Update on Guidelines for Management of Familial Hypercholesterolemia.

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Gulf Medical & Diabetes Center
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1st Saudi Familial Hypercholesterolemia Symposium & 3rd Severe FH Master Class 6-7 December 2019.
Disclosure

• Advisory board for: Sanofi, Abbott, MSD, AstraZeneca.
• Speaker for: Sanofi, Pfizer, MSD, AstraZeneca.
Plasma Disorders and High Prevalence Rates in the Middle East:

- A literature review assessing the prevalence of plasma lipid disorders in Gulf countries, using studies published from 1987 to 2010, found that reported rates ranged from 3% to 52% across varying population types.

- Similarly a further study of hypercholesterolemia in the Gulf region, evaluating data from 1990 to 2014, found the prevalence range to be 17–55% in males and 9–54% in females.

- 70% of stable outpatients who attended general practice clinics had disorders of plasma lipids; in all countries in the study. Of these, only 16% of subjects were receiving lipid-lowering medications and many subjects were not achieving LDL-C goals recommended in international guidelines.

Cardiovascular disease (CVD) is considered the most common cause of deaths accounting for up to 45% of all mortalities.²

A large proportion of very high and high ASCVD patients on LLDs in the Arabian Gulf are not at recommended non–HDL-C targets and hence remain at a substantial residual risk.³

1- Al Rasadi et al, Atherosclerosis 252 (2016) 182e187
3- Al Hashmi K et al, Journal of Clinical Lipidology (2016) 10, 368–377
Cardio Vascular Disease and Dyslipidemia in the Gulf

Facts to consider

- The first presentation of acute myocardial infarction (AMI) in this population is 10–12 years earlier than in their Western counterparts.¹

- High Prevalence
  - Atherogenic dyslipidemia in these populations is characterized by high triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C), and elevated levels of small, dense LDL particles.¹

- Underdiagnosed and undertreated in the Arabian Gulf, which is a common genetic cause of premature coronary heart disease (CHD) due to lifelong elevated plasma LDL-C levels.¹

Consanguinity Marriages Rates in the Gulf ²:

- 54% in Kuwait
- 58% in Saudi Arabia
- 50% in United Arab Emirates
- 52% in Qatar
- 40–47% Yemen
- 50% in Oman

¹Al Rasadi K et al., Oman Med Journal, 2015 Nov; 30(6): 403–405
²A. Bener et al, The Egyptian Journal of Medical Human Genetics 2017

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List of Guidelines

• International Atherosclerosis Society (IAS).
• European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)
• American College of Cardiology (ACC) and American Heart Association (AHA).
• American Association of Clinical Endocrinologists (AACE).
• National Lipid Association (NLA).
Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel

Abdullah Al-Ashwal,1 Fahad Alnouri,2 Hani Sabbour,3 Abdulraof Al-Mahfouz,4 Nasreen Al-Sayed,5 Maryam Razzaghy-Azar,6 Faisal Al-Allaf,7 Khalid Al-Waili,8 Yajnavalka Banerjee,9 Jacques Genest,10 Raul D. Santos,11 and Khalid Al-Rasadi8,*
Guidelines’ Components

• Diagnosis.
• Screening.
• Targets.
• Management.
• Agreement

- Early screening criteria.
- Rule out secondary dyslipidemia.
- Cascade screening.
- Healthy life style interventions.
- Genetic testing if feasible.
- Criteria for PCSK9 inhibitor therapy.
- CVD risk assessment.
- LDL-C as primary target.
- FH is high risk, so global risk calculator should not be used in these patients.

• Differences

- Diagnostic criteria.
- Risk stratification groups.
- Targets vrs. thresholds based on risk stratification groups.
FH diagnosis criteria predominantly used

- **Not...**
- **Simon-Broome 16%**
- **MED...**
- **Country-specific definition 8%**
- **DLCN...**

* Information provided from 61 countries.
** When >1 criteria system were mentioned for the same country, all of them have been included in the graph.
*** See Table 1 in the article for further details.
Evidence that a **Lower Achieved LDL** is Better

Linear Relationship to **Absolute CV Risk** in 24 RCTs

In a meta-analysis of 24 RCTs, each 1 mmol/L lower achieved LDL-C reduces absolute risk of CHD events 4.6% in secondary prevention, and 1.5% in primary prevention.

For all therapies that upregulate LDL-R activity

Silverman, MG, Ference, BA et al. JAMA 2016;316(12):1289-1297

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Evidence that **More LDL Lowering is Better**

Linear Relationship to **Relative CV Risk in 14 RCTs**

In a meta-analysis of 14 RCTs, each 1 mmol/L decrease in LDL reduces Relative Risk of MACE by 22% = HR 0.78, and Total Deaths by 12% across risk groups.

