Familial Hyperlipidemia

- Recognition
- Diagnosis
- Natural history
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Natural History worse than many cancers

- Very aggressive progression of CARDIOVASCULAR disease
- Death by 33 and CV eventS even in childhood and by 20
- Premature diffuse severe atherosclerosis with CV and CCerbrivascular disease events at very early age
- Lack of recognition leads to diagnosis often after event (stroke in young or MI/Sudden death in young)
- Death and events can definitely be impacted by as early as possible treatment that changes the natural he and age at death or first event
The Threshold for Coronary Heart Disease is Reached Earlier in Life in FH Patients

- Coronary heart disease occurs above a theoretical LDL exposure
- This threshold can be lower in men or the presence of additional risk factors such as hypertension, diabetes or smoking
- This threshold can be higher in women
- This threshold is crossed in normal individuals late in life
- HeFH individuals reach this threshold in early middle age, while HoFH individuals do so in childhood
Populations with increased prevalence of homozygous FH:

- French Canadians in northeastern Quebec (Moorjani et al. 1989; Leitersdorf et al. 1990)
- Afrikaners in South Africa (Steyn et al. 1989; Kotze et al. 1991)
- Ashkenazi Jew (AJ) individuals (Seftel et al. 1990; Meiner et al. 1991)
  - Druze (Landsberger et al. 1989)
  - Christian Lebanese (Lehrman et al. 1987)
- Finns (Aalto-Setala et al. 1992; Koivisto et al. 1992) → Mut found in the St. Petersburg region
  - Tunisians (Slimane et al. 1993)

Lithuanian Allele (LDLR mut Cys197Gly)

Christian Lebanese Allele (LDLR mut C681X)
Unmet Medical Need: EEMEA has a high prevalence of severe FH*

Population Palestine and occupied: ~ 8 Mio
23 patients with homozygous FH are described → no registry
No information on He FH, however based on feedback received in the field there must be ‘quite’ a N of patients with very high LDL (>300 mg/dL)
(Feedback from local OLs)

Population Lebanon: ~ 4 Mio
40 patients with homozygous FH* are described (A.C. Fahed et al. MGM 2011)
As a consequence, they estimate a high prevalence of He FH
(A.C. Fahed et al. MGM 2011 → 80 pts are homozygous but only 40 do have the phenotype of FH)

*also named: Autosomal Dominant Hypercholesterolemia (ADH)

Population SA: ~ 50 Mio
120-150 patients with homozygous FH are described → no registry
Estimated N of pts with He FH, 120,000 → probably underreported, in particular in the black population !!
(Feedback from local OLs)
FH, Clinical Sequelae: Coronary Artery Disease & Stroke by Mutation

'Premature CHD'
Lack of recognition is the greatest problem in HOFH

**Figure 1** Estimated per cent of individuals diagnosed with familial hypercholesterolaemia in different countries/territories, as a fraction of those theoretically predicted based on a frequency of 1/500 in the general population. As most countries do not have valid nationwide registries for familial hypercholesterolaemia, several values in this figure represent informed estimates from clinicians/scientists with recognized expertise in and knowledge of familial hypercholesterolaemia in their respective countries. Numbers were provided by Michael Livingston, Steve E. Humphries (UK), Olivier S. Descamps (Belgium).
Hallmarks of the disease

- Very elevated TC and LDL at very early age
- FAMILY history of high LDL (1st and 2nd deg) and/or Early CVD
- Remember that the newborn LDL is 30 mg/dl
- The degree and severity of athreosclerosis and CV events is directly proportional to elevation in LDL
- This is turn is directly related to the severity of the gene abnormality (partial or complete) and total or partial inability to break down and excrete LDL
- CLUES - Finding a very high LDL above 200 or 4.9 is trigger point to start formal evaluation
Phenotype and physical exam

- Patients should be recognized and detected by family screening and lab BEFORE and clinical feature and events occur!
- Lipid profile and family history are universally available and should trigger the specific investigation and advanced CV testing and early treatments
- The higher LDL can die in childhood of CVD
- THE less severe may survive to adolescence but are almost always unrecognized as screening and investigation in adults is not part of Cardiology or IM Resident training as is ignored in the ACC guidelines due to lack of RCTs
Physical Exam

- Xanthomas esp eruptive
- Tendon xanthomas
- Epically Achilles' tendon in young
- Premature corneal arcus
- Aortic stenosis murmur
- Carotid bruit
- Distal pulses
Meticulous Assessment of ASCVD at ANY AGE

- Initial assessment of the patient and periodic reassessment after treatment
- ECHO assess aortic valve thickening and Supravalvular plaque
- Carotid Doppler any plaque is significant
- Cardiac CT assess calcium and with contrast this assess soft plaque in coronary and aorta
- Peripheral artery disease ABI and doppler
- Presence of plaque in any arterial bed established disease profession and risk of plaque rupture
Family History = Family screening

