What we know about Familial Hypercholesterolemia today

Khalid Al-Rasadi, BSc, MD, FRCPC
Head of Biochemistry Department, SQU
Head of Lipid and LDL-Apheresis Unit, SQUH
President of Oman society of Lipid & Atherosclerosis (OSLA)
Disclosures

• Honoraria for Speakers Bureau (Pharma)
  AstraZeneca, Sanofi, Amgen, Pfizer

• Advisory Boards: Sanofi, Amgen, Aegerion, AstraZeneca

• Research Funding: Sanofi
Elevated LDL cholesterol

Liver with only 50% functional LDL receptors

Mutations in LDL receptor, apolipoproteinB or PCSK9

Atherosclerosis

Coronary heart disease

Myocardial infarction

Angina pectoris

Familial hypercholesterolaemia

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
<table>
<thead>
<tr>
<th>FH heterozygotes</th>
<th>FH homozygotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occur in ~ 1 in 500 persons worldwide&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Occur in ~ 1 in 1,000,000 persons worldwide&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 mutated allele&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2 mutated alleles&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>TC: 350 to 500 mg/dL&lt;sup&gt;3&lt;/sup&gt; (9-12.9 mmol/L)</td>
<td>TC: &gt; 500 to &gt; 1,000 mg/dL&lt;sup&gt;1&lt;/sup&gt; (12.9-25.9 mmol/L)</td>
</tr>
<tr>
<td>LDL-C: 200–400 mg/dL&lt;sup&gt;1,2&lt;/sup&gt; (5.1-10.3 mmol/L)</td>
<td>LDL-C: &gt; 600 mg/dL&lt;sup&gt;2&lt;/sup&gt; (15.5 mmol/L)</td>
</tr>
<tr>
<td>Half the number of LDLR expressed&lt;sup&gt;3&lt;/sup&gt;</td>
<td>LDLR activity absent&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Characterized by 2- to 3-fold elevation in the plasma LDL-C levels and often develop myocardial infarctions as early as 30 to 40 years of age&lt;sup&gt;2,4&lt;/sup&gt;</td>
<td>Characterized by more severe hypercholesterolemia than heterozygotes, with LDL-C levels elevated 6- to 10-fold from birth, and heart attacks in childhood&lt;sup&gt;2,4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

TC = total cholesterol.


<sup>2</sup> Robinson JG. *J Manag Care Pharm.* 2013;19:139-149.


Diagnostic Criteria for FH

Three groups have developed diagnostic tools for FH:

• The US Make Early Diagnosis to Prevent Early Deaths (MEDPED) Program
• Simon Broome Register Group in the UK
• Dutch Lipid Clinic Network
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>First degree relative with FH</th>
<th>Second degree relative with FH</th>
<th>Third degree relative with FH</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>220 (5.7)</td>
<td>230 (5.9)</td>
<td>240 (6.2)</td>
<td>270 (7.0)</td>
</tr>
<tr>
<td>20 - 29</td>
<td>240 (6.2)</td>
<td>250 (6.5)</td>
<td>260 (6.7)</td>
<td>290 (7.5)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>270 (7.0)</td>
<td>280 (7.2)</td>
<td>290 (7.5)</td>
<td>340 (8.8)</td>
</tr>
<tr>
<td>&gt;=40</td>
<td>290 (7.5)</td>
<td>300 (7.8)</td>
<td>310 (8.0)</td>
<td>360 (9.3)</td>
</tr>
</tbody>
</table>

*The total cholesterol cutpoints for FH is dependent upon the confirmed cases of FH in the family. If FH is not diagnosed in the family, then the cutpoint for diagnosis is as per “general population.”


