Update on the Management of Hyperlipidemia
Carolyn Finocchiaro, ARNP
DISCLOSURES

• Speakers’ Bureau for Boehringer Ingelheim.
• There has been no commercial support or sponsorship for this program.
• The program co-sponsors do not endorse any products in conjunction with any educational activity.
Boston College Connell School of Nursing Continuing Education Program is accredited as a provider of continuing nursing education by the American Nurses Association Massachusetts, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.
SESSION OBJECTIVES

• Summarize the current ACC/AHA prevention guidelines and the rationale for the recommendations.
• Discuss risk calculation and how this will guide lipid management.
• Discuss the importance of lifestyle management in association with medication in order to help prevent cardiovascular events.
Dyslipidemia and CV Risk: A Clinical Overview
Carolyn Finocchiaro, APRN, CLS
Objectives

Review and Discuss

- Cholesterol metabolism and pathophysiology of atherogenic dyslipidemia
  - Role of lipids (cholesterol) and lipoproteins (e.g., LDL)
  - Lipid values and testing
- Predictors of cardiovascular risk
- Application of current guidelines
- Overview of current therapies for dyslipidemia
Major Arteries of the Heart and Atherosclerosis Formation

The role of these arteries is to bring oxygenated blood to the heart (which is a giant muscle).

Atherosclerosis: Buildup of cholesterol and other material, called plaque, on the arterial walls.
Risk Factors Associated with CHD

Major Risk Factors for CHD

- High blood pressure
- High blood cholesterol
- Tobacco use
- Unhealthy diet
- Physical inactivity
- Diabetes
- Advancing age
- Inherited (genetic) disposition

Other Risk Factors

- Poverty
- Low educational status
- Poor mental health (depression)
- Inflammation and blood clotting disorders

Lipid/Cholesterol Metabolism and Dyslipidemia
Lipids

- Cholesterol: fat (lipid) found in many food sources and produced naturally in the body
- Triglycerides: type of fat (lipid) in the bloodstream and adipose tissue. Consists of three fatty acids on 1 glycerol backbone

*apo(a) = apolipoprotein (a).
There Are Three Major Lipid Classes

LIPIDS

TRIGLYCERIDES
- **ENERGY**
  - **FATTY ACIDS**
  - **GLYCEROL**

PHOSPHOLIPIDS
- **STRUCTURE**
  - **FATTY ACIDS**
  - **GLYCEROL**
  - **PHOSPHO CONTAINING « HEAD »**

STEROIDS
- **COMMUNICATION**
  - **CHOLESTEROL**
  - **BILE SALTS**
  - **VITAMINE D**
  - **HORMONES**
    - (sex hormones, adrenal cortical hormones)

RELATED TO DYSLIPIDEMIAS
Cholesterol Has an Important Function in the Body

• Cholesterol is a type of fat (lipid) found in many food sources and produced naturally in the body\(^1\)

• It has 3 main functions within the body\(^2\)
  – Necessary part of cell walls
  – Precursor chemical for steroid compounds
  – Formation of bile acids for digestion

The liver is the main organ for the regulation of cholesterol.\(^3\)

Of the cholesterol absorbed in the intestines: 25% is from dietary sources (exogenous); 75% is from biliary sources undergoing enterohepatic circulation (endogenous).

Synthesis
Mainly in the liver, endocrine organs, muscle and skin

Absorption
From the diet and excretion into bile

Lipoproteins

Lipoproteins:

• Particles that transport cholesterol and triglycerides and are comprised of proteins (apolipoproteins), phospholipids, triglycerides, and cholesterol

• Range in density, depending on amount of triglycerides

• Names reflect density:
  – VLDL (Very Low Density Lipoproteins)
  – IDL (Intermediate Density Lipoproteins)
  – LDL (Low Density Lipoproteins)
  – HDL (High Density Lipoprotein)
  – Lp(a) stands for lipoprotein(a); the abbreviation reflects its structure as an LDL particle (lipoprotein) attached to the protein, apo(a)*

• Most made in liver and have large proteins (called apolipoproteins) as their structural core
  – VLDL has Apo B 100, Apo CI, Apo CII, Apo C III and Apo E.
  – IDL has Apo E and Apo B 100
  – LDL and Lp(a), has Apo B
  – HDL has Apo AI and Apo AII
Why Lipoproteins?

Oil and water don’t mix

Lipids (triglycerides, phospholipids, sterols) need vehicles (lipoproteins) to travel through aqueous media:\(^1,2:\)
- Lymph
- Plasma

Lipoproteins help transport lipids:\(^1,3:\)
- Absorb/distribute dietary/intestinal lipids
- Re-distribute endogenous lipids
- Energy use/storage
- Cell structure

Structure of a Lipoprotein

- Lipoproteins are a grouping of different lipid molecules and proteins that vary in size.

- There are 4 major elements: cholesterol, TGs, phospholipids, and specific proteins called apolipoproteins.

Artwork used with permission from the National Lipid Association.

# 3 Major Classes of Lipoproteins

- The 3 major classes of lipoproteins are LDL, HDL, and VLDL$^1$

<table>
<thead>
<tr>
<th>Lipoproteins$^1$</th>
<th>Percent of Total Serum Cholesterol$^1$</th>
<th>Major Apolipoproteins$^1$</th>
<th>Function$^{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL$^a$</td>
<td>60% to 70%</td>
<td>Apo B-100 (Apo B)</td>
<td>Delivers cholesterol</td>
</tr>
<tr>
<td>HDL$^a$</td>
<td>20% to 30%</td>
<td>Apo AI and Apo All</td>
<td>Reverse cholesterol transport</td>
</tr>
<tr>
<td>VLDL$^a$</td>
<td>10% to 15%</td>
<td>Apo B, Apo Cs, and Apo E</td>
<td>Transports endogenous triglycerides, phospholipids, cholesterol, and cholesteryl esters</td>
</tr>
</tbody>
</table>

$^1$More commonly measured as cholesterol concentration [-C]: LDL-C, HDL-C, and VLDL-C.

LDL= high-density lipoprotein; HDL = high-density lipoprotein; VLDL = very low-density lipoprotein.

Atherogenic, Apo B-Containing Lipoproteins Deposit Cholesterol, Initiating CVD

- Cholesterol is carried through the arteries by atherogenic lipoproteins
  - 70% of cholesterol is carried by LDL (low density lipoprotein) particles
  - Other lipoproteins include VLDL, IDL, and Lp(a)
- Each atherogenic lipoprotein has one Apo B molecule, a single large protein as its structural core
Elevated Plasma Levels of LDL, HDL, and Triglycerides

<table>
<thead>
<tr>
<th>Lipoprotein Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-density lipoprotein (LDL)</strong></td>
<td>• 60-70% of the total cholesterol in the bloodstream</td>
</tr>
<tr>
<td></td>
<td>• LDL-C is commonly quoted as ‘bad’ cholesterol</td>
</tr>
<tr>
<td></td>
<td>• Major cause of atherosclerosis and cardiovascular diseases</td>
</tr>
<tr>
<td><strong>High-density lipoprotein (HDL)</strong></td>
<td>• HDL-C is commonly quoted as ‘good’ cholesterol</td>
</tr>
<tr>
<td></td>
<td>• High HDL-C levels are anti-atherogenic</td>
</tr>
<tr>
<td></td>
<td>• Higher risk for atherosclerosis when low HDL-C levels</td>
</tr>
<tr>
<td><strong>Triglycerides (TG)</strong></td>
<td>• High levels of TG may contribute to the stiffening of the arteries</td>
</tr>
<tr>
<td></td>
<td>and increase in plaque buildup</td>
</tr>
</tbody>
</table>
What Is Non–HDL-C?

Non–HDL-C = Total-C − HDL-C

Composition of Lipoproteins

- **Chylomicron**
  - 80%-95%
  - 3%-9%
  - 2%-7%
  - 1%

- **VLDL**
  - 55%-80%
  - 10%-20%
  - 5%-15%
  - 8%

- **IDL**
  - 20%-50%
  - 15%-25%
  - 20%-40%
  - 11%

- **LDL**
  - 5%-15%
  - 20%-25%
  - 45%-50%
  - 21%

- **HDL**
  - 5%-10%
  - 20%-30%
  - 15%-25%
  - 33%-57%

**Triglyceride**

**Phospholipid**

**Cholesterol**

**Protein**

IDL = intermediate-density lipoprotein.

Apolipoproteins (apo) coat lipoprotein particles and serve a number of functions including the transport of lipids in the blood and recognition of lipoprotein particles by enzymes which process or remove lipids from the lipoprotein particles.