- Identification of family members with very high Ldl
- Screen these family members with CV tests
- Genotyping if available beware of novel mutations
- Treat family members according to severity and target
- Cascade and screening for broader assessment of family members

REGISTRY LOCALLY IS ESSENTIAL
COMMON CRITERIA IN THE RECOGNITION & DIAGNOSIS

HOW TO RECOGNIZE VERY HIGH LDL STATIN AND NON RESPONDER

PATIENT WITH PREMATURE CVD EVENT OR IMAGING

GENETIC TESTING

FAMILY HX OF VERY HIGH HDL

FAMILY MEMBER WITH POSITIVE GENE

PREMATURE CVD
THE NEGLECTED GROUP

Patients ≥21 y of age without heart failure or ESRD
Screen for ASCVD risk factors
Measure LDL-C

Clinical ASCVD
Secondary Prevention
Secondary prevention: moderate- to high-intensity statin therapy; ≥50% reduction in LDL-C

DM (type 1 or 2) and aged 40–75 y and LDL-C 70–189 mg/dL
Primary Prevention

No DM and aged 40–75 y and LDL-C 70–189 mg/dL
Primary Prevention

LDL-C ≥190 mg/dL
Primary Prevention
Primary prevention: high-intensity statin therapy

a 1.8–5.0 mmol/L. b 5.0 mmol/L.
Acute Coronary Syndrome 2013
SKMC UAE vs 450 US Hospitals (same size and same setting)

**Age Groups**

Our patients are 10-15 years younger than the Europe and USA
CEPHEUS GULF STUDY

Objective

To gain a unique perspective on the potential under treatment of hypercholesterolemia in the Gulf

Methodology

9,457 patients were enrolled from consecutive patients who come for a regularly scheduled visit by 177 specialists & PCPs in Bahrain, Oman, Qatar, UAE, KSA & Kuwait. Started November 2009 and ended July 2010.

Results

<table>
<thead>
<tr>
<th>Type of Prevention</th>
<th>(N)</th>
<th>% Patients at Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td>2,242</td>
<td>59%</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>473</td>
<td>33%</td>
</tr>
</tbody>
</table>

1 in 2 Gulf patients is NOT at LDL-C goal


20/10/2017
INterHeart Gulf

- In the states of The Gulf Co-operation Council (GCC), cardiovascular disease (CVD) is the most common cause of death, accounting for up to 45% of all deaths [1]. The INTERHEART study showed that CVD risk factors like dyslipidaemia and smoking were prevalent in young populations in the region with a mean age of the first presentation of acute myocardial infarction (MI) 10 years younger in the Middle East countries than in other regions [2].
Recently, the Gulf Locals with Acute Coronary Syndrome Events Registry (Gulf COAST), including 3,188 regional patients admitted with a diagnosis of acute coronary syndrome (ACS) found that the Gulf ACS population is characterised as young with a very high-risk profile [4]. The projected future burden of CVD in the Middle East is set to exceed that of other global regions [5]. Therefore, conditions that overtly raise cardiovascular (CV) risk are of particular interest in the region, and clinical practice guidelines are needed.
GULF RACE

- The Gulf Registry of Acute Coronary Events (Gulf RACE)-2 study showed that the Middle East also has a poor record with treatment of elderly-at-risk CVD patients, and that adherence to clinical practice guidelines could be much improved [3].
Middle East Prevalence

- Data on the prevalence of HoFH in the Middle East are lacking, and there are no national registries currently collecting data.

- In the past, the overall prevalence of HoFH was estimated to be around 1 in 1 million [6], but recent studies, particularly from The Netherlands, suggest that it may affect as many as 1 in 160,000-300,000 people [9, 10]. For the Middle East, HoFH may have a higher prevalence than in the Western world because consanguineous marriages are more common than in the West [11].
Predictive factors for not achieving LDL target*

EURO CEPHEUS

Poor LDL-c control

- Other therapy than statins
- Familial hypercholesterolemia
- Several drug changes in the past
- Lipid control every 3 months versus once a year
- Patient declaring never to forget drugs

Better LDL-c control

- Other therapy than statins [0.52;0.73]
- Familial hypercholesterolemia [0.35;0.88]
- Several drug changes in the past [0.57;0.85]
- Patient declaring never to forget drugs [1.00;1.73]
- Lipid control every 3 months versus once a year [1.32;1.67]

*Results from the Belgium cohort
Recognize FH Signs and Symptoms

**Index cases** for FH should be identified if the plasma total cholesterol is:
- $\geq 310 \text{ mg/dL (} \geq 8 \text{ mmol/L)}$ in an adult or adult family member(s)
- $\geq 230 \text{ mg/dL (} \geq 6 \text{ mmol/L)}$ in a child or child family member(s)
  (or $>95$th percentile by age and gender for country)

**Obtain clinical history**
- Premature CHD* in the subject
- Positive family history of hypercholesterolemia or premature CHD* in relatives

**Look for physical signs**
- Corneal arcus
- Tendon xanthomas in the subject or family member(s)

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*An index case is defined as an individual with FH from whom the starting point for cascade screening of additional family members should be performed for the diagnosis of further cases of FH. CHD: $<55$ in males and $<60$ in females, in subject and first-degree relatives; $<50$ in men and $<55$ in females, in second-degree relatives. CHD, coronary heart disease.