Simon Broome Register criteria

- definite FH
  - TC > 7.5 or LDL-C > 4.9 mmol/l
  - (TC > 6.7 or LDL-C > 4.0 for children < 16 yr)
  - plus Tendon xanthomata in 1st or 2nd degree relative
  - or LDL-receptor or apoB-100 or PCSK9 mutations

- possible FH
  - Lipids as above plus family history of *either* MI at <50yr in 2nd degree or <60yr in 1st degree relative or TC > 7.5 in 1st or 2nd degree relative

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature coronary and/or vascular disease (men &lt;55 years, females &lt;60 years) OR First-degree relative with known LDL-C above the 95th percentile for age and sex</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C above the 95th percentile for age and sex</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
</tr>
<tr>
<td>Premature coronary artery disease (men &lt;55 years, females &lt; 60 years)</td>
<td>2</td>
</tr>
<tr>
<td>Premature cerebral or peripheral vascular disease (men &lt;55 years, females &lt;60 years)</td>
<td>1</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>LDL-C (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>- 8.5 or higher</td>
<td>8</td>
</tr>
<tr>
<td>- 6.5 to 8.4</td>
<td>5</td>
</tr>
<tr>
<td>- 5.0 to 6.4</td>
<td>3</td>
</tr>
<tr>
<td>- 4.0 to 4.9</td>
<td>1</td>
</tr>
<tr>
<td>DNA analysis: functional mutation in the LDLR, APOB or PCSK9 gene</td>
<td>8</td>
</tr>
</tbody>
</table>

Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria:
- **Definite FH** = total score greater than 8
- **Probable FH** = total score between 6 and 8
- **Possible FH** = total score between 3 and 5
- **Unlikely FH** = total score of less than 3
**Known Genetic Mutations Associated With Familial Hypercholesterolemia***

<table>
<thead>
<tr>
<th>Gene</th>
<th>LDLR</th>
<th>ApoB</th>
<th>PCSK9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome</td>
<td>19p13</td>
<td>2p23-24</td>
<td>1p32</td>
</tr>
<tr>
<td>Clinical Effect</td>
<td>LDL-C increased</td>
<td>LDL-C increased</td>
<td>LDL-C increased</td>
</tr>
</tbody>
</table>

*Autosomal Dominant Hypercholesterolemia.
Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolaemia.

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

- HoFH: 1:300,000
- heFH: 1:230
Diagnosis of familial hypercholesterolemia (FH) in 2017 based on a frequency of 1:250

- Canada 146,000 FH
  - Diagnose: <15%
  - On LDL-C: 0%
  - On genes: 15%

- USA 1,304,000 FH
  - Diagnose: <10%
  - On LDL-C: 0%
  - On genes: <5%

- Latin America 2,580,000 FH
  - Diagnose: <1%
  - On LDL-C: 0%
  - On genes: <1%

- Rest of Europe 2,284,000 FH
  - Diagnose: 1%
  - On LDL-C: 0%
  - On genes: 30%

- Netherlands 68,000 FH
  - Diagnose: 86%
  - On LDL-C: 0%
  - On genes: 100%

- Norway 20,000 FH
  - Diagnose: 37%
  - On LDL-C: 0%
  - On genes: 100%

- Russia 576,000 FH
  - Diagnose: <1%
  - On LDL-C: 0%
  - On genes: <1%

- Japan 508,000 FH
  - Diagnose: 26%
  - On LDL-C: 0%
  - On genes: 2%

- Rest of Asia 17,236,000 FH
  - Diagnose: <1%
  - On LDL-C: 0%
  - On genes: <1%

- South Africa 212,000 FH
  - Diagnose: 2%
  - On LDL-C: 0%
  - On genes: 80%

- Rest of Africa 4,652,000 FH
  - Diagnose: <1%
  - On LDL-C: 0%
  - On genes: <1%

- Australia New Zealand 116,000 FH
  - Diagnose: 4%
  - On LDL-C: 0%
  - On genes: 30%
The Gulf Familial Hypercholesterolemia Registry (Gulf FH): Design, Rationale and Preliminary Results


Journal Name: Current Vascular Pharmacology

DOI: 10.2174/15701611116666181005125459 (https://doi.org/10.2174/15701611116666181005125459)
FH in the Arabian Gulf Countries

- The expected FH prevalence based on a frequency of 1/250 is 104,554

- The number of FH diagnosed 3%
  - Based on LDL-C 100%
  - Based on genetic 6%
Screening for FH in Children and Adolescent

- If DNA testing is available, cascade screening of families is recommended using both a phenotypic and genotypic strategy. If DNA testing is not available, a phenotypic strategy based on country, age- and gender-specific LDL-C levels should be used.
- Children with suspected HeFH should be screened from the age of 5 years; screening for HoFH should be undertaken when clinically suspected (both parents affected or xanthoma present) and as early as possible.
- Age at screening should be similar for boys and girls.
- Universal screening in childhood may also be considered.
Barriers for FH Diagnosis