Apo B occurs as 1 molecule per LDL particle, either Apo B-48 (chylomicron) or Apo B-100 (VLDL, IDL or LDL), is present on each lipoprotein particle.

Apo B-Containing, Atherogenic Lipoproteins:

Apolipoprotein B (Apo B) as a Measure of Circulating LDL Particle Number (LDL-P) Concentration

Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices:

- LDL cholesterol (LDL-C) has been the cornerstone measurement for the assessment of cardiovascular disease (CVD) risk.
- Awareness gradually developed that Apo B, occurring as 1 molecule per LDL particle, was a more representative indicator of the concentration of LDL.

Results from prospective studies generally demonstrate the superiority of Apo B or LDL-P over LDL-C measurement for the assessment of risk.

The Lipid Transport System in Plasma Involves 2 Pathways: Lipid Metabolism

**Exogenous Pathway**
Route for the transport of cholesterol and TGs absorbed from dietary fat in the intestine

**Endogenous Pathway**
Route for cholesterol and TGs to reach the plasma from the liver and other nonintestinal tissues

Predictors of Cardiovascular Risk
Coronary Risk Profile (Lipid Panels)

- Measure the cholesterol or triglyceride content of lipoproteins, expressed as mg/dL (or mmol/L) of cholesterol or triglyceride.

- A standard lipid panel includes:
  - Total cholesterol (TC)
  - Low-density lipoprotein (LDL) cholesterol
  - High-density lipoprotein (HDL) cholesterol
  - Triglycerides
Example of Standard Lipid Panel

Identifies basic lipid parameters (LDL-C, TGs, and HDL-C)…

…TC/HDL ratio and estimated CHD risk

<table>
<thead>
<tr>
<th>Tests</th>
<th>Result</th>
<th>Flag</th>
<th>Units</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, Total</td>
<td>210</td>
<td>High</td>
<td>mg/dL</td>
<td>100-199</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>236</td>
<td>High</td>
<td>mg/dL</td>
<td>0-149</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>36</td>
<td>Low</td>
<td>mg/dL</td>
<td>&gt;39</td>
</tr>
<tr>
<td>LDL Cholesterol Calc</td>
<td>127</td>
<td>High</td>
<td>mg/dL</td>
<td>0-99</td>
</tr>
</tbody>
</table>

According to ATP-III Guidelines, HDL-C >59 mg/dL is considered a negative risk factor for CHD.

Comment

If initial LDL-cholesterol result is >100 mg/dL, assess for risk factors.

<table>
<thead>
<tr>
<th>T. Chol/HDL Ratio</th>
<th>5.8</th>
<th>High</th>
<th>ratio units</th>
<th>0.0-5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated CHD Risk</td>
<td>1.2</td>
<td>High</td>
<td>times avg.</td>
<td>0.0-1.0</td>
</tr>
</tbody>
</table>

Men  Women
1/2 Avg.Risk  3.4   3.3
Avg.Risk  5.0   4.4
2X Avg.Risk  9.6   7.1
3X Avg.Risk  23.4  11.0

The CHD Risk is based on the T. Chol/HDL ratio. Other factors affect CHD Risk such as hypertension, smoking, diabetes, severe obesity, and family history of premature CHD.
Advanced Lipid Panels

**Advanced Lipid Panels**

- Used to enhance CVD risk assessment, especially in individuals with low or normal LDL cholesterol, by detecting the:
  - Presence of higher concentrations of atherogenic lipoprotein particle concentrations (e.g., apoB) or,
  - Presence of small dense LDL particles

<table>
<thead>
<tr>
<th>Lipid Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo B</td>
<td>Direct measurement of the number of lipoprotein particles, including LDL, IDL, and VLDL</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>LDL particle with an inherited apoprotein (a) variant attached</td>
</tr>
<tr>
<td>Apo A1</td>
<td>Major protein component of HDL</td>
</tr>
<tr>
<td>LDL-P</td>
<td>Direct measure of LDL particle number</td>
</tr>
<tr>
<td>LDL particle size</td>
<td>Smaller LDL particles appear to be more atherogenic</td>
</tr>
<tr>
<td>Lp-PLA₂</td>
<td>Marker for vascular-specific inflammation</td>
</tr>
<tr>
<td>hsCRP</td>
<td>One of a number of acute phase reactant proteins that increases in response to inflammatory stimuli</td>
</tr>
</tbody>
</table>
Advanced Lipid Panels

Examples of Advanced Lipid Panels

• **“NMR Lipoprobe” (LipoScience):** FDA approved technology that gives a direct measure of LDL particle number (LDL-P) along with standard cholesterol results.

• **“VAP Test” (Atherotech):** Directly measures LDL-C, measurement of LDL pattern density (Pattern B), and lipoprotein subclasses such as HDL2 and HDL3.

• **“Berkeley” (Berkeley Heart Lab):** Lipoprotein subfractionation by ion mobility that captures the size and subclasses of the entire lipoprotein particle range, including VLDL, IDL, LDL, and HDL.
Examples of Advanced Lipid Panels

NMR Lipoprofile®

- LDL particle number (LDL-P) and optimal levels

The VAP® Test

- Lipoproteins, subclasses, and desired amounts
**Classification of Lipid Disorders: Dyslipidemia**

- Dyslipidemia is defined as *abnormal levels of lipids in the blood*

### Frederickson Classification of Lipid Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Elevated Particles</th>
<th>Associated-clinical Disorders</th>
<th>Serum TC</th>
<th>Serum TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Chylomicrons</td>
<td>LPL deficiency, Apo C-II deficiency</td>
<td>→</td>
<td>↓↓</td>
</tr>
<tr>
<td>Type IIa</td>
<td>LDL</td>
<td>Familial hypercholesterolemia (FH), polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia</td>
<td>↑↑</td>
<td>→</td>
</tr>
<tr>
<td>Type IIb</td>
<td>LDL, VLDL</td>
<td>Familial combined hyperlipidemia</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Type III</td>
<td>IDL</td>
<td>Dysbetalipoproteinemia</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Type IV</td>
<td>VLDL</td>
<td>Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes</td>
<td>→↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Type V</td>
<td>Chylomicrons, VLDL</td>
<td>Diabetes</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

↑ = increased;  ↑↑ = greatly increased;  → = normal;  →↑ = normal or increased
Too Much Cholesterol in the Blood, Along With Other Substances, Can Lead to Atherosclerosis

Cholesterol (lipid) is transported to and deposited in artery walls by lipoproteins

1. Atherosclerosis (or hardening of the arteries) is a progressive disease caused when fat, cholesterol, and other substances, build up in the inner walls of arteries and form hard structures called plaques.

2. Sometimes this plaque can break open.

3. When this happens, a blood clot forms and blocks the artery causing heart attacks and strokes.

---


Early Stages of Atherogenesis Involve Apo B

- Serum total Apo B has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events\(^1\)

Artwork used with permission from the National Lipid Association.

Non–HDL-C Is Stronger than LDL-C in Predicting CHD Risk

The Framingham Study

- Within Non–HDL-C levels, no association was found between LDL-C and the risk for CHD.
- Strong, positive, graded association of Non–HDL-C with CHD seen at every LDL-C level.

Dyslipidemia Management Guidelines
Management of Dyslipidemia Guidelines

- Several national and international associations have issued guidelines to recommend therapeutic levels of lipoproteins.
NCEP ATP III Guidelines: CV Risk Assessment

Major Risk Factors Other Than LDL-C Used In Risk Factor Counting

- Age (men ≥45 years; women ≥55 years)
- Current cigarette smoking
- Hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL-C (<40 mg/dL)
- Family history of premature CHD (Myocardial infarction or sudden death in male first-degree relative <55 years of age and in female first-degree relative <65 years of age)

Assessment tool: Framingham Risk Score

- Determines an individual’s 10-year absolute CHD risk and is based on 5 major independent risk factors
  - High systolic blood pressure
  - Cigarette smoking
  - High TC
  - Low HDL-C
  - Age
- It’s recommended for patients with 2 or more risk factors

NCEP ATP III = The NCEP Adult Treatment Panel III (ATP III).
**NCEP ATP III Guidelines**

**Dyslipidemia Risk Stratification**

- The initial step in dyslipidemia management is to stratify a patient based on his/her level of risk for an acute cardiovascular event.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very High Risk</strong></td>
<td>CHD or CHD risk equivalents and a 10-year risk of &gt;20%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>≥2 risk factors and a 10-year risk of 10 to 20%</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>≥2 risk factors and a 10-year risk of &lt;10%</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td>0 to 1 risk factor</td>
</tr>
</tbody>
</table>

