Familial Hypercholesterolemia

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The importance of familial hypercholesterolemia

- Familial hypercholesterolemia (FH) is an inherited genetic disorder causing high cholesterol concentrations and increased risk of premature cardiovascular disease.
- Lifetime exposure to high LDL levels, essentially from birth
- Untreated, FH leads to substantial CVD risk in men and women, with early onset of cardiovascular disease
- Not rare but under-diagnosed
- Treatable but undertreated
- Early diagnosis and treatment mitigate the excess CVD risk
**Definition of Familial Hypercholesterolemia**

- Autosomal co-dominant high LDL
  - Most families have only heterozygotes
- Gene dosage effect
  - Homozygotes (or compound heterozygotes) have much higher LDL-C and much earlier CAD onset (childhood and adolescence) than heterozygotes
- Autosomal recessive hypercholesterolemia — very rare, homozygotes for LDL receptor adaptor protein
- FH is not usually associated with extreme hypertriglyceridemia

**Genetics of FH**

- Genetic causes lead to impaired LDL receptor function and decreased LDL removal
  - ½ LDL catabolic rate → 2-fold or greater increase in LDL
- LDLR mutations (most common—85-90% of cases)—→900 known, most pathogenic
- APOB mutations (impair LDL receptor binding)
  - Also called familial defective apo B
- PCSK9 (proprotein convertase subtilisin-like / kexin type 9) gain of function mutations—rare
  - Note: Loss of function leads to lifelong low levels and decreased CVD risk


**Mutations**

- LDLR
  - Missense, nonsense, insertions, deletions spread throughout LDLR affecting number and function
- ApoB
  - Most common is in the area around apoB3500, which affects binding of LDL to the LDL receptor
- PCSK9
  - Gain of function leads to increased PCSK9 causing increased degradation of LDL receptors
- LDLRAP1
  - Facilitates the interaction between the LDL receptor and the cell machinery regulating the endocytic process, LDLR-LDL complex internalization impaired

Cuchel M et al. Eur Heart J 2014;eurheartj.ehu274
Proteins affecting low-density lipoprotein receptor function

Prevalence of FH
- Common “single gene” disease
- Heterozygous FH
  - 1 in 200 to 500 people
  - 1 in 100 in French Canadian, S. African, others
- Homozygous FH
  - 1 in 250,000 to 1 million people (more common in some groups)
- Over 12 million FH patients worldwide
- United States, from 620,000 to 1.5 million people with FH

FH prevalence based on recent genetic studies
- Historically homozygous FH 1 in 1 million and heterozygous FH 1 in 500
- With genetic testing in a central laboratory in the Netherlands, homozygous FH estimated prevalence 1 in 300,000
- In Denmark, genetic testing of clinically defined cases, heterozygous FH 1 in 200
Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolemia

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

Familial Hypercholesterolemia

- Autosomal co-dominant high LDL
- Heterozygotes: untreated LDL-C 155 to 500 mg/dL
  - Premature CAD
- Homozygotes often have untreated LDL-C >500 mg/dL
  - CAD typically onset in childhood and adolescence
  - Insufficient response to usual lipid lowering medication, even in combination
  - Pre 1990: average age at death 18.4 years, age at first cardiac event 12.8
  - Post 1990: average age at death 32.9 years, age first event 28.3 years

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
FH Increases Risk of Premature CVD

- Mean age of onset of cardiovascular events in men with heterozygous FH is early 40s; women early 50s
- Although <5% of acute MIs occur in persons ≤40 yrs of age, the presence of the familial hypercholesterolemia phenotype is associated with a 20-fold increase in risk of MI by age 40

Non-Fatal CAD in FH (Utah) vs. General U.S. Population
Diagnosis of FH

- Suspect FH at these LDL cholesterol levels:
  - LDL-C ≥250 mg/dL in a patient aged 30 or more
  - LDL-C ≥220 mg/dL for patients aged 20 to 29
  - LDL-C ≥190 mg/dL in patients under age 20
- Obtain further family history
- Rule out secondary causes: hypothyroidism, nephrotic syndrome

Heterozygous FH: physical findings

Not all patients have physical findings

Corneal arcus: not specific for FH but suspect FH with both upper and lower arcs before age 40
Estimated per cent of individuals diagnosed with FH as a fraction of those predicted, based on a frequency of 1/500

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
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Cascade Screening

- Cascade screening: testing lipid levels in all first-degree relatives of diagnosed FH patients.
- Cost-effective means to find FH
- Infrequently performed in a clinical setting
- High yield
  - 50% have FH among 1st degree relatives
  - 25% among 2nd degree relatives
  - 12.5% among 3rd degree relatives
  - 0.02% in general population
- Within a known FH pedigree, LDL-C alone is 90-95% sensitive and specific versus genetic testing.
- Goal: find younger FH patients and prevent CAD

Hopkins PN et al. J Clin Lipidol 2011; 5 (3 Suppl.):S9–S17

FH Screening: finding the first case in a family and then finding more cases

- Universal cholesterol screening is recommended
  - All adults should be screened by age 20
  - All children by age 9-11 (family history alone misses cases)
  - Consider screening beginning at age 2 for children with a family history of premature cardiovascular disease or elevated cholesterol
- Cascade screening if FH suspected
  - Lipid panel on all first degree relatives of patient with LDL-C > 190 mg/dl


Pedigree of a family with familial hypercholesterolemia.