Components of FH Diagnosis

A diagnosis of FH is multifaceted and can include:¹

• A family history of elevated LDL-C levels and premature CHD
• An individual clinical history of premature CHD
• Systematic physical examination for the presence of tendon and tuberous xanthomas and corneal arcus in individuals <45 years
• Biochemical laboratory results showing repeated measurements of very high LDL-C levels
  • Molecular genetic testing to determine the presence of a known causal mutation
  • The absence of a known mutation does not exclude FH

Further considerations:

• Presence of hypertriglyceridemia does not exclude the diagnosis of FH²
• Secondary causes of hypercholesterolemia should be investigated and excluded¹,²
  • Determine liver enzymes, renal function and thyroid hormones are normal¹
  • Rule out hyperglycemia and albuminuria¹
• Patients should be assessed to evaluate other CV risk factors including elevated Lp(a)²
• Imaging techniques (electro- and echocardiography, CCS, CT angiography, IVUS) can be used to highlight asymptomatic atherosclerosis¹,³,⁴
• Cascade screening (LDL-C and genetic testing) can identify previously undiagnosed family members with FH¹,²

A formal clinical diagnosis of FH can be determined with a validated set of criteria: Simon Broome, US MEDPED, DLCN

Risk of CAD is Increased in FH Patients\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Statin Type</th>
<th>Statin Status</th>
<th>No. of Participants</th>
<th>No. of CADs</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely FH</td>
<td>Off</td>
<td>58,158</td>
<td>2592</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>On</td>
<td>6061</td>
<td>1884</td>
<td>5.6 (5.2–6.0)</td>
</tr>
<tr>
<td>Possible FH</td>
<td>Off</td>
<td>3380</td>
<td>604</td>
<td>4.8 (4.3–5.3)</td>
</tr>
<tr>
<td></td>
<td>On</td>
<td>915</td>
<td>406</td>
<td>14.8 (12.9–17.1)</td>
</tr>
<tr>
<td>Definite or probable FH</td>
<td>Off</td>
<td>260</td>
<td>84</td>
<td>13.2 (10.0–17.4)</td>
</tr>
<tr>
<td></td>
<td>On</td>
<td>242</td>
<td>84</td>
<td>10.3 (7.8–13.8)</td>
</tr>
</tbody>
</table>

- Untreated patients with a lifetime exposure to high LDL-C levels as a result of definite/probable FH have a \textbf{~13-fold increased risk of CAD} compared to patients with unlikely FH.

- Only 50\% of individuals with definite/probable FH and 40\% of individuals with possible FH were treated with statins despite having CAD.

- Shortfall in treatment of individuals with FH.

\textsuperscript{1} Data based on 69,016 individuals from the Copenhagen General Population Study. CAD, coronary artery disease; CI, confidence interval. \textsuperscript{2} Benn M et al. J Clin Endocrinol Metab. 2012;97:3956–3964.
FH is One of the Most Common Genetic Disorders Yet Remains Underdiagnosed

- Estimated % of Diagnosed HeFH by Country/Territory*

<table>
<thead>
<tr>
<th>Country/Territory</th>
<th>Estimated % of Diagnosed HeFH (Estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>1%</td>
</tr>
<tr>
<td>France</td>
<td>1%</td>
</tr>
<tr>
<td>Denmark</td>
<td>1%</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>1%</td>
</tr>
<tr>
<td>Belgium</td>
<td>2%</td>
</tr>
<tr>
<td>Spain</td>
<td>3%</td>
</tr>
<tr>
<td>UK</td>
<td>5%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>10%</td>
</tr>
<tr>
<td>Iceland</td>
<td>20%</td>
</tr>
<tr>
<td>Norway</td>
<td>40%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>70%</td>
</tr>
</tbody>
</table>

- Graph prepared using a theoretical HeFH frequency of 1 in 500 of the general population

- However, prevalence of definite or probable HeFH according to Dutch Lipid Clinic Network criteria in a large population study was shown to be closer to 1 in 200

- A 2014 study in the Netherlands estimated the prevalence of HoFH to be 1 in 300,000, with a calculated HeFH prevalence of 1 in 200