<sup>a</sup>CHD=history of MI, unstable or stable angina, coronary artery procedure, or evidence of clinically significant myocardial ischemia; CHD risk equivalents = manifestations of non coronary forms of atherosclerotic disease, diabetes, and 2 risk factors with 10-year risk of CHD>20%.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment Goals</th>
<th>LDL-C (mg/dL)</th>
<th>Non–HDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk</td>
<td>CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 (optional goal: &lt;70)</td>
<td>&lt;130 (optional goal: &lt;100)</td>
</tr>
<tr>
<td>High Risk</td>
<td>≥2 risk factors (10-year risk 10%-20%)</td>
<td>&lt;130 (optional goal: &lt;100)</td>
<td>&lt;160 (optional goal: &lt;130)</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>≥2 risk factors (10-year risk &lt;10%)</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0-1 risk factors</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>

**ASCVD Risk Reduction Is Goal**

**Update to 2004 ATP III cholesterol guidelines update**

<table>
<thead>
<tr>
<th>Then:</th>
<th>Now:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin therapy to achieve LDL-C &amp; non-HDL-C targets</td>
<td>Statin therapy for all individuals at increased ASCVD risk who are likely to benefit from risk reduction</td>
</tr>
</tbody>
</table>

→ *“Statin benefit” groups*

Lifestyle modification is the cornerstone before and during cholesterol-lowering therapy

ASCVD = atherosclerotic cardiovascular disease
Statin Benefit Groups for ASCVD Prevention

Recommendation:
• High- or moderate-intensity statin therapy for all who will benefit from ASCVD risk reduction
• Lifestyle modification before, during statin therapy

4 statin benefit groups:
1. Clinical ASCVD
2. Primary elevations of LDL-C ≥190 mg/dL
3. Age 40-75 yrs with diabetes and LDL-C 70-189 mg/dL
4. Age 40-75 with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk ≥7.5%

ASCVD risk reduction benefit outweighs risk of adverse effects

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

ASCVD Statin Benefit Group 1: Secondary Prevention

Secondary prevention

Adults with clinical ASCVD (candidates for statin therapy)

<table>
<thead>
<tr>
<th>Age ≤ 75 yrs</th>
<th>High-intensity statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 yrs</td>
<td>Moderate-intensity statin</td>
</tr>
<tr>
<td>or Not candidate for high-intensity statin</td>
<td></td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization.

ASCVD Statin Benefit Group 2: Primary Prevention LDL-C ≥ 190

Primary prevention

Adults with primary LDL-C ≥ 190 mg/dL—familial hypercholesterolemia (candidates for statin therapy)

High-intensity statin

If not candidate for high-intensity statin: Moderate-tolerated statin

High-intensity statin

↓ LDL-C by ≥50%

Moderate-intensity statin

↓ LDL-C by 30%-50%

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Primary prevention—diabetes

Adults aged 40-75 yrs with diabetes and LDL-C 70-189 mg/dL (candidates for statin therapy)

Moderate-intensity statin  If estimated 10-yr ASCVD risk ≥7.5%:
High-intensity statin

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

ASCVD Statin Benefit Group 4: Primary Prevention ≥7.5% 10-Yr Risk, No Diabetes

Primary prevention—no diabetes

Adults aged 40-75 yrs with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk ≥7.5%*

Moderate- to high-intensity statin

<table>
<thead>
<tr>
<th>High-intensity statin</th>
<th>Moderate-intensity statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ LDL-C by ≥50%</td>
<td>↓ LDL-C by 30%-50%</td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Estimated 10-Yr ASCVD Risk Guides Statin Therapy

- For primary prevention of ASCVD in individuals with LDL-C 70-189 mg/dL

Estimated absolute 10-yr ASCVD risk guides statin initiation

- For primary prevention of ASCVD in individuals with diabetes

Estimated absolute 10-yr ASCVD risk guides statin intensity

- For individuals with clinical ASCVD or LDL-C ≥190 mg/dL already in a statin benefit group

Not appropriate to estimate 10-yr ASCVD risk

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

# High- and Moderate-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL-C by ~≥50%</td>
<td>Lowers LDL-C by ~30% to &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin 40*-80 mg</td>
<td>Atorvastatin 10 mg (20 mg)</td>
</tr>
<tr>
<td>Rosuvastatin 20 mg (40 mg)</td>
<td>Rosuvastatin (5 mg) 10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg†</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 mg (80 mg)</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

*Down titrate if unable to tolerate atorvastatin 80 mg;
†Initiation of or titration to simvastatin is not recommended by the FDA due to increased myopathy risk

Italics denotes FDA-approved doses that were not tested in trials reviewed for guideline development

Once-daily doses unless otherwise specified. Avg LDL-C-lowering potential listed expected to vary in clinical practice.
The Argument Against LDL-C, Non-HDL-C Targets

- No RCTs demonstrating
  - Titrated drug therapy to achieve targets reduces ASCVD risk
  - What targets should be
- Unknown magnitude of incremental ASCVD risk reduction with one target compared to another
- Unknown rate of adverse events from multidrug therapy to attain targets
- Use of LDL targets may result in under-treatment with statin therapy
  - Suboptimal dose used when target achieved
- ...Or overtreatment with nonstatin drugs
  - Adding nonstatin therapy to achieve target results in down-titration of statin for safety reasons
  - Nonstatin drugs have not been shown to reduce ASCVD risk

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Role of Biomarkers & Imaging Tests

Select individuals *not* in 1 of 4 statin benefit groups
— Decision to initiate statin unclear

May consider other factors influencing ASCVD risk:
- Primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset <55 yrs in first-degree male relative, <65 yrs female
- hs-CRP ≥2 mg/L
- CAC score ≥300 Agatston units (or ≥75th percentile for age, sex, ethnicity)
- ABI <0.9
- Elevated lifetime ASCVD risk

Also consider:
- Potential ASCVD risk benefits, adverse effects
- Drug-drug interactions
- Patient preferences for statin treatment

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

ABI = ankle-brachial index; CAC = coronary artery calcium; hs-CRP = high-sensitivity C-reactive protein

### LDL-C, Non–HDL-C Targets

#### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>ACC/AHA COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No recommendations for or against specific LDL-C or non–HDL-C targets for primary or secondary ASCVD prevention</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

No evidence supporting titration of cholesterol-lowering drug therapy to achieve optimal LDL-C or non–HDL-C levels

ASCVD = atherosclerotic cardiovascular disease: acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

COR = class of recommendation; LOE = level of evidence

### Statin Therapy for Secondary Prevention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>ACC/AHA COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Prevention: Clinical ASCVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Adults aged ≤75 yrs: Initiate or continue high-intensity statin therapy as first-line therapy unless contraindicated</td>
<td>A (Strong)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2. Moderate-intensity statin therapy: If high-intensity contraindicated or statin intolerant</td>
<td>A (Strong)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>3. Age &gt;75 yrs: Evaluate potential for ASCVD risk-reduction benefits, adverse effects, DDIs; and consider patient preferences when initiating high- or moderate-intensity statin Continue statin therapy if tolerant</td>
<td>E (Expert Opinion)</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
COR = class of recommendation; DDIs = drug-drug interactions; LOE = level of evidence

# Statin Therapy for Primary Prevention—LDL-C ≥190

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBII Grade</th>
<th>ACC/AHA COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention: LDL-C ≥190 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. LDL-C ≥190 mg/dL or TG ≥500 mg/dL: Evaluate for secondary causes of hyperlipidemia</td>
<td>B (Moderate)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2. High-intensity statin therapy for primary LDL-C ≥190 mg/dL unless contraindicated 10-yr ASCVD risk estimation not required</td>
<td>B (Moderate)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>If high-intensity statin intolerant: use maximum-tolerated statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Untreated primary LDL-C ≥190 mg/dL: Intensify statin therapy to achieve ≥50% LDL ↓</td>
<td>E (Expert Opinion)</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>4. Untreated primary LDL-C ≥190 mg/dL after maximum intensity of statin therapy achieved: May consider adding nonstatin drug to further lower LDL-C*</td>
<td>E (Expert Opinion)</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

*Evaluate potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions; consider patient preferences