Multiplicative

Per *individual participant* data

New Evidence that Lower Is Better
IMPROVE-IT – Statin + Ezetimibe Post-ACS if LDL >70 mg/dL

% with a 1st MACE including CV Death

- Simvastatin monotherapy 34.7%
- Simvastatin-Ezetimibe 32.7%

6% RRR - HR 0.94
(95% CI, 0.89-0.99 p=0.016)

Years of Follow-Up

IMPROVE IT Design
N = 18,144 post-ACS
Age ≥ 50 + High risk
LDL ≥ 70 (Median 94 mg/dL)
Randomized to
- Simvastatin 40 mg + EZ
- Simva 40 mg + Placebo
Endpoint – MACE
Median F/U - 6 years

Results in Treatment Arm
Median LDL = 53 mg/dL
HR for 1st MACE 0.94
HR for recurrent MI 0.88

New Evidence that Even Lower is Even Better
FOURIER - PCSK9-Inhibition in Stable CAD when LDL ≥70 mg/dL

FOURIER Design
N = 27,564 with stable ASCVD
LDL-C ≥70 or non-HDL-C ≥100
On high intensity statin (90%)
Randomized to
- Evolocumab 140 mg q 2 wks
- Placebo
Endpoint – MACE
Median F/U - 26 months

Results in Treatment Arm
Median LDL = 30 mg/dL
HR for MACE = 0.85
AE’s - injection site reactions

Patients with Primary Endpoint (%)

Placebo
14.6%
12.6%
Evolocumab
15% RRR
HR 0.85
(95% CI, 0.79-0.92)
P<0.0001

0% 2% 4% 6% 8% 10% 12% 14% 16%
0 6 12 18 24 30 36


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More Evidence that Even Lower is Better

ODYSSEY Outcomes - PCSK9i Post-ACS when LDL ≥70 mg/dL

ODYSSEY Design
N = 18,924 w/ recent ACS
LDL ≥70 non-HDL-C ≥100 or ApoB ≥80
On maximal statin therapy
Randomized to
- Alirocumab 75-150 q 2 weeks
- Placebo
Endpoint – MACE
Follow up - 2.8 years

Results in Treatment Arm
Median LDL @ 48 mos 53 mg/dL
Median LDL @ 4 mos 38 mg/dL
HR for MACE = 0.85
AEs – Injection site reactions

15% RRR
HR 0.85
(95% CI, 0.78-0.93)
P<0.0001

Once FH is diagnosed, a comprehensive CVD risk assessment should be performed. The risk of CHD among individuals with definite or probable FH is estimated to be increased at least 10-fold.
Cardiovascular Manifestations in FH

- Severe coronary atherosclerosis.
- Acute myocardial infarction.
- Supravalvular and aortic valve stenosis.
- Sudden death.
# FH genetics and CHD risk!

<table>
<thead>
<tr>
<th>Genetic mutation</th>
<th>Risk for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LDLR (null allele LDLR mutations).</td>
<td>HIGH RISK</td>
</tr>
<tr>
<td>• Specific gain-of-function PCSK9 mutation (p.Asp374Tyr).</td>
<td></td>
</tr>
<tr>
<td>• Lipoprotein lipase gene (p.Asn291Ser).</td>
<td></td>
</tr>
<tr>
<td>• Genetic polymorphisms, for example, presence of E2 and E4 alleles in</td>
<td></td>
</tr>
<tr>
<td>apolipoprotein E.</td>
<td></td>
</tr>
<tr>
<td>• Some PCSK9 loss-of-function variants</td>
<td>LOWER RISK</td>
</tr>
<tr>
<td>• APOB gene mutations</td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>Patients with CHD (n)</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>None</td>
<td>55</td>
</tr>
<tr>
<td>LDLR</td>
<td>91</td>
</tr>
<tr>
<td>APOB</td>
<td>6</td>
</tr>
<tr>
<td>PCSK9</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 1
The OR for coronary heart disease (CHD) by mutation type adjusted for risk factors (table from Humphries et al10)

*OR for having CHD adjusted for age, sex, smoking and systolic blood pressure at recruitment compared with the patients where no mutation was identified.

• APOB, apolipoprotein B; CHD, coronary heart disease; LDLR, LDL-receptor gene; PCSK9, protein convertase subtilisin/kexin 9.
CVD Risk Assessment, Imaging

• Carotid intima-media thickness measurement.
• Coronary CT angio and MRI.
• IVUS.
• Echocardiography.
• CAC Score
• Myocardial stress evaluation
Coronary computed tomography angiography

Federico Vancheri, Diagnostics 2019,

1st Saudi Familial Hypercholesterolemia Symposium & 3rd Severe FH Master Class 6-7 December 2019.

Miname MH, Bittencourt MS, Moraes SR, et al.