- **Physician related**
  - Lack of knowledge and familiarity
  - Insufficient staff, time and consultative support

- **Patient related**
  - Lack of acceptance
  - Psychological issues
  - Cost of testing/insurance coverage

- **Lack of Government support**
  - Insufficient screening program for children, adolescents, and young adults
  - Treatment guidelines
Resources for the international FH Community

Discussion group for FH patients
facebook.com/groups/fhfoundation
Find an FH Specialist

Find an FH Specialist

Specialist First Name

Specialist Last Name

Specialty

Street

City

State

Zip Code

Country

Distance

12000 miles

Show All

Submit

Map

Satellite

https://thefhfoundation.org/find-fh-specialist
Familial Hypercholesterolemia

FH is different
FH is life threatening

FH is manageable
FH is undiagnosed

*If left untreated
Treatment goals for the Familial Hypercholesterolemia population

Dr. Meral KAYIKCIOGLU, MD, FACC
Ege University, Medical School
Department of Cardiology TURKEY

@MeralKayikcio1 (Dr Meral Kayikcioglu)
meral.kayikcioglu@gmail.com
Meral Kayikcioglu
Professor of Cardiology

Disclosure potential conflicts of interest

Consulting, Research contracts
Abbot, Amyrit, Amgen, Pfizer, Sanofi, Abdi Ibrahim, Regeneron, Esperion, Novanordisk
Familial Hypercholesterolemia

FH is different

FH is life threatening

2.5-10 FOLD
higher risk of heart disease

FH is manageable

FH is undiagnosed

90% UNDIAGNOSED

Therapies
Life Style

*If left untreated

Kayikcioglu M. Data on file
Treatment Goals FH population

As a NCD
The primary treatment goal:
Prevention of the complications of the disease
FH Exposes People to Very High Cholesterol from Birth, thus Reaching a Threshold for CHD Earlier in Life

This figure illustrates the cumulative LDL exposure over a lifetime in FH patients and normal individuals. CHD occurs after a theoretical threshold of LDL exposure is exceeded. This threshold is reached in childhood in FH homozygotes and in early middle age in FH heterozygotes.

For a HeFH patient:

Threshold for CHD: reached by age 40 for those with HeFH and age 20 for HoFH, > 70 yrs in healthy individuals

190 mg/dl x 48 years = 9000

Pretreatment + Post treatment= total exposure
If treatment has initiated when 30 years
(190 mg x 30) + (90 mg/dl x 36) = 9000 (At 66 years)
If treatment has initiated when 20 years
(190 mg x 20) + (90 mg/dl x 58) = 9000 (At 78 years)
FH and Guidelines

High risk in all ages
No need for risk calculation
Early and effective LDL reduction

As low as to prevent (cure) atherosclerosis

Table 3
Recommended LDL cholesterol targets for FH patients: EAS Consensus Panel and Joint ESC/EAS guidelines [2,70].

- Children: < 3.5 mmol/L (<135 mg/dL)
- Adults: < 2.5 mmol/L (<100 mg/dL)
- Adults with CHD or diabetes < 1.8 mmol/L (<70 mg/dL)

Targets are the same in heterozygous and homozygous FH.

As low as to prevent (cure) atherosclerosis
<table>
<thead>
<tr>
<th></th>
<th>Without Event (1196)</th>
<th>With New Event (84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate/ 100 Patient Years</td>
<td>0</td>
<td>2.21</td>
</tr>
<tr>
<td>No Prior CAD; N = 41/1196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Rate/ 100 Patient Years</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Prior CAD; N = 43/704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment LDL</td>
<td>231 mg/dl</td>
<td>247 mg/dl</td>
</tr>
<tr>
<td>Treated LDL</td>
<td>103 mg/dl</td>
<td>79 mg/dl</td>
</tr>
<tr>
<td>% on &gt; 2 meds</td>
<td>77%</td>
<td>83%</td>
</tr>
</tbody>
</table>
5- vs 10-year risk of developing incident ASCVD for pts with FH and LDL-C <100 mg/dL.