COR=class of recommendation; LOE=level of evidence

Statin Therapy for Primary Prevention—Diabetes & LDL-C 70-189

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>ACC/AHA COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention: Diabetes &amp; LDL-C 70-189 mg/dL—no clinical ASCVD</td>
<td>A (Strong)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1. Age 40-75 yrs with diabetes: Moderate-intensity statin therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Age 40-75 yrs with diabetes and estimated 10-yr ASCVD risk* ( \geq 7.5% ) :</td>
<td>E (Expert Opinion)</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>High-intensity statin therapy unless contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Age &lt;40 or &gt;75 yrs with diabetes: Evaluate potential for ASCVD benefits, adverse effects, DDIs; consider patient preferences when initiating, continuing, or intensifying statin therapy</td>
<td>E (Expert Opinion)</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

*Estimated 10-yr ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

COR = class of recommendation; DDIs = drug-drug interactions; LOE = level of evidence
## Statin Therapy for Primary Prevention—LDL-C 70-189, No Diabetes

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>ACC/AHA COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention: LDL-C 70-189 mg/dL—no diabetes or clinical ASCVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Estimate 10-yr ASCVD risk* to guide statin therapy initiation for primary prevention</td>
<td>E (Expert Opinion)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2. Age 40-75 yrs with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk* ≥7.5%: Moderate-to-high-intensity statin therapy</td>
<td>A (Strong)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>3. Age 40-75 with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD* risk 5% to &lt;7.5%: Moderate-intensity statin therapy</td>
<td>C (Weak)</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>4. Before initiating statin: HCP and patient to discuss potential for ASCVD risk reduction benefits, adverse effects, DDIs, patient preferences</td>
<td>E (Expert Opinion)</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>5. LDL-C &lt;190 and not in a statin benefit group or risk assessment unclear, consider: LDL-C ≥160, family hx premature ASCVD, hs-CRP &gt;2, CAC score ≥300, ABI &lt;0.9, lifetime ASCVD risk Eval risk reduction benefits, AEs, DDIs, patient prefs</td>
<td>E (Expert Opinion)</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

---

*Estimated 10-yr ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke
ASCVD=atherosclerotic cardiovascular disease; history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; peripheral arterial disease or revascularization
AEDs=adverse effects; COR=class of recommendation; DDIs=drug-drug interactions; LOE=level of evidence

## Heart Failure and Hemodialysis

### Recommendations

<table>
<thead>
<tr>
<th>NHLBI Grade</th>
<th>ACC/AHA COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

1. No recommendations regarding initiation or discontinuation of statins in patients with NYHA class II-IV ischemic systolic heart failure or those on maintenance hemodialysis.

*Treating clinician to consider *before* prescribing statin for these patients:
- Potential ASCVD risk reduction benefit, adverse effects, DDIs, cautions, contraindications
- Choice of statin dose

---

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization.

COR = class of recommendation; DDIs = drug-drug interactions; LOE = level of evidence; NYHA = New York Heart Association.

High-Intensity Statin for Secondary ASCVD Prevention

- Individuals with clinical ASCVD at increased risk for
  - Recurrent ASCVD
  - ASCVD death
- High-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy in adults aged ≤75 yrs

<table>
<thead>
<tr>
<th><strong>Initiate high-intensity statin</strong></th>
<th><strong>for adults ≤75 yrs with clinical ASCVD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If on low or moderate statin therapy, increase intensity</strong></td>
<td><strong>— unless history of intolerance to higher dose, other factors influencing safety</strong></td>
</tr>
<tr>
<td><strong>If high-intensity contraindicated or potential for adverse effects</strong></td>
<td><strong>moderate-intensity as second option if tolerated</strong></td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Secondary ASCVD Prevention for Age >75 Yrs

- Moderate-intensity statin therapy shown to reduce ASCVD events in adults aged >75 yrs

<table>
<thead>
<tr>
<th>Moderate-intensity statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider for individuals aged &gt;75 yrs with clinical ASCVD</td>
</tr>
<tr>
<td>Individualize therapy based on potential for ASCVD risk reduction benefits, adverse effects, DDIs, patient preferences</td>
</tr>
<tr>
<td>Continue statin therapy if no tolerance issues</td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

Statin Initiation for Secondary Prevention: Age ≤ 75 Yrs

Age ≤ 75 yrs with clinical ASCVD: not on statin therapy

1. Initial evaluation before initiating statin therapy:
   - Fasting lipid panel
   - ALT
   - CK
   - Consider eval for secondary causes or conditions influencing statin safety

2. No contraindications, comorbidities, DDIs influencing statin safety, or history of statin intolerance

3. Initiate high-intensity statin therapy
   - Counsel on lifestyle

4. Monitor statin therapy

Evaluate and treat lab abnormalities
1. TG ≥ 500 mg/dL
2. LDL-C ≥ 190 mg/dL

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; ALT = alanine aminotransferase; CK = creatinine kinase; DDIs = drug-drug interactions; FH = familial hypercholesterolemia; ULN = upper limit of normal

Statin Initiation for Secondary Prevention: Age >75 Yrs

Age > 75 yrs* with clinical ASCVD or with conditions or DDIs influencing statin safety, or history of statin intolerance: not on statin therapy

1. Initial evaluation before initiating statin therapy:
   - Fasting lipid panel
   - ALT
   - CK
   - Consider eval for secondary causes or conditions influencing statin safety

2. Initiate moderate-intensity statin therapy
   - Counsel on lifestyle

3. Monitor statin therapy

Evaluate and treat lab abnormalities
1. TG ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes
   - If primary, screen for FH
3. Unexplained ALT >3X ULN

*Reasonable to evaluate for ASCVD potential benefits and adverse effects, and to consider patient preferences in initiating or continuing a moderate- or high-intensity statin
ASCVD=atherosclerotic cardiovascular disease; history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; ALT=alanine aminotransferase; CK=creatine kinase; DDIs=drug-drug interactions; FH=familial hypercholesterolemia; ULN=upper limit of normal

Primary ASCVD Prevention for LDL-C ≥190 mg/dL

- Primary, severe LDL-C elevations (≥190 mg/dL) confer a high lifetime risk for ASCVD events
  - Lifetime exposure to markedly high LDL-C from genetic causes
- High-intensity statin therapy for all adults aged ≥21 yrs with LDL-C ≥190
  - If not already diagnosed and treated before age 21
- Substantial LDL-C reductions, intensive risk factor management needed to reduce ASCVD risk

Each 39 mg/dL ↓ in LDL-C equals 20% ↓ in ASCVD risk

- High-intensity statin therapy to achieve ≥50% LDL-C reduction
- But—maximal statin therapy may not be adequate for sufficient LDL reduction to blunt ASCVD risk: nonstatin medications often needed

ASCVD = atherosclerotic cardiovascular disease

No clinical ASCVD, not on lipid-lowering treatment

1. Initial evaluation before initiating statin therapy:
   - Fasting lipid panel
   - ALT
   - A1C (if diabetes status unknown)
   - CK
   - Consider eval for secondary causes or conditions influencing statin safety

2. Assign to statin benefit group: Diabetes & age 40-75 or LDL ≥190
   - Counsel on lifestyle

3. Discuss with patient
   - ASCVD risk reduction benefits
   - Adverse effects
   - DDIs
   - Patient preferences

4. Initiate statin therapy based on statin benefit group assignment
   - Reinforce need for healthy lifestyle

5. Monitor statin therapy

Eval & treat lab abnormalities
1. TG ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes
   - If primary, screen for FH
3. Unexplained ALT >3X ULN

ASCVD=atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization;
ALT=alanine aminotransferase; CK=creatine kinase; DDIs=drug-drug interactions; ULN=upper limit of normal

Statin Initiation for Primary ASCVD Prevention: Age 40-75, LDL 70-189, No Diabetes

1. Initial evaluation before initiating statin therapy:
   - Fasting lipid panel
   - ALT
   - CK
   - Consider eval for secondary causes or conditions influencing statin safety

2. Assign to statin benefit group: No diabetes, age 40-75, LDL 70-189
   - Counsel on lifestyle

3. Estimate 10-yr ASCVD risk with Pooled Cohort Equations
   - ≥7.5%
   - 5% to <7.5%
   - <5%

4. Initiate statin therapy based on statin benefit group assignment
   - Reinforce need for healthy lifestyle

5. Monitor statin therapy

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization; *Includes age <40 or ≥75 and LDL <190; †Incl primary LDL ≥160 or other evidence of genetic hyperlipidemias, family history early ASCVD, hs-CRP ≥2, CAC score ≥300, ABI <0.9, elevated lifetime ASCVD risk

ALT = alanine aminotransferase; CK = creatine kinase; ULN = upper limit of normal