**Study Questions:**
Is coronary artery calcium (CAC) score a predictor of atherosclerotic cardiovascular disease (ASCVD) events in asymptomatic primary prevention molecularly proven heterozygous familial hypercholesterolemia (HeFH) patients receiving standard lipid-lowering therapy?
Coronary Artery Calcium and Cardiovascular Events in Patients With Familial Hypercholesterolemia Receiving Standard Lipid-Lowering Therapy.

This paper suggests patients with FH could also benefit from CAC testing to determine whether additional lipid-lowering therapies beyond statins are necessary and cost-effective. It also help further “personalize” risk to weigh expected benefits and costs of newly available lipid lowering agents.
Myocardial stress evaluation


- A larger group of 653 asymptomatic heterozygous FH patients (42% male subjects with an average age of 42 years, 70% using lipid-lowering therapy), a positive stress test was found in 9% of the subjects. Pitsavos CH, Atherosclerosis. 2004; 173:347–352.

Considering the accelerated development of CAD in those with heterozygous FH, it seems reasonable to perform stress testing and to evaluate exercise capacity periodically in asymptomatic heterozygous FH patients, particularly those with late diagnosis, with lipid-lowering treatment started in adulthood, with a family history of early cardiac events, and with an interest in competitive sports. ACC/AHA 2015.
Cost-effectiveness issues

- **Highly cost-effective:**
  when the cost per quality-adjusted life-year (QALY) gained is less than $20,000 to $25,000,

- **Moderately high in cost effectiveness:**
  when the cost per QALY is between $25,000 and $50,000,

- **Borderline cost-effective:**
  when the cost per QALY is between $50,000 and $100,000. However, more recent expert analyses have suggested that the $50,000 per QALY threshold, in use since the 1990s, could reasonably be increased to $100,000 or $150,000.
Cost-effectiveness issues

**Statins:**
$ 50,000

The yearly cost of weekly, intensive, lipoprotein apheresis:
US$100,000.

**Mipomersen:**
$176,000 per year

**Lomitapide:**
$235,000–295,000 per year

**PCSK9 monoclonal antibodies**
$14,000 per year in the USA (but about half this cost in Europe and Canada).
International Atherosclerosis Society (IAS)

• The Lancet Diabetes & Endocrinology
• Volume 4, Issue 10, October 2016, Pages 850–861
Range of LDL cholesterol concentrations in severe hypercholesterolaemia, according to monogenic defects

≥10-13 mmol/L
(≥400-500 mg/dL)

- Homozygotes for LDLR null mutations
- Compound heterozygotes for LDLR null and LDLR defective mutations
- Homozygotes for LDLR defective mutations or LDLRAP1
- Homozygotes for defective APOB or PCSK9 gain-of-function mutations
- Double heterozygotes (eg, LDLR and PCSK9 gain-of-function, or LDLR and defective APOB mutations)

≥5 mmol/L
(≥190 mg/dL)

- Homozygotes for LDLR null mutations
- Homozygotes for LDLR defective mutations

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THREE RISK CATEGORIES

• At presentation (untreated LDL cholesterol).
• Presence of advanced subclinical atherosclerosis.
• Presence of clinical atherosclerotic cardiovascular disease.
Proposed criteria for definition of severe familial hypercholesterolaemia and LDL cholesterol treatment goals: At presentation (untreated LDL cholesterol)

Severe familial hypercholesterolaemia diagnosed if LDL cholesterol >10 mmol/L (400 mg/dL); or LDL cholesterol >8·0 mmol/L (310 mg/dL) and one high-risk feature;* or LDL cholesterol >5 mmol/L (190 mg/dL) and two high-risk features

*High-risk features are:
- Age >40 years without treatment.
- Smoking.
- Male sex.
- Lipoprotein(a) >75 nmol/L (50 mg/dL); HDL cholesterol <1 mmol/L (40 mg/dL).
- Hypertension.
- Diabetes mellitus.
- Family history of early cardiovascular disease in first-degree relatives (age <55 years in men and <60 years in women).
- Chronic kidney disease (ie, estimated glomerular filtration rate <60 mL/min per 1·73 m2).
- BMI >30 kg/m2.

Realistic goal is to reduce LDL cholesterol by ≥50%; the ideal goal is to achieve LDL cholesterol <2·5 mmol/L (100 mg/dL)
Proposed criteria for definition of severe familial hypercholesterolaemia and LDL cholesterol treatment goals: **Presence of advanced subclinical atherosclerosis**

Advanced subclinical atherosclerosis diagnosed with a coronary artery calcium score >100 Agatston units, or >75th percentile for age and sex; or CT angiography with obstructions >50% or presence of non-obstructive plaques in more than one vessel†Calcium scores calculated using criteria from the Multi-Ethnic Study of Atherosclerosis.