Estimated diagnosis of FH is much lower than prevalence estimates

*Percentage derived from expert clinician/scientists in local areas as well as prevalence of 1 in 500 in the general population as FH heterozygotes

FH is Common but Underdiagnosed and Undertreated

Recognize Familial Hypercholesterolemia

- An estimated 1.8–4.5 million people in the EU suffer from FH\(^1\)
- Rate of diagnosis of FH in the EU is <1%, based on estimates\(^1\)

Address LDL-C Levels

- HeFH and HoFH patients typically have untreated total cholesterol levels of 310–580 mg/dL (8–15 mmol/L) and 460–1160 mg/dL (12–30 mmol/L), respectively\(^1\)
- In individuals with FH, <5% fail to achieve recommended LDL-C targets\(^1\)

Consequences of FH

- Untreated FH patients are at a 13 times greater risk of CAD than the overall population\(^2\)

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Overview of FH Diagnostic Systems

- **Simon Broome Criteria**¹
- **US MEDPED²** (Make Early Diagnosis Prevent Early Death)
- **Dutch Lipid Clinic Network³**

**Simon Broome Criteria**

**Definite FH defined as:**

Cholesterol concentrations as shown in the table

plus

Tendon xanthomas in patient, or evidence of these signs in 1st or 2nd degree relative*

or

DNA-based evidence of an LDLR mutation, familial defective apo B-100, or a PCSK9 mutation

**Possible FH as:**

Cholesterol concentrations as shown in the table

plus

Family history of myocardial infarction:

- <50 years in 2nd degree relative*
- <60 years in 1st degree relative*

or

Family history of raised total cholesterol:

- >290 mg/dL (>7.5 mmol/L) in adult 1st or 2nd degree relative*
- >260 mg/dL (>6.7 mmol/L) in child or sibling <16 years

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**Total Cholesterol** | **LDL-C**
--- | ---
Child | >260 mg/dL (>6.7 mmol/L) | >155 mg/dL (>4.0 mmol/L)
Adult | >290 mg/dL (>7.5 mmol/L) | >190 mg/dL (>4.9 mmol/L)

*1st degree relative, parent, sibling, child; 2nd degree relative, grandparent, uncle, aunt

US MEDPED: Evaluate Lipid Panel for Biochemical Cues of FH \(^1\) broader for screening

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>First-Degree Relative</th>
<th>Second-Degree Relative</th>
<th>Third-Degree Relative</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>220 (155)</td>
<td>230 (165)</td>
<td>240 (170)</td>
<td>270 (200)</td>
</tr>
<tr>
<td>20–29</td>
<td>240 (170)</td>
<td>250 (180)</td>
<td>260 (185)</td>
<td>290 (220)</td>
</tr>
<tr>
<td>30–39</td>
<td>270 (190)</td>
<td>280 (200)</td>
<td>290 (210)</td>
<td>340 (240)</td>
</tr>
<tr>
<td>≥40</td>
<td>290 (205)</td>
<td>300 (215)</td>
<td>310 (225)</td>
<td>360 (260)</td>
</tr>
</tbody>
</table>

• These predicted total cholesterol (and LDL-C) in mg/dL cut points achieve ≥80% probability for an individual to have HeFH, \(^2\) with a 98% specificity. \(^1\)
• First-degree relatives: parents, offspring, brothers, sisters.
• Second-degree relatives: aunts, uncles, grandparents, nieces, nephews.
• Third-degree relatives: first cousins, siblings of grandparents.

### Dutch Lipid Clinic Network: Criteria for HeFH Diagnosis in Adults

#### Group 1: Family history

<table>
<thead>
<tr>
<th>Points</th>
<th>Group 1: Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First-degree relative with known premature CHD*, or</td>
</tr>
<tr>
<td>1</td>
<td>First-degree relative with known LDL-C &gt;95th percentile by age and gender for country</td>
</tr>
<tr>
<td>2</td>
<td>First-degree relative with tendon xanthoma and/or corneal arcus, or</td>
</tr>
<tr>
<td>2</td>
<td>Child(ren) &lt;18 years with LDL-C &gt;95th percentile by age and gender for country</td>
</tr>
</tbody>
</table>

#### Group 2: Clinical history

<table>
<thead>
<tr>
<th>Points</th>
<th>Group 2: Clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Subject has premature CHD*</td>
</tr>
<tr>
<td>1</td>
<td>Subject has premature cerebral or peripheral vascular disease*</td>
</tr>
</tbody>
</table>

#### Group 3: Physical examination

<table>
<thead>
<tr>
<th>Points</th>
<th>Group 3: Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Tendon xanthoma</td>
</tr>
<tr>
<td>4</td>
<td>Corneal arcus in a person &lt;45 years</td>
</tr>
</tbody>
</table>