2013 ACC/AHA Guideline: Cholesterol Treatment to Reduce ASCVD Risk in Adults

KnowledgePoint360 Group, LLC

©2013
Primary ASCVD Prevention in Individuals With Diabetes

- **Moderate-intensity** statin therapy for individuals with diabetes aged 40-75
- **High-intensity** statin therapy if diabetes, age 40-75, and 10-yr ASCVD risk ≥7.5%

<table>
<thead>
<tr>
<th>Diabetes aged 40-75 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Substantially increased lifetime risk for ASCVD events and death</td>
</tr>
<tr>
<td>✓ Greater morbidity and worse survival after ASCVD onset</td>
</tr>
</tbody>
</table>

- Individualize statin therapy based on ASCVD risk reduction benefits, potential for adverse effects and DDIs, patient preferences

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
Primary ASCVD Prevention in Individuals With LDL 70-189—No Diabetes

- Estimated 10-yr ASCVD risk guides initiation of statin therapy
- *Moderate- or high-intensity* statin therapy to reduce ASCVD risk if age 40-75 with 10-yr ASCVD risk \( \geq 7.5\% \)
  - Reduction in ASCVD risk outweighs potential for adverse effects

---

**LDL-C 70-189—No clinical ASCVD or diabetes**

Age 40-75

- Initiate statin therapy if 10-yr ASCVD risk \( \geq 7.5\% \)*

---

ASCVD = atherosclerotic cardiovascular disease: history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization.

*If not already candidates for statin therapy based on the presence of ASCVD, diabetes or LDL-C \( \geq 190\) mg/dL.
Primary ASCVD Prevention for Individuals Not in A Statin Benefit Group

- Adults with LDL-C <190 who are not identified in statin benefit group or
- Adults for whom risk-based treatment is uncertain after risk assessment

Factors influencing decision to initiate statin therapy

- Clinician knowledge, experience, and skill
- Patient preferences

Before initiating statin therapy, clinician and patient to discuss

- Potential for ASCVD risk reduction benefits, adverse effects, DDIs

Additional factors to consider for select individuals

<table>
<thead>
<tr>
<th>LDL-C ≥160 mg/dL*</th>
<th>Family history of premature ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP ≥2 mg/dL</td>
<td>CAC score ≥300 Agatston units</td>
</tr>
<tr>
<td>ABI &lt;0.9</td>
<td>Elevated lifetime ASCVD risk</td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease; history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization

*C or other evidence of genetic dyslipidemias

CAC = coronary artery calcium; DDIs = drug-drug interactions; hs-CRP = high-sensitivity C-reactive protein

10-Yr ASCVD Risk Assessment Calculator—Primary Prevention

- Comprehensive assessment of 10-yr risk for ASCVD event
  - Includes CHD and stroke
- Use Pooled Cohort Risk Assessment Equations
  - [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)
- Predicts stroke and CHD events in non-Hispanic Caucasian and African American men and women aged 40-79 years with or without diabetes and LDL-C 70-189 mg/dL

ASCVD=atherosclerotic cardiovascular disease; history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack of atherosclerotic origin; and peripheral arterial disease or revascularization
CHD=coronary heart disease
Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk

MI = Myocardial Infarction

Effect of Partial Ileal Bypass Surgery on Mortality and Morbidity from Coronary Heart Disease in Patients with Hypercholesterolemia

POSCH Trial

Total Plasma Cholesterol Levels in the Control and Surgery Groups

Values are means with 95 percent confidence intervals. The difference between the groups at each follow-up interval was significant (P<0.0001).

Confirmed Myocardial Infarction and Death Due to Atherosclerotic Coronary Heart Disease as a Combined End Point (“Event”) in the Study Groups

The difference between the groups was significant (P<0.001). The numbers of patients at risk for an event are shown at two-year intervals.

Low HDL-C Greatly Increases CHD Risk

*Data represent men age 50–70 yr from the Framingham Study.
Adapted from and reprinted with permission from Castelli WP. Can J Cardiol. 1988;4(suppl A):5A. Reprinted by permission.
Lipid Lowering Therapy
Objectives

- Understand importance of treating serum cholesterol
- Understand current and future therapies for dyslipidemia
- Understand primary and secondary outcomes data with available treatments for dyslipidemia
- Understand important information regarding commonly used lipid lowering therapies
Primary and secondary outcomes data
Outcomes Data by Class

- **Primary Prevention of Cardiovascular Disease (CVD)**: Preventing CVD before it occurs
- **Secondary Prevention of Cardiovascular Disease (CVD)**: Preventing additional attacks of CVD after the first attack has occurred


<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. Trials</th>
<th>No. Treated</th>
<th>Mean Cholesterol Reduction (%)</th>
<th>Non-fatal MI</th>
<th>CHD Incidence (% Change)</th>
<th>CHD Mortality (% Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins**</td>
<td>12</td>
<td>17,405</td>
<td>20</td>
<td>NA</td>
<td>-30</td>
<td>-29</td>
</tr>
<tr>
<td>Nicotinic Acid (Niacin)**</td>
<td>7</td>
<td>5,137</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-16</td>
</tr>
<tr>
<td>Fibric Acid Derivatives (Fibrates)**</td>
<td>6</td>
<td>11,590</td>
<td>NA</td>
<td>-21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bile Acid Sequestrants**</td>
<td>3</td>
<td>1,992</td>
<td>9</td>
<td>NA</td>
<td>-21</td>
<td>-32</td>
</tr>
</tbody>
</table>

*Outcomes data presented in Prescribing Information for Pravachol, Lipitor, Crestor, Mevacor, and Zocor.*
MRFIT showed strong correlation between serum cholesterol and CVD mortality

Objective
• To test the effect of a multifactor intervention program on mortality from coronary heart disease (CHD)

Design
• Randomized, primary prevention trial; N=361,662

Results
• Each 1% reduction in total cholesterol level resulted in a 2% decrease in CHD risk
Current and Future Management Options for Dyslipidemia

**Current Therapies**
- Statins (HMG-CoA Reductase Inhibitors)
- Cholesterol Absorption Inhibitor (CAI)
- Bile Acid Sequestrants (BAS)
- Nicotinic Acid (Niacin)
- Omega-3 Fatty Acids (FAs)
- Fibric Acid Derivatives (Fibrates)
- Microsomal Triglyceride Transfer Protein (MTP) Inhibitor
- LDL Apheresis

**Future Therapies**
- PCSK9 Monoclonal Antibody (mAB)
- Cholesterol Ester Transfer Protein (CETP)
Statins
(HMG-CoA Reductase Inhibitors)
Statin Mechanism of Action:

- Inhibit HMG CoA reductase (rate-limiting step in cholesterol biosynthesis)
- Reduce hepatic cholesterol content
- Increase expression of LDL receptors

In a Meta-analysis of 14 Primary and Secondary Prevention Trials with Statins

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Treatment (n = 45,054)</th>
<th>Control (n = 45,002)</th>
<th>Treatment Better</th>
<th>Control Better</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular causes:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>3.4</td>
<td>4.4</td>
<td></td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Other vascular</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Any non-CHD vascular</td>
<td>1.2</td>
<td>1.3</td>
<td></td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Any vascular</td>
<td>4.7</td>
<td>5.7</td>
<td></td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td><strong>Nonvascular causes:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>2.4</td>
<td>2.4</td>
<td></td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Any nonvascular</td>
<td>3.8</td>
<td>4.0</td>
<td></td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td><strong>Any death</strong></td>
<td><strong>8.5</strong></td>
<td><strong>9.7</strong></td>
<td></td>
<td><strong>0.88</strong></td>
<td></td>
</tr>
</tbody>
</table>

A reduction in LDL-C of 39 mg/dL sustained for 5 years would result in a reduction in risk of major vascular events of approximately 20%, regardless of the baseline LDL-C.