Realistic goal is to reduce LDL cholesterol by ≥50%; the ideal goal is to achieve LDL cholesterol <1.8 mmol/L (70 mg/dL)
Proposed criteria for definition of severe familial hypercholesterolaemia and LDL cholesterol treatment goals: Presence of clinical atherosclerotic cardiovascular disease.

Clinical atherosclerotic cardiovascular disease defined as previous myocardial infarction, angina, coronary revascularisation, non-embolic ischaemic stroke, or transitory ischaemic attack, and intermittent claudication

Realistic goal is to reduce LDL cholesterol by ≥50%; the ideal goal is to achieve LDL cholesterol <1·8 mmol/L (70 mg/dL)
Step 1

Patient with severe familial hypercholesterolaemia
High-intensity statin therapy (atorvastatin or rosuvastatin) at maximum tolerated dose plus ezetimibe

LDL cholesterol not at ideal goal or <50% reduction

Step 2

Triple-drug therapy
Add PCSK9 inhibitor (bile acid sequestrants, or niacin optional depending on availability, toxic effects, and costs)

LDL cholesterol still not at ideal goal

Step 3

Maintain treatment
Minimum LDL cholesterol reduction ≥50% or at ideal LDL cholesterol goal

Consider four-drug therapy
Add lomitapide or mipomersen (approved for homozygous familial hypercholesterolaemia in some countries), or lipoprotein apheresis, or liver transplantation (in homozygous familial hypercholesterolaemia)
European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

• European Heart Journal, ehz455.
• Published: 31 August 2019
Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolaemia.

Adapted from Luis Masana
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490
© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology
• **Very High Risk:** ASCVD or with major risk factors.

• **High Risk:** Without ASCVD or no risk factors.
Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that a diagnosis of FH is considered in patients with CHD aged &lt;55 years for men and &lt;60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C [in adults &gt;5 mmol/L (&gt;190 mg/dL), in children &gt;4 mmol/L (&gt;150 mg/dL)], and in first-degree relatives of FH patients.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that FH should be diagnosed using clinical criteria and confirmed, when possible, via DNA analysis.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Once the index case is diagnosed, family cascade screening is recommended.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and that those with no prior ASCVD or other risk factors are treated as high-risk.

For FH patients with ASCVD who are at very-high risk, treatment to achieve a $\geq50\%$ reduction from baseline and an LDL-C $<1.4$ mmol/L ($<55$ mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.

In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of $\geq50\%$ from baseline and an LDL-C goal of $<1.4$ mmol/L ($<55$ mg/dL) should be considered.
### ESC/EAS 2019 Risk Group Categories:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very high</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 55 mg/dl (&lt; 1.4 mmol/l)</td>
<td>• ASCVD either clinical or equivocal.</td>
</tr>
<tr>
<td>NON-HDL &lt; 80 mg/dl (&lt; 2.2 mmol/l)</td>
<td>• FH with ASCVD or other major risk factor.</td>
</tr>
<tr>
<td>LDL-C &lt; 55 mg/dl (&lt; 1.4 mmol/l)</td>
<td>• Diabetes with target organ damage or smoking, Hypertension.</td>
</tr>
<tr>
<td>NON-HDL &lt; 80 mg/dl (&lt; 2.2 mmol/l)</td>
<td>• Severe CKD GFR &lt; 30</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C &lt; 70 mg/dl (&lt; 1.8 mmol/l)</td>
<td>• FH without risk factor</td>
</tr>
<tr>
<td>NON-HDL &lt; 100 mg/dl (&lt; 2.6 mmol/l)</td>
<td>• TC &gt; 8 mmol/l (&gt; 310), LDL &gt; 4.9 mmol/l (&gt; 190 mg/dl)</td>
</tr>
<tr>
<td>LDL-C &lt; 70 mg/dl (&lt; 1.8 mmol/l)</td>
<td>• Bp &gt; 180/110 mmHg</td>
</tr>
<tr>
<td>NON-HDL &lt; 100 mg/dl (&lt; 2.6 mmol/l)</td>
<td>• Diabetes without end organ damage, or DM&gt; 10 years or with one risk factor</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Calculated SCORE &gt; 1% and &lt; 5%</td>
</tr>
<tr>
<td></td>
<td>• Young patients with DM (typ1 &lt; 35 and type2 &lt; 50.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Calculated SCORE &lt; 1%</td>
</tr>
</tbody>
</table>
Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.
Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Children with FH should be educated to adopt a proper diet and treated with a statin from 8–10 years of age. Goals for treatment should be LDL-C $&lt; 3.5 \text{ mmol/L} ( &lt; 135 \text{ mg/dL})$ at $&gt;10$ years of age.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
Recommendations for the detection and treatment of patients with familial hypercholesterolaemia in Children.

• FH is diagnosed in children based on phenotypic criteria including elevated LDL-C plus a family history of elevated LDL-C, premature CAD, and/or positive genetic testing.

