Institut für Klinische Chemie
Arnold von Eckardstein

Familial Hypercholesterolemia – What a cardiologist should know
Etiology of Hypercholesterolemia

**monogenic:** (rare):
- e.g. familial hypercholesterolemia

**polygenic, multifactorial** (frequent):
- e.g. diet, drugs, gene-interactions

**monocausally acquired:**
- e.g. cholestasis

**Genes**

**Environment**
## Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>total cholesterol mmol/L (mg/dL)</th>
<th>LDL-Cholesterol mmol/L (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90th percentile, m = f*</td>
<td>7.5 (290)</td>
<td>5.0 (190)</td>
</tr>
<tr>
<td>&gt;95th percentile, m = f*</td>
<td>8.0 (310)</td>
<td>5.5 (210)</td>
</tr>
</tbody>
</table>

### Target values

- **low risk (primary prevention)**: 
  - Total Cholesterol: < 4.1 (< 160)
- **intermediate risk (primary prevention)**: 
  - Total Cholesterol: < 3.4 (< 130)
- **high risk (primary prevention)**: 
  - Total Cholesterol: < 2.6 (< 100)
- **very high risk (primary prevention and secondary prevention)**: 
  - Total Cholesterol: < 1.8 (< 70)

*: rounded numbers of SAPALDIA-study (N > 6000); data for adults of middle age (30 – 70 years); cave much lower percentiles for children, adolescents, and young adults
Differential diagnostics of hypercholesterolemia

Vertically transmitted

Autosomal codominant hypercholesterolemia (familial hypercholesterolemia):
- LDL-receptor
- Familial defective apoB
- Proprotein convertase subtilisin/kexin type 9 (PCSK9)

Not transmitted

Autosomal recessive hypercholesterolemia:
- Autosomal recessive hypercholesterolemia (ARH)
- Sitosterolesemia

Secondary hypercholesterolemia
- Hypothyreoidism
- Cholestasis
- Nephrotic syndrome
- Some drugs
Familial hypercholesterolaemia is more common than other genetic diseases

Pathophysiology of heterozygous familial hypercholesterolemia

- Prevalence 0.2 – 0.5%
- Mutations in LDLR, APOB or PCSK9
- If untreated: premature cardiovascular morbidity and mortality

Nordestgaard B G et al.
Eur Heart J 2013;eurheartj.eht273
Disturbed uptake and degradation of LDL by the LDL-receptor-pathway


The *LDLR* gene

**A**  
*LDLR* gene  
Exon number  
1 2 3 4 5 6 7–10 11 12 13 14 15 16 17 18  
LDLR protein  
Domain  
Signal peptide  
Ligand binding with cys-rich repeats  
EGF precursor-like  
OLS  
TM  
Cytoplasmic  

**B**  
Missense/nonsense mutations per exon/domain  
10 22 32 52 35 68 29 42 29 47 44 38 27 38 26 40 10 7 20 3  

**C**  
Number of known mutations  
Point mutations/minor deletions or insertions  
Major gene rearrangements  

Heterozygosity prevalence:  
1:500 – 1:200  

18 Exons  
>1’000 Mutations  
Ca. 60% missense Mutations  
Ca. 20% small rearrangements  
(1-24 bp)  
Ca. 15% large rearrangements  
(up to 10 kb)  
Ca. 5% splice site mutations

R3500Q Mutation in Apo-B100 Leading to Familial Defective Apolipoprotein B (FDB)

Prevalence of the R3500Q Mutation in Apo-B100
(J Lipid Res. 1994 Apr;35(4):574-83)

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>1 / 500</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1 / 600</td>
</tr>
<tr>
<td>Germany</td>
<td>1 / 700</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1 / 209</td>
</tr>
</tbody>
</table>

Distribution

Cholesterol
## Kriterien für klinische Diagnose der HeFH (LDLR-Defekt)
(Dutch Lipid Clinic Network)