Statin Therapy

| Indication1,2 | As adjunctive to diet to reduce elevated Total-C, LDL-C, Apo B, non-HDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia
| | As adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C, and LDL-C to target levels (Crestor); reduce risk of stroke, myocardial infarction, and arterial revascularization procedures.
| | To reduce risk of non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for CHF, and angina.
| | To reduce Total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia (HoFH) (ZOCOR®); To reduce Total-C and LDL-C in adult patients with HoFH, as an adjunct to other lipid lowering treatments (e.g., LDL apheresis) (LIPITOR®); To reduce Total-C, LDL-C, and Apo B in patients with HoFH (CRESTOR®).

| Available Drugs (Generics)3 | MEVACOR® (lovastatin), PRAVACHOL® (pravastatin), ZOCOR® (simvastatin), LESCOL® (fluvastatin), LIPITOR® (atorvastatin), LIVALO® (pitavastatin), CRESTOR® (rosuvastatin)

| Lipid/lipoprotein Effects3,4 | LDL-C: ↓ 18-55%
| HDL-C: ↑ 5-15%
| TGs: ↓ 14-28%
| Apo B: ↓ 33%

| Effectiveness in Persons with HoFH5,7 | LDL-C: ↓ 14-28%

---

### Statin Therapy (cont.)

<table>
<thead>
<tr>
<th>Major Side/Adverse Effect</th>
<th>Myopathy, increased liver transaminases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>X</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Active or chronic liver disease, concomitant use of cyclosporine, macrolide antibiotics, various anti-fungal agents and cytochrome P-450 inhibitors</td>
</tr>
</tbody>
</table>
| Dosage Range and Available Preparations | Lovastatin: 10, 20, 40 mg tablets  
Pravastatin: 10, 20, 40 mg tablets  
Simvastatin: 5, 10, 20, 40, 80 mg tablets  
Fluvastatin: 20, 40 mg capsules, 80 mg XL tablets  
Atorvastatin: 10, 20, 40, 80 mg tablets  
Rosuvastatin: 5, 10, 20, 40 mg tablets  
Pitavastatin: 1, 2, 4 mg tablets |
| Outcomes Data | Statin therapy reduces risk for acute coronary syndrome (ACS), coronary procedures, and other coronary outcomes in both primary and secondary prevention. They also reduce risk for stroke in secondary prevention.  
Primary prevention: WOSCOPS, AFCAPS/TexCAPS, CARDS, ASCOT-LLA, JUPITER  
Secondary Prevention: 4S, CARE LIPID, HPS, TNT |
| Recommendation(s) | Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. |
### Statin Therapy: Primary Prevention Outcomes Data in Key Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug evaluated</th>
<th>No. patients, demographic s</th>
<th>Study length</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS1,2</td>
<td>Pravachol (pravastatin)</td>
<td>6595 men, 45-64 years; elevated LDL-C</td>
<td>Median follow-up, 4.8 years</td>
<td>First coronary event (CHD death, nonfatal MI)</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS3</td>
<td>Mevacor (lovastatin)</td>
<td>5608 men, 997 women; average TC, LDL-C, below average HDL-C</td>
<td>Median follow-up, 5.2 years</td>
<td>First acute major coronary event (fatal/nonfatal MI, unstable angina, sudden cardiac death)</td>
</tr>
<tr>
<td>CARDS4,5</td>
<td>Lipitor (atorvastatin)</td>
<td>2838 patients with type 2 diabetes, 40-75 years; normal LDL-C</td>
<td>Median follow-up, 3.9 years</td>
<td>First acute CHD event, coronary revascularization, stroke</td>
</tr>
<tr>
<td>ASCOT-LLA4,6</td>
<td>Lipitor</td>
<td>10,305 patients with hypertension, 40-79 years; normal TC</td>
<td>Median follow-up, 3.3 years</td>
<td>First nonfatal MI, fatal CHD</td>
</tr>
<tr>
<td>JUPITER7,8</td>
<td>Crestor (rosuvastatin)</td>
<td>17,802 patients; LDL&lt;130 mg/dL, hsCRP≥2.0 mg/L</td>
<td>Median follow-up, 1.9 years</td>
<td>MI, stroke, arterial revascularization, hospitalization for unstable angina, CV death</td>
</tr>
</tbody>
</table>

# Statin Therapy: Secondary Prevention

## Outcomes Data in Key Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug evaluated</th>
<th>No. patients, demographic(s)</th>
<th>Study length</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S(^1,2)</td>
<td>Zocor (simvastatin)</td>
<td>4,444 patients, 35-71 years; baseline CHD</td>
<td>Median follow-up, 5.4 years</td>
<td>All-cause mortality, CHD mortality, nonfatal MI, revascularization, fatal/nonfatal stroke</td>
</tr>
<tr>
<td>CARE LIPID(^3)</td>
<td>Pravachol (pravastatin)</td>
<td>3583 men, 576 women; MI in previous 3-20 months, normal TC</td>
<td>Median follow-up, 4.9 years</td>
<td>First recurrent coronary events (CHD death, nonfatal MI), revascularization procedure, stroke/TIA</td>
</tr>
<tr>
<td>HPS(^1,4)</td>
<td>Zocor</td>
<td>20,536 patients, 40-80 years; CHD, history of CHD, diabetes, stroke, peripheral vessel disease, hypertension (in males ≥65 years)</td>
<td>Mean follow-up, 11.0 years</td>
<td>All-cause, CHD mortality</td>
</tr>
<tr>
<td>TNT(^5,6)</td>
<td>Lipitor (atorvastatin)</td>
<td>10,001 patients, ≥65 years; clinical evident CHD, initially achieved LDL-C target of &lt;130 mg/dL</td>
<td>Median follow-up, 4.9 years</td>
<td>Death due to CHD, nonfatal MI, resuscitated cardiac arrest, fatal/nonfatal stroke</td>
</tr>
</tbody>
</table>
Cholesterol Absorption Inhibitor (CAI)
Cholesterol Absorption Inhibitor (CAI)

Mechanism of Action:

- Inhibits intestinal and biliary cholesterol absorption by blocking NPC1L1 protein in the jejunal brush border
- Increases expression of LDL receptors
- Lowers LDL-C
- Lowers Non-HDL-C

# Cholesterol Absorption Inhibitor

| Indication\(^1\) | Administered alone: As adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and non-high density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia.  
In combination with statins: As adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, ApoB, and non-HDL-C in patients with primary hyperlipidemia.  
In combination with atorvastatin or simvastatin: To reduce elevated Total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH). |
| Available Drugs (Generics) | ZETIA\(^\circ\) (Ezetimibe) |
| Lipid/lipoprotein Effects (Monotherapy)\(^1\) | LDL-C: ↓ 18%  
HDL-C: ↑ 1%  
TGs: ↓ 8%  
Apo B: ↓ 16% |
| Effectiveness in Persons with HoFH\(^2\) | LDL-C: ↓ 21% |
| Major Side/Adverse Effect\(^2\) | Similar elevations in transaminases (three times the upper limit of normal with alanine transaminase or aspartate transaminase) as compared to placebo when given as monotherapy. |
| Pregnancy Category\(^1\) | C |
| Contraindications\(^1\) | In patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels; nursing mothers, patients with known hypersensitivity to any component of ezetimibe. |

## Cholesterol Absorption Inhibitor (cont.)

<table>
<thead>
<tr>
<th>Available Preparations¹</th>
<th>10 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendation(s)¹</td>
<td>Ezetimibe should remain a viable adjunct to statin therapy in the treatment of hypercholesterolemia</td>
</tr>
</tbody>
</table>

Bile Acid Sequestrants (BAS)
Bile Acid Sequestrants (BAS)

Mechanism of Action

BAS Mechanism of Action:

- Bind bile acids in the intestine reducing the enterohepatic recirculation of bile acids, which releases feedback regulation on conversion of cholesterol to bile acids in the liver.

- The resulting decrease in hepatocyte cholesterol content enhances LDL-receptor expression, which in turn lowers serum LDL-cholesterol concentration.
# Bile Acid Sequestrants (BAS)

<table>
<thead>
<tr>
<th>Indication¹</th>
<th>As an adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with a statin. (WELCHOL PI) Not indicated in HoFH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available Drugs (Generics)</td>
<td>WELCHOL® (colesevelam), QUESTRAN® (cholestyramine), COLESTID® (colestipol)</td>
</tr>
</tbody>
</table>
| Lipid/lipoprotein Effects¹,² | LDL-C: ↓ 15-30%  
HDL-C: ↑ 3-5%  
TGs: no effect or increase  
Apo B: ↓ 12% (Monotherapy) |
| Effectiveness in Persons with HoFH³ | ↓ 21% |
| Major Side/Adverse Effect² | Upper and lower gastrointestinal complaints common; decrease absorption of other drugs |
| Pregnancy Category¹ | B |
| Contraindications² | Familial dysbetalipoproteinemia (Triglycerides > 400 mg/dL), triglycerides > 200 mg/dL |
| Dosage Range and Preparations² | Cholestyramine: 4-24g  
Colestipol: 5-30 (5g packets, 1g tablets)  
Colestevlam: 625–4.4g (625 mg tablets) |