#### Group 4: Biochemical results (LDL-C)

<table>
<thead>
<tr>
<th>Points</th>
<th>Group 4: Biochemical results (LDL-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>&gt;325 mg/dL (&gt;8.5 mmol/L)</td>
</tr>
<tr>
<td>5</td>
<td>251–325 mg/dL (6.5–8.4 mmol/L)</td>
</tr>
<tr>
<td>3</td>
<td>191–250 mg/dL (5.0–6.4 mmol/L)</td>
</tr>
<tr>
<td>1</td>
<td>155–190 mg/dL (4.0–4.9 mmol/L)</td>
</tr>
</tbody>
</table>

#### Group 5: Molecular genetic testing (DNA analysis)

<table>
<thead>
<tr>
<th>Points</th>
<th>Group 5: Molecular genetic testing (DNA analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Causative mutation shown in the LDLR, APOB or PCSK9 genes</td>
</tr>
</tbody>
</table>

- **Definite FH**: total points >8
- **Probable FH**: total points 6–8
- **Possible FH**: total points 3–5
- **Unlikely FH**: total points <3

*Premature defined as <55 years in males and <60 years in females
Nordestgaard BG et al. Eur Heart J. 2015;36:3478–3490*
The result is a **probability** of a patient having FH.

**Usage for HoFH patients**

- "Usually, those algorithms are not used for HoFH patients for whom the FH diagnosis is self-evident. We use algorithms to assess the severity of the condition for heterozygous patients" – Dr. Steinhagen.
- Dutch MEDPED and Simon Broome are the two sets that clinicians use most in the countries of the scope (which may be due to the fact that most were in Europe).
- KOLs agree on the fact **homozygous and compound heterozygous patients cannot be differentiated on the base of clinical diagnosis only**: genotyping is necessary.
LDLR Recycling is Important for Efficient Clearing of LDL Particles – many genotype variants are possible with variable activity
DEFINITION OF HOFH (EMA) Regulatory and insurance

- **Untreated Total Cholesterol (TC) ≥13 mmol/L (500 mg/dL)**

- **Treated Low Density Lipoprotein Cholesterol (LDL-C) ≥7.76 mmol/L (300 mg/dL)**

- **Treated LDL-C ≥6.47 mmol/L (250 mg/dL)** with clinically evident cardiovascular disease

- **DNA confirmation of 2 mutant alleles in genes for LDLR, ApoB, PCSK9 or autosomal recessive hypercholesterolaemia (ARH)**

- **Other evidence of HoFH such as cutaneous or tendinous xanthoma in childhood or history**

- **Of familial hypercholesterolemia (FH) in both parents (except in ARH)**

*For patients on apheresis, laboratory assessment obtained immediately prior to the next apheresis session.*
Consequences of Markedly Elevated LDL-C in HoFH patients:

- Typically develop cardiovascular disease before the age of 20¹
- Coronary artery disease
- Myocardial infarction
- Severe aortic stenosis
- Heart failure
- Stroke
- Sudden death
- Joint symptoms such as tendonitis or arthralgia’s; unusual skin lesions - xanthomas
- Significant Unmet Medical Need

Homozygous Familial Hypercholesterolemia (HoFH)

- 32 year-old female
- Cutaneous xanthomas beginning at age 3 years
- Obstructive coronary artery disease and CABG at age 12 years
- LDL cholesterol = 780 mg/dL (20.2mmol/l)
Elevated LDL-C is the cause of cardiovascular disease in HoFH

- LDL-C is a causal factor in the development of CVD
- Patients with HoFH typically develop cardiovascular disease before the age of 20 years\(^1\)
- Even with currently existing therapies, the mean age of death is 33 years\(^2\)

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Patients with HoFH typically develop cardiovascular disease before the age of 20 years\(^1\):

- Coronary artery disease
- Myocardial infarction
- Severe aortic stenosis
- Heart failure
- Stroke
- Sudden death
- Statin treatment, mean age of death delayed from 18 to 32 years\(^2\)


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### Table 1. Cardiovascular Morbidity and Mortality Characteristics of Patients With Homozygous Familial Hypercholesterolemia Pre-1990 and Post-1990