<table>
<thead>
<tr>
<th>Kriterien</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familienanamnese</strong></td>
<td></td>
</tr>
<tr>
<td>Verwandter 1. Grades mit vorzeitiger KHK¹ und/oder Verwandter 1. Grades mit LDL-C &gt; 95. Perzentile nach Alter, Geschlecht und Land</td>
<td>1</td>
</tr>
<tr>
<td>Verwandter 1. Grades mit Sehnenxanthomen und/oder Arcus lipoides corneae und/oder Kinder &lt; 18 J. mit LDL-C &gt; 95. Perzentile nach Alter, Geschlecht und Land</td>
<td>2</td>
</tr>
<tr>
<td><strong>Persönliche Anamnese</strong></td>
<td></td>
</tr>
<tr>
<td>Vorzeitige KHK¹</td>
<td>2</td>
</tr>
<tr>
<td>Vorzeitige cerebrale/periphere Gefäßkrankheit¹</td>
<td>1</td>
</tr>
<tr>
<td><strong>Körperliche Untersuchung</strong></td>
<td></td>
</tr>
<tr>
<td>Sehnenxanthome</td>
<td>6</td>
</tr>
<tr>
<td>Arcus lipoides corneae unter 45 J.</td>
<td>4</td>
</tr>
<tr>
<td><strong>LDL-C (mmol/l)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 8.5</td>
<td>8</td>
</tr>
<tr>
<td>6.5–8.4</td>
<td>5</td>
</tr>
<tr>
<td>5.0–6.4</td>
<td>3</td>
</tr>
<tr>
<td>4.0–4.9</td>
<td>1</td>
</tr>
<tr>
<td><strong>Genetische Tests</strong></td>
<td></td>
</tr>
<tr>
<td>Nachweis kausaler Mutationen für LDLR, APOB oder PCSK9</td>
<td>8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
</tr>
<tr>
<td>Summe der Punktwerte</td>
<td></td>
</tr>
<tr>
<td>Bewertung</td>
<td></td>
</tr>
<tr>
<td>Definitive FH</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Wahrscheinliche FH</td>
<td>6–8</td>
</tr>
<tr>
<td>Mögliche FH</td>
<td>3–5</td>
</tr>
<tr>
<td>Keine Diagnose</td>
<td>&lt; 3</td>
</tr>
</tbody>
</table>

¹ Mann < 55 J., Frau < 60 J.

Prevalence of definitive or probable FH* in a Danish general population according to Dutch Lipid Clinic Networks criteria

Nordestgaard B G et al. Eur Heart J 2013; 34, 3478–3490

N = 69’000
Estimated proportions of diagnosed FH-patients in various countries
Assuming a prevalence of 1/500 in the general population

To be multiplied with 2.5 if the prevalence is 1/200
(40'000 rather than 16'000 affected patients in CH)

Nordestgaard B G et al. Eur Heart J 2013; 34, 3478–3490
EAS-Strategy for diagnostics and treatment of familial hypercholesterolemia (part 1)
Nordestgaard B G et al. Eur Heart J 2013; 34, 3478–3490

Who to screen: index person or family member with
- Familial hypercholesterolaemia (FH)
- Cholesterol ≥8mmol/L (≥310mg/dL) for an adult >95th percentile by age and gender for country
- Cholesterol ≥6mmol/L (≥230mg/dL) for a child >95th percentile by age and gender for country
- Premature coronary heart disease
- Tendon xanthomas
- Sudden premature cardiac death in a family member

Diagnostic and treatment summary:
Familial hypercholesterolaemia

Diagnosis: Use the Dutch Lipid Clinic Network criteria (Table 1). This cannot be used in children.