Changes in risk profile can be observed according the modifications in the risk factors. Lp(a) indicates lipoprotein(a).

Available Treatment for HeFH to Achieve Desired LDL-C Levels

STATIN → Ezetimibe → PCSK9 - inh → Apheresis

Cumulative event-free survival (%) in FH

Follow-up (years)

Statin treatment: N = 413
No statin treatment: N = 1537

EAS Consensus
Nordestgaard, EHJ 2013;54(45):3478-86
Ezetimibe in FH

### Recommendations of 2016 ESC /EAS Dyslipidemia Guidelines

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH pts have to be treated with intense dose statin, often in combination with ezetimibe</td>
<td>I</td>
</tr>
</tbody>
</table>

#### Table 4 Mean LDL-C response to ezetimibe in patients with homozygous familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Treatment (daily dose)</th>
<th>N</th>
<th>LDL-C (mmol/L)</th>
<th>Change(^a)</th>
<th>% Change(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV or SV (80 mg)</td>
<td>17</td>
<td>−0.51</td>
<td>−7%</td>
<td></td>
</tr>
<tr>
<td>E + AV or SV (40, 80 mg)</td>
<td>33</td>
<td>−1.76</td>
<td>−21%</td>
<td></td>
</tr>
<tr>
<td>E + AV or SV (80 mg)</td>
<td>17</td>
<td>−2.00</td>
<td>−27%</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** \(^a\) Mean absolute change from baseline (mmol/L). \(^b\) Mean percent change from baseline.

**Abbreviations:** AV, atorvastatin; SV, simvastatin; E, ezetimibe.
## Case- 34 y/o Male FH with severe family history of premature ASCVD

<table>
<thead>
<tr>
<th>Date</th>
<th>LDL -C</th>
<th>CAD</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.03.2018</td>
<td>249 mg/dl (6.44 mmol/l)</td>
<td>post-AMI</td>
<td>-</td>
</tr>
<tr>
<td>18.04.2018</td>
<td>160 mg/dl (4.14 mmol/l)</td>
<td>Post CABG</td>
<td>A-80</td>
</tr>
<tr>
<td>18.06.2018</td>
<td>112 mg/dl (2.89 mmol/l)</td>
<td>Post CABG</td>
<td>A-80 EZE</td>
</tr>
<tr>
<td>30.07.2018</td>
<td>60 mg/dl (1.55 mmol/l)</td>
<td>Post CABG</td>
<td>A-80 EZE Evolocumab</td>
</tr>
</tbody>
</table>

Kayikcioglu M. Data on file
PCSK9 Inhibitors: New Horizons for Heterozygous FH

With an 50-60 % LDL reduction

LDL goal attainment rate
LDL-C values < 1.8 mmol/L (70 mg/dL) in refractory FH patients

- Rutherford-2\(^1\)
  - 61-66% treated with evolocumab

- Odyssey FH I and II\(^2\) (at week 24)
  - 60-68% in those receiving alirocumab

Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study

Frederick J Raal, G Kees Hovingh, Dirk Blom, Raul D Santos, Mariko Harada-Shiba, Eric Bruckert, Patrick Couture, Handrean Soran, Gerald F Watts, Christopher Kurtz, Narimon Honarpour, Lihua Tang, See Kasichayanula, Scott M Wasserman, Evan A Stein

Figure 2: LDL cholesterol change from baseline to week 12, by underlying genetic abnormality
Mean change in LDL cholesterol is shown in parentheses after each genetic abnormality category. GoF=gain of function. *Apheresis patient. †Patient missed apheresis before week 12 blood draw due to snowstorm. ‡Week 12 immediately after vacation; dietary indiscretion suspected. ARH=autosomal recessive hypercholesterolaemia.
• The 14 subjects aged 12 to < 18 years Evolocumab provides an effective option to further lower LDL-cholesterol levels in paediatric patients with HoFH, particularly in those with defective LDLR.
Lipid Lowering Therapy and The LDL Receptor

**Effects Independent of LDLR Expression/Function**

- **Statins**
  - HMGCR inhibition
  - **VLDL Production**
    - Cholesterol Synthesis
    - ApoB Synthesis
    - MTP inhibition
    - Triglyceride Transfer To ApoB