<table>
<thead>
<tr>
<th></th>
<th>Pre-1990 (n=36)</th>
<th>Post-1990 (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/males, n</td>
<td>24/12</td>
<td>59/55</td>
</tr>
<tr>
<td>Age at death, y, mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>18.4±10.1 (n=27)</td>
<td>32.9±15.5 (n=38)</td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first nonfatal MACE, y, mean±SD</td>
<td>12.8±5.9 (n=6)</td>
<td>28.3±10.8 (n=44)</td>
</tr>
<tr>
<td>Nonfatal cardiovascular events, No. of patients</td>
<td>6 (14 Events)</td>
<td>44 (90 Events)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>5 (7 MIs)</td>
<td>10 (11 MIs)</td>
</tr>
<tr>
<td>Coronary procedures (CABG, AVR, PTCA, stent)</td>
<td>5 (7 Procedures)</td>
<td>43 (69 Procedures)</td>
</tr>
<tr>
<td>Other vascular procedures (carotid surgery, aortofemoral bypass surgery)</td>
<td>None</td>
<td>5 (8 Procedures)</td>
</tr>
<tr>
<td>Cerebrovascular events (TIA, stroke)</td>
<td>None</td>
<td>2 (2 Events)</td>
</tr>
</tbody>
</table>

MACE indicates major adverse cardiac event; MIs, myocardial infarctions; CABG, coronary artery bypass surgery; AVR, aortic valve replacement; PTCA, percutaneous coronary angioplasty; and TIA, transient ischemic attack.

*\(P<0.0001\). †\(P<0.001\). ‡\(P<0.01\).
Current cholesterol-lowering drugs are insufficient in HoFH.

<table>
<thead>
<tr>
<th>Class</th>
<th>Major Effect</th>
<th>Typical LDL-C-Lowering Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (e.g. atorvastatin, rosvastatin)</td>
<td>↑ LDLR activity</td>
<td>&lt;10 to 25%</td>
</tr>
<tr>
<td>Bile acid sequestrants (e.g. cholestyamine, colestipol)</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors (e.g. ezetimibe)</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Nicotinic acid (ie, niacin)</td>
<td>Unknown</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Cardiovascular disease continues to progress despite standard of care

In a cohort of 7 patients treated with maximal tolerated lipid lowering therapies plus weekly apheresis:

- Lipid lowering therapy initiated at 9yrs
- Weekly apheresis initiated at 10yrs
- LDL-C levels reduced by 72% (mean 18.2 to 5.1 mmol/L)

Yet cardiovascular manifestations progressed in 6 of the 7 patients

- Aortic, Tricuspid and/or Mitral valve incompetence
- Aortic stenosis
- Calcified plaques in coronaries and aorta
- Occluded coronary arteries/grafts requiring surgical intervention

Palmar Xanthomas
Wide range of LDL in proven HoFH
Clinical aspects

Cardiovascular complication and natural history. Emphasis on the aortic stenosis and the worsening even when cholesterol is normalized.

Cardiovascular imaging – methodology and frequency
- US examination
- Stress ECG
- Risk of angiography
- Other: CT scan, MRI

Biological characteristics and genetic assessment.
- True homozygote, compound and double heterozygote, ARH
- Evidence that we need more aggressive treatment based on the severity of mutations?

Heterogenous disease; different clinical presentations

Diagnostic issues: sitosteroolemia
Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease

Consensus Statement of the European Atherosclerosis Society

**LDL cholesterol targets**

We recommend the following LDL cholesterol targets in FH, in accordance with recent ESC/EAS guidelines:

(i) children <3.5 mmol/L (<135 mg/dL),
(ii) adults <2.5 mmol/L (<100 mg/dL),
(iii) adults with CHD or diabetes <1.8 mmol/L (<70 mg/dL).

These targets are for both heterozygous and homozygous FH regardless of age. However, in children and adults with homozygous FH, these values are extremely difficult to achieve with current treatments.
LDL cholesterol targets for FH: Consensus statement of the European Atherosclerosis Society

- In accordance with recent ESC/EAS Guidelines:
  
  (i) Children < 3.5 mmol (135 mg/dL)

  (ii) Adults < 2.5 mmol (< 100 mg/dL)

  (iii) Adults with CHD or diabetes < 1.8 mmol (< 70 mg/dL)

- These targets are for both heterozygous and homozygous FH regardless of age

- However, in patients for homozygous FH these treatment targets are difficult to achieve

Nordestgaard et al. EHJ accepted 3 June 2013
Lack of clinical or mutational diagnosis does not preclude treatment

<table>
<thead>
<tr>
<th>Family history</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with known premature* coronary and vascular disease, OR</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known LDL-C level above the 95th percentile</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis, OR</td>
<td></td>
</tr>
<tr>
<td>Children aged less than 18 years with LDL-C level above the 95th percentile</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Patient with premature* coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>Patient with premature* cerebral or peripheral vascular disease</td>
<td>&lt;55y Males, &lt;60y Female</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cholesterol levels mg/dl (mmol/liter)</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C (\geq 330 \text{ mg/dL} (\geq 8.5))</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 250 – 329 mg/dL (6.5–8.4)</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 190 – 249 mg/dL (5.0–6.4)</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 155 – 189 mg/dL (4.0–4.9)</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Functional mutation in the LDLR, apo B or PCSK9 gene</td>
<td>8</td>
</tr>
<tr>
<td><strong>Diagnosis (diagnosis is based on the total number of points obtained)</strong></td>
<td></td>
</tr>
<tr>
<td>Definite Familial Hypercholesterolemia</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable Familial Hypercholesterolemia</td>
<td>6–8</td>
</tr>
<tr>
<td>Possible Familial Hypercholesterolemia</td>
<td>3–5</td>
</tr>
<tr>
<td>Unlikely Familial Hypercholesterolemia</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>
INDIVIDUAL PATIENTS WITH LDL > 6.0 MMOL/L OUT OF 9563 UNIQUE LIPID PROFILES
TOTAL NUMBER 46 PATIENTS IN A 4 WEEK PERIOD JUNE 2015