• In children with a family history of high cholesterol or premature CHD, an accepted cut-off is ≥4.0 mmol/L (≥160 mg/dL). If a parent has a known genetic defect, the diagnostic level for the child is ≥3.5 mmol/L (≥130 mg/dL). If possible, genetic testing of the child is suggested.

• Statin treatment should be started with low doses and the dose should be increased to reach goals. The goal in children >10 years of age is an LDL-C <3.5 mmol/L (<135 mg/dL) and at younger ages a ≥50% reduction of LDL-C.
Clinical update

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society


*Department of Medicine and Therapeutics, University of Hong Kong, Queen Mary Hospital, Hong Kong, People’s Republic of China

Received 15 March 2014; revised 11 May 2014, accepted 13 June 2014. Available online 28 June 2014

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Homozygous Familial Hypercholesterolaemia

LDL-C targets:
<2.5 mmol/L [<100 mg/dL] (adults)
<3.5 mmol/L [<135 mg/dL] (children)
<1.8 mmol/L [<70 mg/dL] if clinical CVD

At diagnosis
Lifestyle and Diet + Statin
(most efficacious at highest dose depending on tolerability)

Ezetimibe 10 mg + resins or other drugs*
*Fibrate, nicotinic acid, probucol (use of these additional treatments may be limited by tolerability and drug availability)

New Therapeutic options

Future Therapeutic options

LDL-Apheresis
As early as possible if available (by 5 years, no later than 8 years) every 1 or 2 weeks

In selected patients
Liver Transplant

Lomitapide
Approved by FDA, EMA

Mipomersen
Approved by FDA
American College of Cardiology (ACC) and American Heart Association (AHA).
The Agenda for Familial Hypercholesterolemia
A Scientific Statement From the American Heart Association
Samuel S. Gidding, Mary Ann Champagne, Sarah D. de Ferranti, Joep Defesche, Matthew K. Ito, Joshua W. Knowles, Brian McCrindle, Frederick Raal, Daniel Rader, Raul D. Santos, Maria Lopes-Virella, Gerald F. Watts, and Anthony S. Wierzbicki

Circulation. 2015;132:2167–2192
### ACC/AHA FH Diagnostic Criteria

<table>
<thead>
<tr>
<th>ICD-10 Category</th>
<th>Clinical Criteria</th>
<th>With Genetic Testing Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous FH</td>
<td>LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)</td>
<td>Presence of 1 abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect Diagnosed as heterozygous FH if LDL-C–raising defect positive and LDL-C &lt;160 mg/dL (4 mmol/L) Occasionally, heterozygotes will have LDL-C &gt;400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect(s) and LDL-C–lowering gene variant(s) with LDL-C &lt;160 mg/dL (4 mmol/L)</td>
</tr>
<tr>
<td>Homozygous FH</td>
<td>LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C–raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH</td>
<td>Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects; includes the rare autosomal-recessive type</td>
</tr>
<tr>
<td></td>
<td>If LDL-C &gt;560 mg/dL (14 mmol/L) or LDL-C &gt;400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at &lt;20 y of age, homozygous FH highly likely</td>
<td>Occasionally, homozygotes will have LDL-C &lt;400 mg/dL (10 mmol/L)</td>
</tr>
<tr>
<td>Family history of FH</td>
<td>LDL-C level not a criterion; presence of a first-degree relative with confirmed FH</td>
<td>Genetic testing not performed</td>
</tr>
</tbody>
</table>
AHA Scientific Statement

The Agenda for Familial Hypercholesterolemia
A Scientific Statement From the American Heart Association

Initial drug monotherapy

↓

Two-drug Combination

↓

Three-drug Combination

↓

Complex-therapy Combination

High-intensity Statin Therapy (>50% LDL-C reduction)
Rosuvastatin or atorvastatin

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to two-drug combination

Rosuvastatin or Atorvastatin

↓

Ezetimibe

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to three-drug combination

Rosuvastatin or Atorvastatin + Ezetimibe

PCSK9 inhibitors

Colacevelam or other bile acid sequestrant

Niacin

If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to complex-therapy combination

Consider four-drug combination† and LDL Apheresis


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ACC/AHA 2013 Risk Group Categories

Secondary prevention
- Patients with Clinical Atherosclerotic Cardiovascular Disease (ASCVD)*
- if not:
  - Patients with LDL ≥190 mg/dL
  - if not:
    - Patients with diabetes (Age 40-75; LDL 70 to 189 mg/dL)
    - if not:
      - Assess 10-year ASCVD risk
        http://tools.acc.org/ASCVD-risk-estimator

Primary prevention
- Patients with LDL ≥190 mg/dL
  - if not:
    - moderate-intensity statin
    - unless 10-year ASCVD risk ≥7.5%

