Defining Severe Familial Hypercholesterolemia

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Disclosure

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Familial Hypercholesterolemia: Need for Risk Stratification

• Elevated lifetime risk of cardiovascular disease

• However, heterogeneity in this risk
  – LDL levels
  – Other risk factors
  – Susceptibility= subclinical disease

• Newer treatments
  – PCSK9 inhibitors 6-14,000 US dollars year
  – Mipomersen/Lomitapide US- 150-360,000 year
  – Lipid Apheresis US 100,000 year
Higher LDL-C = Greater Risk
Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: A study of a cohort of 14,000 mutation carriers

Joost Besseling, Iris Kindt, Michel Hof, John J.P. Kastelein, Barbara A. Hutten, G. Kees Hovingh

CVD risk vs. non severe FH
1.25 [95% CI: 1.05-1.51], p = 0.015

Fig. 1. Kaplan–Meier incidence estimates for severe and non-severe HeFH patients.
Overlap in LDL-C Between Homozygous and Heterozygous FH
Distribution of serum total cholesterol levels in normal subjects, and heterozygous and homozygous FH patients

Serum cholesterol mmol/L (mg/dL)

Number of patients

Normal
Heterozygous FH
Homozygous FH
Molecular Defect and LDL-C Phenotype

Figure 1: Range of LDL cholesterol concentrations in severe hypercholesterolaemia, according to monogenic defects

Santos RD et al Lancet Diab Endocrinol 2016;4: 850-61
Secondary vs. Primary Prevention of Cardiovascular Disease
Secondary vs. Primary Prevention in FH and Mortality in the UK: Effects of Statins

• N=3382 patients (FUP 1980-2006)

• 370 deaths

• Standardized mortality ratios

• All aged 20–79 years CHD mortality reduced by 37% (95% CI 7–56) from 3.4- to 2.1-fold excess.
  – Primary prevention: 48% reduction in CHD mortality from 2.0-fold excess to none
  – Secondary prevention: 25% reduction in CHD mortality from 5.2 (95% CI 3.4–7.6) to a 3.9-fold excess (95% CI 3.2–4.7)

Other Risk Factors

The usual suspects
## Table 2
Risk factors for CVD in heterozygous FH patients.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariable OR 95% CI</th>
<th>p-value</th>
<th>Multivariable OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.72 1.53–1.92 &lt;0.001</td>
<td></td>
<td>2.44 2.07–2.88 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.08 1.08–1.09 &lt;0.001</td>
<td></td>
<td>1.08 1.08–1.09 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.13 1.12–1.15 &lt;0.001</td>
<td></td>
<td>1.04 1.03–1.06 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.70 1.50–1.94 &lt;0.001</td>
<td></td>
<td>1.59 1.36–1.86 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.02 7.08–9.07 &lt;0.001</td>
<td></td>
<td>2.38 2.01–2.82 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.40 5.21–7.86 &lt;0.001</td>
<td></td>
<td>1.37 1.03–1.82 0.03</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>0.55 0.46–0.65 &lt;0.001</td>
<td></td>
<td>0.61 0.48–0.77 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L²)</td>
<td>1.16 1.13–1.19 &lt;0.001</td>
<td></td>
<td>1.08 1.04–1.12 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L³)</td>
<td>1.76 1.59–1.94 &lt;0.001</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Besseling et al.  Atherosclerosis 2014; 233 219-223
Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry

Leopoldo Pérez de Isla, Rodrigo Alonso, Nelva Mata, Cristina Fernández-Pérez, Ovidio Muñiz, José Luis Díaz-Díaz, Adriana Saltijeral, Francisco J. Fuentes-Jiménez, Raimundo de Andrés, Daniel Zambón, Mar Piedecausa, José María Cepeda, Marta Mauri, Jesús Galiana, Angel Brea, Juan F. Sanchez Muñoz-Torrero, Teresa Padró, Rosa Argueso, José Pablo Miramontes-González, Lina Badimón, Raúl D. Santos, Gerald F. Watts and Pedro Mata

For the SAFEHEART investigators

Multivariate impact of Lp(a) >50 mg/dL:
OR 1.52
95%CI 1.05-2.21 p=0.028
Risk Equation for FH?