224 PATIENTS WITH LDL > 190 (4.9)
46 PATIENTS OVER 6.0 – POSSIBLE FH
11 PATIENTS OVER 8.0 – definite FH

11 patients with DUTCH score of 8
Based on LDL only
HOFH / HEFH SCREENING USING CENTRALIZED LAB EMR June 2015 LDL>6

Male n=15  Female n=31

Age in years of individual patients

DUTCH lipid network score 5 Possible Score of 8 definite
Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel

Abdullah Al-Ashwail¹, Fahad Alnouri², Hani Sabbour³, Abdulraof Al-Mahfouz⁴, Nasrcaen Al-Saydi⁵, Maryam Razzaghy-Azar⁶, Faisal Al-Allaf⁷, Khalid Al-Waili⁸, Yajnavalka Banerjee⁹, Jacques Genest¹⁰, Raul D. Santos¹¹ and Khalid Al-Rasadi¹²

¹Medical & Clinical Affairs, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; ²Head of Cardiovascular Prevention, Rehabilitation and Patients Education Unit, Prince Sultan Cardiac Center, Riyadh, Saudi Arabia; ³Consultant Cardiologist, Sheikh Khalifa Medical City, Abu Dhabi, UAE; ⁴Head Section of Endocrinology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; ⁵Medical Director, Gulf Diabetes Specialist Center, Manama, Bahrain; ⁶Tehran University of Medical Sciences, Tehran, Iran; ⁷Department of Medical Genetics, Faculty of Medicine, Umm Al-Qura University, Makkah 21955, Saudi Arabia; ⁸Department of Biochemistry, Sultan Qaboos University hospital, Muscat, Oman; ⁹Department of Biochemistry, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman; ¹⁰Faculty of Medicine, McGill University, Montreal, Quebec, Canada; ¹¹Cardiology, Lipid Clinic Heart Institute, University of Sao Paulo, Sao Paulo, Brazil
Gulf FH Registry
Current therapy options for FH:

**Pharmacotherapies:**

- Statins (provide an average of 15% LDL-C reduction in LDLR negative patients and 26% for LDLR deficient patients\(^1\))
- Others such as niacin, fibrates or ezetimibe (activity is not LDLR dependent) are used as well\(^1\)
- More recently approved Mipomersen and Lopipapide (both interfering with hepatic lipoprotein assembly) reduced LDL-C by 25% and 38%\(^2\)
- AMG 145 reduced LDL-C by 26% in 6 patients with LDLR deficiency when given 420 mg every 2 weeks (very recently published data)\(^2\)

**Non-Pharmacotherapies:**

- Lipid Apheresis (weekly or every two week) reduces LDL-C by 54 to 84% (45% as an average) however there’s a rebound after the first week
- Liver transplantation, however problem of donor

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2. Stein et al, Circulation Sep 2013
Familial Hypercholesterolemia

- Familial hypercholesterolemia (FH) is the lifelong elevation of low-density lipoprotein cholesterol (LDL-C) levels.

- Heterozygous FH (HeFH) is caused by one of the following*:
  - A loss-of-function mutation** in one allele of the LDLR (LDL receptor) gene
  - A loss-of-function mutation** in one allele of the APOB (apolipoprotein B) gene
  - A gain-of-function mutation in one allele of the PCSK9 (proprotein convertase subtilisin/kexin type 9) gene

- Homozygous FH (HoFH) results from either homozygous or compound heterozygous mutations in the LDLR or ARH† (autosomal recessive hypercholesterolemia) genes

- Double heterozygotes carry mutations in two of the four genes (LDLR, ARH, ApoB and PCSK9)
  - Usually leads to a phenotype that is intermediate between heterozygous and homozygous FH

*There are other currently unknown SNPs linked with phenotypic FH.
**Some protein function may remain after a loss-of-function mutations, a complete loss of function is a null mutation.
†Also known as the low density lipoprotein receptor adaptor protein 1 (LDRAF1)
Nordestgaard BG et al. Eur Heart J. 2013;34:3478–3493
Genetic Mutations Associated with FH$^1,2$