- Patients with diabetes (Age 40-75; LDL 70 to 189 mg/dL)
  - if not:
    - moderate-intensity statin
    - Risk ≥7.5%: high-intensity statin
    - Risk >5% but <7.5%: moderate-intensity statin

*Clinical ASCVD: acute coronary syndrome (ACS), myocardial infarction (MI), angina, revascularization, stroke, TIA, or peripheral arterial disease.
## ACC/AHA 2018 Lipid Guidelines

### High-Risk Conditions

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
</tr>
<tr>
<td><strong>Heterozygous familial hypercholesterolemia; LDL threshold 100 mg/dl and above, reduction by 50%.</strong></td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>CKD (eGFR 15-59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>History of congestive HF</td>
</tr>
</tbody>
</table>
### Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL (≤3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.</td>
</tr>
</tbody>
</table>
### Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

**Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])**

<table>
<thead>
<tr>
<th>COR</th>
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<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher and who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.</td>
</tr>
</tbody>
</table>

**Value Statement:**

**Uncertain Value (B-NR)**

Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at 2018 U.S. list prices.
### Primary Prevention in Other Age Groups (Children and Adolescents)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL (4.1 mmol/L) or higher with a clinical presentation consistent with FH (see Section 4.2.) and who do not respond adequately with 3 to 6 months of lifestyle therapy, it is reasonable to initiate statin therapy.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In children and adolescents with a family history of either early CVD* or significant hypercholesterolemia,† it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia.</td>
</tr>
</tbody>
</table>
Primary Prevention in Other Age Groups (Children and Adolescents)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia.</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome.</td>
</tr>
</tbody>
</table>
TWO RISK CATEGORIES

- **Extreme Risk**: Established ASCVD.
- **Very High Risk**: Without ASCVD.
<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Targets</th>
</tr>
</thead>
</table>
| Extreme risk  | – Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL.  
– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH.  
– History of premature ASCVD (<55 male, <65 female). | • LDL-C < 55 mg/dl  
• NON-HDL-C < 80 mg/dl |
| Very high risk | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
– Diabetes or CKD 3/4 with 1 or more risk factor(s)  
– HeFH | • LDL-C < 70 mg/dl  
• NON-HDL-C < 100 mg/dl |
| High risk     | – ≥2 risk factors and 10-year risk 10-20%  
– Diabetes or CKD 3/4 with no other risk factors | • LDL-C < 100 mg/dl  
• NON-HDL-C < 130 mg/dl |
| Moderate risk | ≤2 risk factors and 10-year risk <10% | • LDL-C< 100 mg/dl  
• NON-HDL-C < 130 mg/dl |
| Low risk      | 0 risk factors | • LDL-C< 130 mg/dl  
• NON-HDL-C < 160 mg/dl |
Treatment AACE 2017

- Maximum tolerate statin
- Ezetimibe
- PCSK9 inhibitors
- Other lipid lowering agents.
Management of Children with FH/AACE 2017

- Drug therapy in children and adolescents older than 10 years of age who satisfy the following criteria, can be considered:
  - LDL-C ≥190 mg/dL, or
  - LDL-C ≥160 mg/dL and
  - the presence of 2 or more cardiovascular risk factors, even after vigorous intervention;
  - having overweight or obesity, or having other elements of the insulin resistance syndrome; and/or
  - a family history of premature ASCVD (before age 55 years).
National Lipid Association

• Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric and Adult Patients. Journal of Clinical Lipidology (2011)
• Update: 2017
TWO RISK CATEGORIES

• **Very High Risk:** ASCVD or with major risk factors.

• **High Risk:** Without ASCVD or no risk factors.
**Table 1** Characteristics placing FH patient at the highest CVD risk