Lessons from Spain
22 year old women LDL-C < 100 mg/dL
66 year old men LDL-C < 100 mg/dL

Advanced Subclinical Coronary Atherosclerosis
Advanced Subclinical Coronary Atherosclerosis by Computed Tomography Angiography in FH and Cardiovascular Events

A

Receiver-operating characteristic curve

B

Cumulative incidents

Tada et al. Am J Cardiol 2015;115:724e729

n=101
Coronary Artery Calcification and Cardiovascular Events in FH

- 206 molecularly proven heterozygous FH individuals age 45±14 years
- 79.6% with high dose statin
- 64% also with ezetimibe
- On treatment LDL-C 150±56 mg/dL
- CAC present in 105 (51%)
- Follow-up median of 3.7 (quartiles: 2.7 – 6.8) years
- ASCVD events (7.2%)
- Annualized event rate (1,000 patients/year)
  - CAC 0 = 0
  - CAC 1-100= 26.4 (95% CI 12.9 - 51.8)
  - >100 = 44.1 (95% CI 26.0 - 104.1)

Survival free from MACE

- CAC = 0
- CAC 1 - 100
- CAC > 100

Miname, Bittencourt & Santos JACC Cardiovasc Imaging 2018 in press
Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel


Santos RD et al Lancet Diab Endocrinol 2016;4: 850-61
Risk Conditions to Consider

- Older > 40 years old without treatment
- Smoking,
- Male gender
- Lp(a)>50 mg/dL
- Low-HDL-C (<1mmol/L or 40 mg/dL),
- Hypertension
- Diabetes mellitus
- Family history of early cardiovascular disease in first degree relatives (<55 years old in males and < 60 years old in females)
- Chronic kidney disease (defined as an estimated glomerular filtration rare < 60 ml/min/1.73 m²
- BMI >30 kg/m²

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# Severe Familial Hypercholesterolemia-IAS

| At presentation (untreated LDL-C) | LDL –C >10 mmol/L (400 mg/dL)  
LDL-C >8.0 mmol/L (310 mg/dL) + one high risk condition  
LDL-C > 5 mmol/L (190 mg/dL) + two high risk conditions | Realistic goal: reduce ≥ 50% LDL-C  
Ideal goal: LDL-C < 2.5 mmol/L (100 mg/dL) |
|---|---|---|
| With subclinical atherosclerosis assessment | **Advanced subclinical atherosclerosis**  
*Coronary:*  
A-Coronary artery calcium (CAC) score > 100 Agatston units, or > 75th percentile for age and gender*  
B-Computed tomography angiography (CTA) with obstructions > 50% or presence of non-obstructive plaques > one vessel. | Realistic goal: reduce ≥ 50%  
Ideal goal : LDL-C < 1.8 mmol/L (70 mg/dL) |
| Presence of clinical atherosclerotic cardiovascular disease | | Realistic goal: reduce LDL-C ≥ 50%  
Ideal goal: LDL-C < 1.8 mmol/L (70 mg/dL) |

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Treatment
Figure 2: Treatment algorithm for severe familial hypercholesterolaemia
The therapeutic strategy is based on refractoriness of treatment, drug or procedure availability, reimbursement, and approval by local regulatory agencies.

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Conclusions: Severe Familial Hypercholesterolemia

- Elevated lifetime risk of cardiovascular disease
- However, heterogeneity in this risk
  - LDL levels
  - Other risk factors
  - Susceptibility= subclinical disease
  - Previous CVD
- Identify highest risk patients in order to have best treatment cost-effectiveness