### Bile Acid Sequestrants (BAS)

<table>
<thead>
<tr>
<th>Outcomes Data</th>
<th>Sequestrant therapy reduces risk for CHD. CHD risk reduction trial(s): Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation(s)</td>
<td>Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, for persons needing only modest reductions in LDL cholesterol to achieve target goals, and for combination therapy with statins in persons with very high LDL-cholesterol levels</td>
</tr>
</tbody>
</table>
Nicotinic Acid (Niacin)
# Nicotinic Acid (Niacin)

<table>
<thead>
<tr>
<th>Indication</th>
<th>To reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia. Not indicated in HoFH.</th>
</tr>
</thead>
</table>
| Available Drugs (Generics) | Crystalline nicotinic acid  
Sustained-release (or timed-release) nicotinic acid  
NIASPAN® (Extended-release nicotinic acid) |
| Lipid/lipoprotein Effects | LDL-C: ↓ 5-25%  
HDL-C: ↑ 15-35%  
TGs: ↓ 20-50%  
Apo B: ↓ 12% (1500 mg)  
Lipoprotein A: ↓ 8-32% |
| Effectiveness in Persons with HoFH | Not studied |
| Major Side/Adverse Effect | Flushing, hyperglycemia, hyperuricemia or gout, upper gastrointestinal distress, hepatotoxicity, especially for sustained-release form. |
| Pregnancy Category | C |
| Contraindications | Chronic liver disease, severe gout, hyperuricemia; high doses in type 2 diabetes |
| Dosage Range | Crystalline nicotinic acid: 1.5–4.5g  
Sustained-release nicotinic acid: 1–2g  
Extended-release nicotinic acid (Niaspan®): 1–2g |
| Available Preparations | Many OTC preparations by various manufacturers for both crystalline and sustained- release nicotinic acid. The extended-release preparation (Niaspan®) is a prescription drug. |

## Nicotinic Acid (Niacin) (cont.)

<table>
<thead>
<tr>
<th>Outcomes Data</th>
<th>Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid-lowering drugs. CV prevention trials: Coronary Drug Project (CDP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation(s)</td>
<td>Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels.</td>
</tr>
</tbody>
</table>
Omega-3 Fatty Acids (FAs)
Omega-3 Fatty Acid Mechanism of Action:

- Modulating very-low-density lipoprotein (VLDL) and chylomicron metabolism. There is a consistent finding in the literature that the end effect of fish oil is decreased hepatic secretion of VLDL.
- Promotion of apoB degradation in the liver through the stimulation of an autophagic process.

# Omega-3 Fatty Acid

<table>
<thead>
<tr>
<th>Indication¹</th>
<th>As an adjunct to diet to reduce TG levels in patients with severe hypertriglyceridemia (TG ≥ 500 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available Drugs (Generics)</td>
<td>LOVAZA® (omega-3-Acid Ethyl Esters), VASCEPA® (icosapent ethyl), EPANOVA® (omega-3-carboxylic acids)</td>
</tr>
<tr>
<td>Lipid/lipoprotein Effects²</td>
<td>LDL-C: Increase/no change</td>
</tr>
<tr>
<td></td>
<td>HDL-C: Increase/no change</td>
</tr>
<tr>
<td></td>
<td>TGs: ↓ 20-50%</td>
</tr>
<tr>
<td></td>
<td>Apo B: NA</td>
</tr>
<tr>
<td>Effectiveness in Persons with HoFH</td>
<td>Not sufficiently studied</td>
</tr>
<tr>
<td>Major Side/Adverse Effect³</td>
<td>Potential bleeding complications with the co-administration of anticoagulants</td>
</tr>
<tr>
<td>Pregnancy Category¹</td>
<td>C</td>
</tr>
<tr>
<td>Contraindications¹</td>
<td>Patients with known hypersensitivity to O3s or any of their components</td>
</tr>
<tr>
<td>Dosage Range and Preparations</td>
<td>Omega-3-Acid Ethyl esters: 4 g qd capsules Icosapent ethyl: 4 g qd capsules Omega-3-carboxylic acids: 2-4g capsules</td>
</tr>
</tbody>
</table>

### Omega-3 Fatty Acid (cont.)

<table>
<thead>
<tr>
<th>Outcomes Data¹,²</th>
<th>DART Study; Lyon Diet Heart Study; GISSI-Prevenzione trial. The ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation(s)¹</td>
<td>Higher dietary intakes of n-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because of the strength of the evidence is only moderate at present.</td>
</tr>
</tbody>
</table>

Fibric Acid Derivatives (Fibrates)
Fibric Acid Derivatives (Fibrates)

Mechanism of Action

Fibrates increase expression of proteins in yellow

- Down regulate the apo C-III gene
- Up regulate genes for apo A-I, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase
- Enhance the catabolism of TGRLP, whereas increased fatty acid oxidation reduces formation of VLDL triglycerides

### Indication

1. As an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

2. As adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), Triglycerides and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia.

### Available Drugs (Generics)

- LOPID® (gemfibrozil)
- TRICOR® (fenofibrate)
- LIPOFEN®
- TRILIPIX® (fenofibric acid)

### Lipid/lipoprotein Effects

- **LDL-C:** ↓ 5-20%
- **HDL-C:** ↑ 10-35%
- **TGs:** ↓ 20-50%
- **Apo B:** ↓ 5%

### Effectiveness in Persons with HoFH

Not sufficiently studied

### Major Side/Adverse Effect

Dyspepsia, various upper gastrointestinal complaints, cholesterol gallstones, myopathy

### Pregnancy Category

C

---

1. TRILIPIX® (fenofibric acid) Prescribing Information.
2. TRICOR® (fenofibrate) Prescribing Information.
### Fibric Acid Derivatives

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Severe hepatic or renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong>&lt;br&gt;Range and Preparations</td>
<td>Gemfibrozil: 600–1200 mg tablets&lt;br&gt;Fenofibrate: 67 and 200 mg tablets&lt;br&gt;Fenofibric acid: 145 mg tablets</td>
</tr>
<tr>
<td><strong>Outcomes Data</strong></td>
<td>Primary Prevention Trial(s): Helsinki Heart Study (HHS); WHO Clofibrate Study&lt;br&gt;Secondary Prevention Trial(s): Veterans Administration HDL Intervention Trial (VA-HIT)</td>
</tr>
<tr>
<td><strong>Recommendation(s)</strong></td>
<td>Fibrates can be recommended for persons with very high triglycerides to reduce acute pancreatitis. Fibrate therapy should be considered as option for treatment if persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia</td>
</tr>
</tbody>
</table>
Anti-Sense Apo B Inhibitor
Microsomal Triglyceride Transfer Protein (MTP) Inhibitor
Microsomal Triglyceride Transfer Protein (MTP) Inhibitor

**Mechanism of Action**

- Small-molecule MTP inhibitor designed as oral, once-daily treatment for homozygous FH

![Diagram showing the mechanism of action of MTP inhibitor](image)

- MOA: MTP (microsomal triglyceride transfer protein) is responsible for transferring lipid (triglyceride) onto Apo B48 in the intestine and on to Apo B100 in the liver
- MTP inhibition limits secretion of cholesterol and triglycerides from intestine and liver
### Indication
As an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

### Available Drugs (Generics)
JUXTAPID® (lomitapide) capsules

### Lipid/lipoprotein Effects
- **LDL-C**: ↓ 40%
- **HDL-C**: ↓ 7%
- **TGs**: ↓ 45%
- **Apo B**: ↓ 39%

### Effectiveness in Persons with HoFH
↓ 40%

### Major Side/Adverse Effect
Gastrointestinal; diarrhea, vomiting, increased ALT or hepatotoxicity and abdominal pain

### Pregnancy Category
X

### Contraindications
Pregnancy, with moderate or strong CYP3A4 inhibitors, and patients with moderate or severe hepatic impairment (based on Child-Pugh category B or C) and patients with active liver disease, including unexplained persistent elevations of serum transaminases

### Dosage Range and Preparations
Lomitapide: 5–20mg capsules
<table>
<thead>
<tr>
<th>Outcomes Data</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation(s)</td>
<td>JUXTAPID is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available. It is indicated to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)</td>
</tr>
<tr>
<td>REMS Information</td>
<td>Because of the risk of hepatotoxicity associated with JUXTAPID therapy, JUXTAPID is available through a restricted program under the REMS. Under the JUXTAPID REMS, only certified healthcare providers and pharmacies may prescribe and distribute JUXTAPID</td>
</tr>
</tbody>
</table>
PCSK9 Monoclonal Antibody (mAB)
Proprotein convertase subtilisin/kexin type (PCSK9) is a protein secreted by the hepatocytes which “chaperones” the LDL receptor from the cell surface and into the cell for lysosomal degradation.