Intensification of treatment and an LDL-C goal <100 mg/dL (non-HDL-C < 130 mg/dL) is recommended for FH patients with any of these very high risk characteristics.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established CHD or other CVD</td>
<td>History of acute myocardial infarction, stroke, peripheral arterial disease,</td>
</tr>
<tr>
<td></td>
<td>resuscitated cardiac arrest, cardiovascular revascularization, stable</td>
</tr>
<tr>
<td></td>
<td>or unstable angina, transient ischemic attack, carotid artery stenosis &gt;50%,</td>
</tr>
<tr>
<td></td>
<td>aortic abdominal aneurysm</td>
</tr>
<tr>
<td>Smokers</td>
<td>Male current smokers have &gt;2-fold higher risk than female smokers – Encourage</td>
</tr>
<tr>
<td></td>
<td>smoking cessation to reduce risk</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Lifestyle or drug treated diabetes</td>
</tr>
<tr>
<td>Family history of very premature onset CHD</td>
<td>First or second degree male relative onset before age 45</td>
</tr>
<tr>
<td></td>
<td>First or second degree female relative onset before age 55</td>
</tr>
<tr>
<td>2 or more risk factors</td>
<td>See Table 2</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cut-points for risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Men &gt;30 years of age&lt;br&gt;Women &gt;40 years of age&lt;br&gt;&gt;250 mg/dL</td>
</tr>
<tr>
<td>Baseline LDL-C level</td>
<td>First degree male relative onset before age 55&lt;br&gt;First degree female relative onset before age 65</td>
</tr>
<tr>
<td>Male sex</td>
<td>Male sex</td>
</tr>
<tr>
<td>Smoking</td>
<td>Current smoker</td>
</tr>
<tr>
<td>Family history of premature onset CHD</td>
<td>First degree female relative onset before age 65</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3 of 5 characteristics:&lt;br&gt;• Increased waist circumference:&lt;br&gt;Men &gt;40&quot; (&gt;37&quot; in some populations) and women &gt;35&quot;&lt;br&gt;• Blood pressure ≥130 mm Hg/or ≥80 mm Hg or drug treatment&lt;br&gt;• Triglycerides ≥150 mg/dL or drug treatment&lt;br&gt;• Low HDL-C:&lt;br&gt;Men &lt;40 mg/dL and women &lt;50 mg/dL&lt;br&gt;• Elevated glucose ≥100 mg/dL or drug treatment&lt;br&gt;• HDL-C &lt;40 mg/dL&lt;br&gt;• Blood pressure &gt;140/or &gt;90 mm Hg or drug treatment&lt;br&gt;• ≥50 mg/dL using an isoform insensitive assay&lt;br&gt;• Tendon xanthoma</td>
</tr>
<tr>
<td>Low HDL-C level</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>High lipoprotein (a)</td>
<td></td>
</tr>
<tr>
<td>Physical findings</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
### Table 3  Adult FH treatment recommendations

1. **All** adult FH patients should receive long-term cholesterol-lowering therapy to reduce LDL-C by >50%
   - Almost all will require a high dose statin
2. Intensification of cholesterol-lowering therapy should be considered in higher risk FH patients (see Table 1)
   - Clinically evident CHD or other cardiovascular disease
   - Diabetes
   - Family history of very premature onset CHD (first degree relative male <45 years or female <55 years)
   - Current smoking (strongly encourage smoking cessation)
   - Two or more cardiovascular risk factors other than smoking (see Table 2)
   - Most will require ezetimibe or another drug in combination with a high dose statin
   - The potential benefit for an individual patient should be weighed against the potential for adverse effects, cost, and decreasing adherence with multidrug regimens.
3. Intensification of therapy may be considered in lower risk FH patients after the initial >50% reduction in LDL-C
4. Treat other cardiovascular risk factors
   - Emphasize a healthy diet, regular physical activity and weight control
   - Avoid tobacco
   - Control blood pressure <140/<90 mm Hg (Diabetes: <130/<80 mm Hg)
   - Low-dose aspirin for those with cardiovascular disease or diabetes; consider for those with ≥2 risk factors
5. Consider referral to a lipid specialist
   - More aggressive lipid management
   - Cascade testing to identify relatives with FH

Abbreviations: CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
NLA Thresholds for PCSK9 Inhibitor therapy in FH
After Max tolerated statin +Ezetimibe, 2017 Update

Homozygous FH
Very High Risk

Polygenic hypercholesterolemia
Heterozygous FH
Heterozygous FH with HoFH phenotype

Older: 40-80

More Risk Factors
Pre-Rx LDL 190 mg/dl and above
On-Rx LDL 190 mg/dl and above

Less Risk Factors
Pre-Rx LDL 190 mg/dl and above
On-Rx LDL 100 mg/dl and above

Younger: 18-40, with more risk factors

Pre-Rx LDL 190 mg/dl and above
On-Rx LDL 100 mg/dl and above

1st Saudi Familial Hypercholesterolemia Symposium & 3rd Severe FH Master Class 6-7 December 2019.
Treatment in Children

• Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.
• Consideration should be given to starting treatment at the age of 8 years or older. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages.
• The treatment goal of lipid lowering therapy in pediatric FH patients is a >50% reduction in LDL cholesterol or LDL cholesterol, 130 mg/dL.
• More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.
HoFH

• Initiation of therapy early in life and ongoing monitoring of homozygous FH is vital.

• **High dose statins** may be effective in some homozygous FH patients, but the majority will require **LDL apheresis**.

• **Liver transplantation** is also being used in some centers.