Nordestgaard BG et al. Eur Heart J 2013;eurheartj.037733© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology.
**Rationale for treatment of FH in adults**

- No outcomes trials specifically in FH patients
- West of Scotland (mostly primary prevention) and 4S (secondary prevention) enriched with FH patients
- Very high lifetime risk of CHD
- Very high risk of premature onset CHD.
- Early treatment is highly beneficial.
  - Long-term statin treatment largely ameliorates excess CVD risk due to FH
  - Risk of long-term statin-treated FH patients = Risk of general population
- FH requires lifelong treatment and regular follow-up.

Robinson JG, Goldberg AC. J Clinical Lipidol 2011 5:S18-29
Versmissen J et al BMJ 2008; 337: a2423

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**Risk stratification algorithms should not be used in FH patients**

- Individuals with FH are at high short and long-term CHD risk.
  - 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools
  - 10-year assessment of risk is NOT recommended.
- All FH patients require treatment regardless of 10-year CHD risk
  - Lifestyle management
  - Most will require lipid-lowering drug therapy.

Robinson JG, Goldberg A. J Clinical Lipidol 2011 5:S18-29
Drug therapy required for almost all* FH patients

- Drug therapy required for children and adults if (after lifestyle changes):
  - LDL-C ≥ 190 mg/dL OR
  - Non-HDL-C ≥ 220 mg/dL
- For adult FH patients (≥ 20 years of age), drug treatment to lower LDL-C by at least 50%
- Statins should be the initial treatment for all adults with FH.

* Special considerations in women in child-bearing years: No statins, ezetimibe, or niacin during conception, pregnancy, or lactation

Robinson JG, Goldberg A. J Clinical Lipidol 2011 5:S18-29

Treatment of FH: adults

- Lifestyle changes
  - Decrease saturated fatty acids to ≤ 7% of total energy intake; limit dietary cholesterol < 200 mg/day; add plant stanol/sterols (2 g daily); soluble fiber (10-20 g daily)
  - Physical activity and weight control
- Medications: Moderate to high doses of high-potency statins (atorvastatin, rosuvastatin)
  - Increase statin dose to maximum available or tolerable dose to achieve a LDL-C reduction ≥ 50% from baseline
  - If not achieved, add ezetimibe, bile acid sequestrant, and/or niacin
  - LDL-C decrease: ezetimibe 20%, BAS 20%, niacin 10-20%)
- LDL apheresis
- Homozygous patients: medications, apheresis

Treatment of FH: Children and Adolescents

- LDL ≥ 190 mg/dL or ≥ 160 mg/dL with multiple risk factors, after diet
- Clinical trials with medium term follow up suggest safety and efficacy of statins
- Goal: 50% reduction or LDL-C < 130 mg/dL; need for balance between increased dosing and potential for side effects vs achieving goals
- Consider more aggressive LDL targets for those with additional CVD risk factors
- Ideally, prevent the development of atherosclerosis

Mechanism of Action of Lipid Lowering Therapies

<table>
<thead>
<tr>
<th>Statins</th>
<th>Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit HMG-CoA reductase, the rate limiting step in cholesterol synthesis</td>
<td>Localizes at the brush border of the small intestine and inhibits the absorption of cholesterol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bile Acid Sequestrants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Form non-absorbable complex with bile acid, inhibit enterohepatic reuptake and increase fecal loss of bile salts</td>
<td></td>
</tr>
</tbody>
</table>

All work by increasing expression of LDL receptors

Niacin does not work by up-regulating LDL receptors

Mipomersen and lomitapide decrease production of lipoproteins—not dependent on LDL receptors

Combination therapy is often needed in familial hypercholesterolemia

- Patients with FH are at risk of premature atherosclerotic disease
- Many patients with heterozygous FH do not get adequate LDL cholesterol reduction on high dose statins
- Addition of other risk factors put patients at even higher risk making much greater LDL cholesterol reduction desirable
- Even in homozygous FH aggressive medication therapy can help
- Some patients do not tolerate high dose statin therapy

Homozygous FH

- Therapy begins at diagnosis regardless of age
- Statins, other agents may help but LDL apheresis often necessary
- Cardiovascular disease monitoring critical
- Drugs approved specifically for homozygous FH patients over age 18:
  - Mipomersen—apoB antisense oligonucleotide
  - Lomitapide—microsomal triglyceride transport protein inhibitor
Mipomersen

- Weekly SQ injection
- Homozygous FH > age 18
- Added to other lipid meds
- About 25% decrease LDL-C
- Increased liver fat
- Injection site reactions, fatigue, flu-like symptoms
- Long half-life
- No drug-drug interactions
- Large safety data base
- REMS: liver tests

Lomitapide

- Oral: gradual titration
- Homozygous FH > age 18
- Added to other lipid meds
- Low fat diet (20% fat)
- 40-50% decrease LDL-C
- Increased liver fat
- Approved for use with apheresis
- Diarrhea, GI side effects
- CYP 3A4 interactions
- REMS: liver tests and dose adjustments

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LDL cholesterol burden in individuals with or without FH as a function of the age of initiation of statin therapy.

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.ah273

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Conclusions

- FH is a treatable condition
- It is **underdiagnosed** and **undertreated**
- Earlier recognition and appropriate treatment can decrease the risk of developing CHD
- Screen earlier and screen family members
- Potent statin and often combination therapy
- LDL apheresis for many homozygous and some heterozygous patients
- New therapies available and in development
- All health care providers can help raise awareness of FH in order to save lives
What needs to be done

- Screen for FH and do cascade screening
- Treat early with lifestyle change and medications—**Tobacco use is disastrous!**
- Statins first line to obtain at least 50% reduction of LDL cholesterol; combination therapy when needed
- Teach patients and families about FH (learnyourlipids.com; The FH foundation)
- Educate colleagues
- Be an advocate for patients and their families

Thank you!