- **Mipomersen**
  - Reduced ApoB Translation

- **Lomitapide**
  - MTP inhibition

**Effects Dependent of LDLR Expression/Function**

- **Statins**
  - HMGCR inhibition
  - LDLR Synthesis

- **Ezetimibe**
  - SREBP2
  - IDOL
  - Reduced Liver Cholesterol Input

- **PCSK9 inhibitors**
  - LDLR Degradation

**LDL-C**

---

**Figure.** Mechanisms involved with low-density lipoprotein cholesterol (LDL-C) lowering by medications approved for homozygous familial hypercholesterolemia and their possible associations with LDLR (LDL receptor) expression/function.

- apoB indicates apolipoprotein B;
- HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme reductase;
- IDOL, inducible degrader of LDL receptor;
- MTP, microsomal triglyceride transfer protein;
- PCSK9, proprotein convertase subtilisin kexin type 9;
- SREBP2, steroid regulatory element binding protein-2;
- and VLDL, very-low-density lipoprotein.

**Santos RD. Arterioscler Thromb Vasc Biol. 2018;38:481-3**
EA, 21 y/o girl
10 y UAP → proximal 3VD → CABG
Regular apheresis since 10 y/o

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Atorva 80+ EZE</th>
<th>Presession</th>
<th>Postsession</th>
<th>Lomitapide (20 mg/dl) Pre-</th>
<th>Lomitapide (20 mg/dl) Post-</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dl)</td>
<td>509</td>
<td>436</td>
<td>364</td>
<td>142</td>
<td>130</td>
<td>54</td>
</tr>
</tbody>
</table>

No apheresis

Kayikcioglu M. Data on file
First xanthoma: 4y/o, LDL-C: 500mg/dL (13 mmol/L)
8y/o: syncope (diagnosed for aortic stenosis)
11y/o: angina CAD – diagnosed for HoFH
13 y/o: apheresis
25 y/a: died due to AS leading to HF
Children with HoFH

- Initiation of lipid apheresis
- Ideal age < 6-7 years
- with late initiated apheresis Aortic stenosis cannot be prevented

<table>
<thead>
<tr>
<th>Age at symptom</th>
<th>10±10 (0.5-45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at cholesterol measurement</td>
<td>12±11 (1-45)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>13±11 (1-50)</td>
</tr>
<tr>
<td>Age at start of first apheresis</td>
<td>21±12 (3-55)</td>
</tr>
</tbody>
</table>
Real life?

EAS- FSHC Registry > 2500 pts
Among those on LLT:
- <3% with LDL-C < 70 mg/dL
- <8% with LDL-C < 100 mg/dL
### Turkish FH registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>A-HIT1</th>
<th>A-HIT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum LDL-cholesterol (mg/dL) (min-max) on treatment</td>
<td>338±82 (168–561)*</td>
<td>215±72 (54-914)</td>
</tr>
<tr>
<td>LDL goal attainment, n(%) on treatment</td>
<td>5 (5.7%) all were on treatment</td>
<td>23 (2.1) 459 patients were on treatment</td>
</tr>
</tbody>
</table>

only 4.3% of the patients receiving intense doses of statins were reached the LDL-goals

LDL-C Control in FH: SAFEHEART Study

N=2,752, mean follow-up was 5.1 ± 3.1 years; 71.8% of FH cases were on maximum LLT

Treated LDL-C is suboptimal (HoFH)

31% of HoFH Adults and 29% of HoFH Children are on apheresis! Adult HoFH patients are on an average of 3 medications, Pediatric HoFH patients are 2 medications.
Reasons for not reaching the goal

- Limited access to medical therapy
- Non-compliance (patients and physicians-reluctance)
- Side effects especially higher doses of statins are needed, not always well tolerated
- Statins’ low efficacy (Very High Baseline Levels)
- Genetic Variability in Response
- Lack of awareness

Cardiologist Awareness of FH

A survey of 500 Cardiologists on their understanding of FH.