• **Gene therapy** is a potential new treatment in development and may be particularly beneficial for homozygous FH patients.
### Guidelines with Targets

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>AACE</th>
<th>NLA</th>
<th>ESC/EAS</th>
<th>CCS</th>
<th>IAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme</td>
<td>LDL-C &lt; 55 mg/dl</td>
<td>LDL-C &lt; 70 mg/dl</td>
<td>LDL-C &lt; 55 mg/dl (&lt; 1.4 mmol/l)</td>
<td>LDL-C &lt; 2.0</td>
<td>LDL-C &lt; 70 mg/dl</td>
</tr>
<tr>
<td></td>
<td>NON-HDL-C &lt; 80 mg/dl</td>
<td>NON-HDL-C &lt; 100 mg/dl</td>
<td>NON-HDL &lt; 80 mg/dl (&lt; 2.2 mmol/l)</td>
<td>Non-HDL &lt; 2.6 mmol/l</td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>LDL-C &lt; 70 mg/dl</td>
<td>LDL-C &lt; 70 mg/dl</td>
<td>LDL-C &lt; 70 mg/dl (&lt; 2.6 mmol/l)</td>
<td>LDL-C &lt; 2.0</td>
<td>LDL-C &lt; 70 mg/dl</td>
</tr>
<tr>
<td></td>
<td>NON-HDL-C &lt; 100 mg/dl</td>
<td>NON-HDL-C &lt; 100 mg/dl</td>
<td>NON-HDL &lt; 80 mg/dl (&lt; 2.2 mmol/l)</td>
<td>Non-HDL &lt; 2.6 mmol/l</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>LDL-C &lt; 100 mg/dl</td>
<td>LDL-C &lt; 100 mg/dl</td>
<td>LDL-C &lt; 70 mg/dl (&lt; 2.6 mmol/l)</td>
<td>LDL-C &lt; 2.0</td>
<td>LDL-C &lt; 100 mg/dl</td>
</tr>
<tr>
<td></td>
<td>NON-HDL-C &lt; 130 mg/dl</td>
<td>NON-HDL-C &lt; 130 mg/dl</td>
<td>NON-HDL &lt; 100 mg/dl (2.6 mmol/l)</td>
<td>Non-HDL &lt; 2.6 mmol/l</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Prevention**

**Secondary Prevention**
Algorithm for management of FH

**familial hypercholesterolemia**

- LDL-C targets:
  - <1.8 mmol/L (adults)
  - <1.4 mmol/L if clinical CVD or very high risk
  - <3.5 mmol/L (children)

**At diagnosis**
- Lifestyle and diet + statin + Ezetimibe 10 mg (most efficacious at highest dose depending on tolerability)

**HoFH**

**HeFH**

**Newer therapeutic options**
- ANGPT3 inhibitors
- siRNA inhibition
- Gene therapy

**Future therapeutic options**
- PCSK9 inhibitors: Receptor defective, PCSK9 mutations
- Lomitapide: Approved by FDA, EMA
- Mipomersen??

**LDL-apheresis**
- As early as possible if available (by 5 years, no later than 8 years) every 1 or 2 weeks

**In selected patients**
- Liver transplant
Statins
Ezetimibe
PCSK9-inhibitors
Mipomarsen
Lomitapide
Evinacumab
LDL-apheresis

LDLR Function

Frederick Raal, PhD
Conclusion:

- Familial Hypercholesterolemia is under diagnosed and better detection and treatment strategies are needed.
- Middle East region has an established epidemic of diabetes and metabolic syndrome that can complicate treatment and mask a clinical diagnosis of patients with FH.
- FH patients are at great risk of CVD and is estimated to be increased at least 10-fold. Therefore, FH is categorized in high, very high and extreme high risk categories according to latest guidelines.
- CVD risk assessment tools such as CAC may help further ‘personalize’ risk to weigh expected benefits and costs of adding new lipid lowering therapy and defining treatment targets according to risk category.
- Latest guidelines recommend more stringent targets for very high risk FH categories.
- Updated & focused FH guidelines needed especially with emerging new lipid lowering agents.
Resources for FH Education for Patients and Families

- Global genes (globalgenes.org)
- International FH Foundation (www.fh-foundation.org)
- Australia
  - Australian Heart Foundation (www.heartfoundation.org.au)
  - FH Australasian Network (www.athero.org.au)
- Brazil
  - Hipercol Brasil (www.hipercolesterolemia.com.br)
- Spain
  - Fundación Hipercolesterolemia Familiar (www.colesterolfamiliar.org)
- United Kingdom
  - Heart UK–The Cholesterol Charity (www.heartuk.org.uk)
  - British Heart Foundation (www.bhf.org.uk)
- United States
  - The FH Foundation (www.thefhfoundation.org)
  - The Foundation of the National Lipid Association (www.learnyourlipids.com)
  - National Human Genome Research Institute, National Institutes of Health (www.genome.gov/25520184)
  - National Institutes of Health, clinical trials (clinicalstudies.info.nih.gov)
  - National Organization for Rare Disorders (www.rarediseases.org)
  - Preventive Cardiovascular Nurses Association (www.pcna.net/patients/familial-hypercholesterolemia)
THANK YOU