Exclude other causes of hypercholesterolaemia
Risk assessment: evaluate other cardiovascular risk factors, including elevated Lp(a)

Optional: Screen for asymptomatic atherosclerosis
EAS-Strategy for diagnostics and treatment of familial hypercholesterolemia (part 2)
Nordestgaard B G et al. Eur Heart J 2013; 34, 3478–3490

- **Cascade screen** family using LDL cholesterol levels (draw pedigree as in *Figure 7*)
- If Dutch Lipid Clinic Network criteria (Table 1) score > 5
  - Screen for causative mutation in index case (if DNA test is available in country) *
  - Followed by genetic testing of family if causative mutation is found (genetic cascade screening)
- **Lifestyle modifications**, including smoking cessation and dietary advice—if needed from a certified dietitian
- **Treatment priority**:
  - Children: statin, ezetimibe, and bile acid-binding resin
  - Adults: maximal potent statin dose, ezetimibe, bile acid-binding resin, fibrate, (niacin, novel therapies)
  - Lipoprotein apheresis in homozygotes and in treatment-resistant heterozygotes with coronary heart disease

(*: Swiss health insurances may not reimburse)
Benefit of molecular diagnoses in familial hypercholesterolemia

**Diagnostic benefit:**
- Definitive diagnosis
- Increased likelihood to identify affected relatives (100% instead of 50-80% sensitivity and specificity by screening with LDL-C)
- Targeted life style recommendations especially in children and adolescents (e.g. non smoking)
- Earlier start of lipid lowering therapy

**Prognostic benefit:**
- More effektive reduction of cardiovascular risk by earlier start and stronger intensity of lipid lowering therapy, because cardiovascular risk is a function of LDL-C concentration and exposure time (however only post hoc hypothesis from observational studies, that need validation by controlled intervention studies)
Overlap of clinical and molecular diagnoses in heterozygous Familial Hypercholesterolemia

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
Treatment of Familial Hypercholesterolemia

- **Statins** (Mono- or combination therapy with Ezetimib and/or resins)
- **LDL-Apheresis** (if drug therapy is not sufficiently effective or homozygous FH)
- novel therapies in heterozygous FH
  - PCSK9 Inhibitors (not yet approved)
- novel therapies in homozygous FH
  - MTP Inhibitors
  - (apoB antisense: in Europe not approved)
Kaplan–Meier curves on cumulative CHD-free survival of FH patients according to statin therapy

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

Dutch patients with heterozygous FH with (N = 413) or without (N = 1537) statins
Many High Risk Patients Do Not Attain LDL-C Goals


Patients with high or very high CVD risk

- LDL-C goal < 2.6 mmol/L
  - 23% > goal

- LDL-C goal < 1.8 mmol/L
  - 76% > goal

- LDL-C goal < 2.6 mmol/L
  - ~80% > goal

Heterozygous FH-Patients

23% > goal

76% > goal

~80% > goal
Zusätzliche Senkung von LDL-C und kardiovaskulären Ereignissen durch Ezetimib (Improve-It study, presented at AHA meetings 2014)
Alirocumab Maintained Consistent LDL-C Reductions Over 52 Weeks

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin ± Other LLT

Placebo:  
- FH I
- FH II

Alirocumab:  
- FH I
- FH II

Week

Intent-to-treat (ITT) Analysis
LLT = lipid-lowering therapy

Dose ↑ if LDL-C >70 mg/dL at W8
Most heFH Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

Proportion of patients reaching LDL-C goal† at Week 24

FH I

72.2%

FH II

81.4%

P<0.0001

†Very high-risk: <1.81 mmol/L (70 mg/dL); high-risk: <2.59 mmol/L (100 mg/dL). LLT = lipid-lowering therapy.

Intent-to-treat (ITT) Analysis
Relationship between cumulative LDL-C exposure and age

LDL Cholesterol exposure in individuals with or without FH depending on age and start of statin therapy

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
Key messages

- **suspect FH in patients with ...**
  - very high LDL –cholesterol (> 5 mmol/L)
  - premature arteriosclerotic vessel diseases
  - familial history of premature CHD
  - clinical hallmarks, notably xanthomas

- **search diagnosis in the patients and direct relatives by ...**
  - family history and screening (cascade screening)
  - Molecular testing

- **lower LDL-C early and as much as possible because ...**
  - CHD risk is overproportionately elevated (scores do not apply)
  - CHD risk is a function of LDL-C dosage and exposure time