- **60%** did not realize FH is autosomal dominant
- **80%** were unaware of the prevalence of FH
- **70%** did not recognize FH when given an example in a case study
- **NONE** realized that individuals with FH are 20 TIMES more likely to have a premature heart attack

*Journal of Clinical Cardiology* (2014)
A-HIT 2 Registry - TURKEY

Among the FH patients followed in cardiology, endocrinology, or internal medicine outpatient clinics

Awareness of a disease named FH only 9.5 %

Conclusion

Recommendations of 2016 ESC Dyslipidemia Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td>FH pts have to be treated with intense dose statins, often in combination with ezetimibe</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Treatment should be aimed at reaching LDL-C &lt; 100 mg/dl (2.5 mmol/L) or in the presence of CVD &lt; 70 mg/dl (1.8 mmol/L). If targets cannot be reached, max reduction of LDL-C should be considered using appropriate drug combinations.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Treatment with a PCSK9 inh may be considered in FH pts with CVD or with other factors putting them at very high risk for CHD, such as other CV risk factors, family history and high Lp(a)</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
Conclusion

Treatment goals in FH
- Early identification
- Early treatment (LDL reduction)
- Prevention premature CV events.
- Major barrier is lack of awareness
Take home message

Familial Hypercholesterolemia

A severe, premature, diffuse atherosclerotic disease of arteries
Treatment goals for the Familial Hypercholesterolemia population

Dr. Meral KAYIKCIOLGU, MD, FACC
Ege University, Medical School
Depart of Cardiology TURKEY

FOR SLIDES: meral.kayikcioglu@gmail.com
Familial Hypercholesterolemia Foundation & International Atherosclerosis Society Joint Session on Familial Hypercholesterolemia

FH registries tell a story, improves scientific understanding, and drives policy change

Dr. Rodrigo Alonso
Head Department Clinical Nutrition, Clínica Las Condes, Santiago de Chile
President Chilean Working Group on Atherosclerosis
Member at Large International Atherosclerosis Society
Scientific Committee Spanish FH Foundation
Member of the board of the Iberoamerican FH Network Association
<table>
<thead>
<tr>
<th></th>
<th>I.</th>
<th>II.</th>
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<td>I have received (a) research grant(s) / in kind support</td>
<td>I have been a speaker or participant in accredited CME/CPD ...</td>
<td>I have been a consultant / strategic advisor etc. ...</td>
<td>I am a holder of (a) patent / shares / stocks or ownership...</td>
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**SCORE: 3**
Spanish Familial Hypercholesterolemia Foundation
(non-profit organization founded in 1997, www.colesterolfamiliar.org)

- to detect and educate families with FH
- to prevent CV disease and mortality
- to contribute in the development of molecular, clinical and therapeutic research

First national registry (1998-2002)
Clinical characteristics of FH and started with molecular testing

Genetic testing
- DNA-chip (2005-9)

Colaboration with other institutions
- SAFEHEART registry 2004
- Detection through “weekend day work”
- Consensus Statement 2015
- Continuous Medical Education

Reimbursement of LL-T
- 2004 for statins
- 2009 for ezetimibe
- 2014 for LDL Apheresis
- 2016 for PCSK9i

Adequate treatment

Regional detection program with participation of primary care

Cost-effectiveness studies

National Detection Program using molecular testing to prevent premature CVD
SpAnish Familial hypErcHolEsterolemiA cohoRT study (SAFEHEART)

http://safeheart.colesterolfamiliar.org/

Clinical Trial Registration: ClinicalTrials.gov number NCT02693548

- Observational and prospective multicenter (28 lipid clinics and primary care centers) follow-up registry of families with molecular diagnosis of FH.
- Clinical and analitical data of probands and relatives > 14 years old are registered in a centralized database.
- Biological samples (including DNA).
- Standardized phone-call every year.
SAFEHEART 2004-2017

- 4767 subjects registered: 3510 FH (4305 ≥ 18 y/o); 1257 non FH (1099 ≥ 18 y/o)
- mean age at enrollment: 40 years old
- 54% females
- 26% current smokers
- mean LDL-C at inclusion: 165 mg/dL (≈ 80% on LLT at inclusion, mean years of statin initiation ≈ 7)
- 15% with CVD (90% CHD)
30% of FH subjects have Lp(a) > 50 mg/dL
Attainment of LDL-Cholesterol treatment goals in patients with familial hypercholesterolemia. 5-years SAFEHEART registry follow-up

