/dl actually have mutation on genetic testing
What could we gain (or lose) by diagnosing FH based on more than LDL-C > 190 mg/dl alone?
Lifelong exposure to high LDL causes early onset coronary disease.
Lipid panels are not great at classification or risk prediction

- Compared to those with LDL<130 the OR for CAD is:
  - 22 fold if LDL>190 and FH mutation
  - 6 fold if LDL>190 but no FH mutation

Khera et al. JACC 2016
Genetic testing does give more precision at the cost of sensitivity.
FH variants reflect lifelong LDL-C burden

A

B

Noura S. Abul-Husn et al. Science 2016;354:aaf7000
Genotype is partly responsible for phenotypic heterogeneity

Noura S. Abul-Husn et al. Science 2016;354:aaf7000

Khera et al. JACC 2016
Classically defined “FH phenotype” can also be polygenic

<table>
<thead>
<tr>
<th>UK patients with familial hypercholesterolaemia</th>
<th>WHII controls (n=3020)</th>
</tr>
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<tbody>
<tr>
<td>FH with no known mutation (n=321)</td>
<td>FH with known mutation (n=319)</td>
</tr>
<tr>
<td>Men</td>
<td>73/156 (46.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.9 (13.9) (n=320)</td>
</tr>
<tr>
<td>Pretreatment total cholesterol (mmol/L)</td>
<td>7.6 (1.7) (n=266)</td>
</tr>
<tr>
<td>Pretreatment LDL-C (mmol/L)</td>
<td>233 mg/dl</td>
</tr>
<tr>
<td>Post-treatment LDL-C (mmol/L)</td>
<td>4.22 (1.58) (n=136)</td>
</tr>
<tr>
<td>Post-treatment HDL-C (mmol/L)</td>
<td>1.42 (0.34) (n=67)</td>
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</tbody>
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Interpretation: In a substantial proportion of patients with familial hypercholesterolaemia without a known mutation, their raised LDL-C concentrations might have a polygenic cause, which could compromise the efficiency of cascade testing. In patients with a detected mutation, a substantial polygenic contribution might add to the variable penetrance of the disease.

Table 1: Basic characteristics of UK participants

Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study

Philippe Szczesniak, Sonia Shrief, Ria Whiting, Martha Fajas, Philip Howard, Jackie A Cooper, Suzanne C. Manson, Adilah L. Fotheringham, Frederick Kaye, St Andrew M Hend, Oliver S Després, Claudius Langenberg, Natalie Leach, Mika Komulainen, John W Huttner, Dean O'Higgins, Memes Komori, Steve E Humphries
FH is a winnable battle: 
The epitome of personalized prevention for patients and families
Early and aggressive treatment saves lives

- Beginning statins in high risk FH children can “bend the curve” towards normal
LDL-C lowering in FH: Consequences for CAD & mortality

- 44% RR reduction CAD and mortality in statin users vs never users.
- Number needed to treat (NNT) of 222 for 1 year of statin therapy to prevent a *death* in FH patients.
  - In non-FH primary prevention patients NNT: 500
  - In non-FH secondary prevention in non-FH patients NNT: 350

Hard for FH patients to get to optimal LDL-C levels

- ~ 40% achieve LDL-C < 130 mg/dl
- ~ 20% achieve LDL-C < 100 mg/dl
- Statin intolerance is a problem
- Non-statin drugs (ezetimibe, PCSK9i) are standard of care

Cannon, C et al. NEJM 2015
Sabatine, M et al. NEJM 2017
Preferred pharmacotherapy formulary.

- **Initial drug monotherapy**
- **Two-drug Combination**
- **Three-drug Combination**
- **Complex-therapy Combination**

**High-intensity Statin Therapy (>50% LDL-C reduction)**
- Rosuvastatin or atorvastatin

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to two-drug combination
- Rosuvastatin or Atorvastatin
- Ezetimibe

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to three-drug combination
- Rosuvastatin or Atorvastatin
- Ezetimibe
- PCSK9 inhibitors
- Colesevelam or other bile acid sequestrant
- Niacin

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to complex-therapy combination
- Consider four-drug combination† and LDL Apheresis

† Consideration of four-drug combination should be based on individual patient factors and potential for drug interactions.
Most PCSK9i prescriptions are denied in FH and ASCVD
How do we move to more effective cascade based screening approaches?
Dutch national program has been spectacularly successful

- By 2012 found 5,151 index cases of genetically positive FH
- Resulted in screening of 60,000 family members
- In total 27,069 FH cases identified
- Costs for identifying 1 FH patient: €1200
- Costs effectiveness: costs per life year saved: €8700 *
  - Need updated CE analyses with dramatic decrease in FH genetic testing and generic statins, ezetimibe

Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing

Child–Parent FH Screening in Primary Care

- Child–parent screening was feasible in primary care practices at routine child immunization visits.

- For every 1000 children screened, 8 persons (4 children and 4 parents) were identified with FH and were consequently at high risk for CVD.
E78.01: FAMILIAL HYPERCHOLESTEROLEMIA

Z83.42: Family history of familial hypercholesterolemia

EFFECTIVE OCTOBER 1, 2016

ICD-10 CODE

APPROVED
Thank you!