**Incidence of Mutations in FH$^1$**

- 67% LDLR
- 16.7% Others
- 14% ApoB
- 2.3% PCSK9

**FH results from various genetic alterations$^2$**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Exons</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>19p13</td>
<td>18</td>
</tr>
<tr>
<td>PCSK9</td>
<td>1p32</td>
<td>12</td>
</tr>
<tr>
<td>ApoB</td>
<td>2p24–23</td>
<td>29</td>
</tr>
</tbody>
</table>

- There are >1700 sequence variants in the *LDLR* gene, which can cause defects in several different domains of the protein$^2$
- The *PCSK9* gene has ~160 identified sequence variants$^2$
- 3 sequence variants* related to FH exist in *ApoB*, which result in defects to the LDLR-binding region of the protein$^2$

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Many sequence variants exist in the *ApoB* gene; however only those involved in FH are mentioned here.

EAS Consensus Paper Recommendations for LDL-C Targets in FH

In accordance with ESC/EAS guidelines, LDL-C treatment targets are:

- <100 mg/dL (<2.5 mmol/L) for adults with HeFH or HoFH

- <135 mg/dL (<3.5 mmol/L) for children with HeFH or HoFH

- <70 mg/dL (<1.8 mmol/L) for adults with HeFH or HoFH and CHD or diabetes

If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses

All untreated FH individuals >40 years should be considered to have a very high CV risk

There is still however an unmet need in LDL-C goal attainment

- FH patients have a very high starting level of LDL-C
- Increasing statin dose likely to cause more side effects
- Some patients may not be able to tolerate high doses of statins, or statins at all
- Patients still have residual risk of a CV event

References:
Current Management and Treatment Scope for FH in Adults

Patients with FH should receive **intensive education** regarding lifestyle modifications and management:\(^1\)

- Diet, smoking, physical activity, weight control, hypertension

Initiation of **cholesterol-lowering drugs and therapy** should begin:\(^1\)

- Immediately in adults, from age 8–10 in children

**Statins** should be first-line therapy for patients with FH:\(^1,2\)

- High doses of high potency statins are often needed for individuals with FH\(^2\)

**Alternative LDL-C lowering agents** for children or those not achieving goal:\(^2\)
- Ezetimibe
- Bile acid sequestrants

**Lipoprotein apheresis** for residual high LDL-C after aggressive treatment:
- HoFH patients
- Treatment-resistant

**Additional investigational therapeutic options** under investigation:
Importance of FH Registry Data

- Dissemination of information about FH\(^1,2\)
  - Raising awareness of FH prevalence and risk factors at patient and carer level

- Engagement of physicians in the development and adoption of best practices that can lead to improved patient outcomes\(^1,2\)

- Therapy tracking, follow-up of patient-reported outcomes and clinical outcomes over time\(^2\)

- Evaluation of ‘real-world’ clinical practice and patient experiences, contributing to efficiency of treatment\(^2\)
  - Increased proportion of patients meeting guideline-recommended lipid targets

- Reduced healthcare expenditure\(^3\)

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Summary

Diagnosis

- FH is commonly underdiagnosed
- Particularly high LDL-C levels should lead to investigation
  - Untreated values of ≥310 mg/dL (≥8 mmol/L) in adults and ≥230 mg/dL (≥6 mmol/L) in children
- Various diagnostic systems can be used
  - Simon Broome Criteria, US MEDPED, and Dutch Lipid Clinic Network
Summary

- Identification of key clinical criteria and causative genetic mutations in \( \text{LDLR}, \text{PCSK9} \) and \( \text{APOB} \) are important for optimal diagnosis

Prognosis

- Progression of \( \text{CHD} \) is rapid in \( \text{FH} \) patients, and if untreated outcomes are poor

Treatment

- Currently undertreated
  - Diagnostic screening plus development of national registries are needed to enable early and aggressive treatment
  - Promising treatments in development likely to yield a high degree of \( \text{LDL-C} \) reduction and hence goal fulfilment
NORD PHYSICIAN GUIDE ON HOFH

Homozygous Familial Hypercholesterolemia (HoFH)

Visit website at:

nordphysicianguides.org/homozygous-familial-hypercholesterolemia
SUMMARY

- Atherosclerosis is characterized by the thickening of the arterial wall and is the primary cause of CAD and cerebrovascular disease.

- FH is a group of inherited genetic defects resulting in severely elevated serum cholesterol concentrations.

- Most of the available epidemiologic data on FH focus on the LDL-R and Apo B genes because these genes have been studied the longest and are responsible for the majority of cases of FH.

References:
SUMMARY

- Diagnosis of HoFH involves
- Physical examination for xanthomas
- Family history
- Biochemical tests
- Genetic testing