**Adults**
- 2170 FH, 72% on maximum LLT
- LDL-C at inclusion: 163 mg/dL
- LDL-C at follow-up: 137 mg/dL

**Children/adolescents**
- 217 FH, 68% on medication
- LDL-C at inclusion: 156 mg/dL
- LDL-C at follow-up: 138 mg/dL

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Saltijeral A et al. Rev Esp Cardiol 2017;70:444-50
Cost-Effectiveness of a Cascade Screening Program for the Early Detection of Familial Hypercholesterolemia

- Implementation of a NPFH (lipid measurement + DNA & LLT) to detect 9,000 FH cases in one year vs. usual clinical care for a time horizon of 10 years
- Payer (NHS) and social (including the productivity lost) perspectives were considered.
- The outcomes variables were coronary events and deaths avoided, and quality adjusted life years (QALYs) gained

- From the payer perspective, the application of the NPFH during 1 year identifying 9,000 FH will prevent in the next 10 years:
  - 847 Coronary events
  - 203 coronary deaths
  - The intervention will produce 767 extra QALY’s more than no intervention (cost of €29,608/QALY)

Every 8 new cases of FH detected and treated, 1 coronary event can be prevented
Predicting cardiovascular events in familial hypercholesterolemia: The SAFEHEART registry

2,404 adults with FH followed-up for a mean period of 5.5 years: 12 fatal events and 122 non-fatal incident ASCVD.

The SAFEHEART-RE may improve risk stratification and could be used to guide new therapy (iPCSK9) in FH.
National, multicenter registry of patients with clinical (SB, DLCN, MEDPED) or genetic diagnosis.
The AAP recommends screening for high cholesterol at age 2 if child has two parents with FH or high cholesterol; universal screening ages 9-11.

EAS Guidelines recommend universal screening for cholesterol ages 9-11.

ACC/AHA Adult Guidelines recommend universal screening of adults at age 21.

EAS Guidelines recommend US statin initiation for at ages 8-10 for FH.

## Patient Demographics

### ALL SITES OVERALL

<table>
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<th>Patient Characteristics</th>
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<tbody>
<tr>
<td><strong>TOTAL ENROLLED</strong></td>
<td>4549</td>
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### Age

<table>
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<tr>
<td>Median</td>
<td>55</td>
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<tr>
<td>&gt;18</td>
<td>88%</td>
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<tr>
<td>&lt;18</td>
<td>12%</td>
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### Gender

<table>
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<tr>
<th>Gender</th>
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<tbody>
<tr>
<td>Male</td>
<td>39%</td>
</tr>
<tr>
<td>Female</td>
<td>61%</td>
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### Race/ Ethnicity

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<tbody>
<tr>
<td>White</td>
<td>82%</td>
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<tr>
<td>Black/African American</td>
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<tr>
<td>Asian</td>
<td>3%</td>
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<tr>
<td>Other</td>
<td>7%</td>
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<tr>
<td>Hispanic</td>
<td>5.5%</td>
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### Age in Years

- <18: 12%
- 18-30: 9%
- 31-45: 14%
- 46-65: 43%
- >65: 23%

### Age >=18

- Male: 61%
- Female: 39%

*CASCADE FH Registry National Report, Feb 2018*
Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry

- Women are less likely to men to achieve treated LDL-C < 100 mg/dL or ≥ 50% reduction
- Women are less likely to men to receive statin and to receive high-intensity statin
- Compared with whites, Asians and blacks were less likely to achieve LDL-C < 100 mg/dL
- Differences in statin utilization were noted by race/ethnicity (blacks less likely to receive statins, no significant difference; and asians to receive high intensity statins, significant difference).
- Health disparities contribute to the undertreatment of US FH patients
Conclusions

Registries

• are a good tool to demonstrate what and how are we doing with our FH patients (screening, LLT, goal achievement, control of other CVRF, etc)

• Improve the cascade screening

• can identify unmet needs in FH

• rise awareness in FH in families, physicians and policymakers

• Evaluate quality of medical care

• Can contribute to the health planning and economic evaluation

We have improved, but we can still do it better for our FH patients