**mAB MOA:** An antibody to PCSK9 binds to the PCSK9 protein, thereby inhibiting its effect on the LDL receptor.

## PC SK9 Monoclonal Antibodies

**Clinical trials have been in HeFH.**


### Available Drugs (Generics)

- AMG 145 (evolocumab), SAR236553/REGN727 (alirocumab)*
- RN316 (bococizumab)

### Lipid/lipoprotein Effects

- **LDL-C:** ↓28-65%
- **HDL-C:** Not reported
- **TGs:** Not reported
- **Apo B:** Not reported

### Effectiveness in Persons with HoFH

- ↓31%
  (Range: +10.3% to -55.7%)

### Major Side/Adverse Effect

- In clinical trials: Infusion reactions, upper respiratory tract, influenza

### Pregnancy Category

- Pending FDA approval

### Contraindications

- Pending FDA approval

### Dosage Range and Preparations

- **AMG 145 (evolocumab):** 140 mg or 420 mg injection
- **SAR236553/REGN727 (alirocumab):** 150 mg or 300 mg injection
- **RN316 (bococizumab):** 50 mg, 100 mg or 150 mg injection

---

*Clinical trials have been in HeFH.
**PCSK9 Monoclonal Antibodies (cont.)**

<table>
<thead>
<tr>
<th>Outcomes Data</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation(s)</strong></td>
<td>AMG 145 (evolocumab) is a fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9).</td>
</tr>
<tr>
<td></td>
<td>SAR236553/REGN727 (alirocumab) is a potential first-in-class, subcutaneously administered, fully-human antibody that lowers low-density lipoprotein (LDL) cholesterol by targeting PCSK9. A PCSK9 with a late stage development with the broad global 22,000 patient ODYSSEY clinical trial program.</td>
</tr>
</tbody>
</table>
Cholesterol Ester Transfer Protein (CETP)
Cholesterol Ester Transfer Protein

Mechanism of Action

- CETP, a lipid transfer protein secreted by the liver and mainly bound to HDL, facilitates the transfer of cholesteryl esters from HDL particles to apo B–containing VLDL, LDL, and chylomicron particles in exchange for triglyceride.

- MOA: inhibition of CETP through antisense oligodeoxynucleotides, HDL-C levels are markedly increased with substantial reduction in atherosclerotic lesions.

### Cholesterol Ester Transfer

<table>
<thead>
<tr>
<th>Indication</th>
<th>Pending FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available Drugs (Generics)</td>
<td>MK-0859 (anacetrapib), LY2484595 (evacetrapib)</td>
</tr>
<tr>
<td>Lipid/lipoprotein Effects</td>
<td>LDL-C: ↓ 7-40%</td>
</tr>
<tr>
<td></td>
<td>HDL-C: ↑ 34-138%</td>
</tr>
<tr>
<td></td>
<td>TGs: None reported</td>
</tr>
<tr>
<td></td>
<td>Apo B: None reported</td>
</tr>
<tr>
<td>Effectiveness in Persons with HoFH</td>
<td>(A Phase III trial examining the usefulness, of adding anacetrapib to maximum tolerated statin treatment in patients with HoFH, is due to report in 2015)</td>
</tr>
<tr>
<td>Major Side/Adverse Effect</td>
<td>Potential increases in cardiovascular events and total mortality due to aldosterone increases and blood pressure</td>
</tr>
<tr>
<td>Pregnancy Category</td>
<td>Pending FDA approval</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pending FDA approval</td>
</tr>
</tbody>
</table>
| Dosage Range and Preparations | MK-0859 (anacetrapib): 10, 40, 150, 300 mg injection  
                             | LY2484595 (evacetrapib): 30, 100, 500 mg injection |

# Cholesterol Ester Transfer

<table>
<thead>
<tr>
<th>Outcomes Data</th>
<th>REVEAL: Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEFINE: Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib</td>
</tr>
<tr>
<td>Recommendation(s)</td>
<td>MK-0859 (anacetrapib) is an orally active, potent, and selective CETP inhibitor in Phase III development (MERCK)</td>
</tr>
<tr>
<td></td>
<td>LY2484595 (evacetrapib) is a novel benzazepine compound, is a potent and selective inhibitor of CETP (ELI LILLY)</td>
</tr>
</tbody>
</table>
LDL Apheresis
# LDL Apheresis

**Indication¹**

For use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

- **Group A.** Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;
- **Group B.** Functional Hypercholesterolemic Heterozygotes with LDL-C > 300 mg/dl; and
- **Group C.** Functional Hypercholesterolemic Heterozygotes with LDL-C > 200 mg/dl and documented coronary heart disease.

**Available Drugs (Generics)²**

- Cascade filtration
- Immunoabsorption
- Heparin Induced LDL Precipitation (HELP)
- LDL adsorption
- LDL hemoperfusion (DALI)
- LDL hemoperfusion (liposorber)

**Lipid/lipoprotein Effects²**

- LDL-C: ↓ 35-75%
- HDL-C: ↑ 5-50%
- TGs: ↓ 40-70%
- Apo B: None reported

**Effectiveness in Persons with HoFH**

See above for effectiveness

---

**LDL Apheresis** (cont.)

<table>
<thead>
<tr>
<th>Major Side/Adverse Effect(^3,^4)</th>
<th>Allergic reactions, fatigue, nausea, chest pain, dizziness, hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>B</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None reported</td>
</tr>
<tr>
<td>Dosage Range and Preparations(^1)</td>
<td>Cascade filtration: (2,500–3,000 mL plasma) (\text{Immunoadsorption: (4,000–5,000 mL)}) (\text{Heparin Induced LDL Precipitation (HELP): (2,500–3,000 mL)}) (\text{LDL adsorption: (2,500–3,000 mL)}) LDL hemoperfusion (DALI): 1.6 blood volume LDL hemoperfusion (liposrober): 1.5 blood volume</td>
</tr>
<tr>
<td>Outcomes Data</td>
<td>None reported</td>
</tr>
<tr>
<td>Recommendation(s)(^2)</td>
<td>Healthcare practitioners should refer candidates for LDL apheresis to qualified sites. Self-referrals are also possible. A listing of sites qualified to perform LDL apheresis is in development and will be posted on the National Lipid Association website (<a href="http://www.lipid.org">www.lipid.org</a>).</td>
</tr>
</tbody>
</table>

Current Liposorber® Treatment Sites:
40 sites

40 locations
Homozygous Familial Hypercholesterolemia (HoFH)
HoFH: A Rare, Genetic Lipid Disorder

- Characterized by extreme hypercholesterolemia and early and/or progressive atherosclerosis

- Believed to occur in only 6.25 out of every one million persons
  
  - Estimated that HoFH affects about 42,880 people globally
  
  - True prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis

- People with HoFH have inherited mutations that prevent their body from clearing cholesterol properly, leading to very high levels of LDL-C, even after taking standard cholesterol medications

## HoFH: Clinical Profiles From Multiple Phase 3 Trials

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean Age, y</th>
<th>Baseline CHD Status</th>
<th>Baseline LDL-C, mg/dL [LLT status]</th>
</tr>
</thead>
</table>
| Simvastatin    | 26 (range 15-39)     | • 42% had previous CABG  
• 17% had coronary angioplasty  
• 8% had aortic valve replacement                                                                                                                          | 552 [Untreated]  
(range 363-764) |
| Ezetimibe      | 32 (±4)              | • 44% had premature CHD                                                                                                                                                                                                  | ≈322 [Treated]  
(not specified) |
| Rosuvastatin   | 28 (range 8-63)      | • Not specified                                                                                                                                                                                                           | 513 [Untreated]  
(range 293-791) |
| KYNAMRO        | 32 (range 12-53)     | • ≈60% had atherosclerotic disease  
• ≈50% had aortic valve stenosis  
• ≈25% had revascularization                                                                                                                                     | ≈426 [Treated]  
(range 172-704) |
| Lomitapide     | 31 (range 18-55)     | • 93% had CV disease  
• 72% had valvular disease  
• 72% had CAD                                                                                                                                                    | 336 [Treated]  
(range 152-564) |
| Evolocumab     | 31 (range 13-57)     | • 43% had CAD  
• 25% had previous CABG  
• 14% had previous aortic valve replacement                                                                                                                                 | 348 [Treated]  
(not provided) |

*Represents values in all patients at baseline, including control group.
CABG = coronary artery bypass graft; CAD = coronary artery disease; LLT = lipid-lowering therapy.
## HoFH: Comparable in Prevalence to Other Rare, Genetic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Estimated US Pop.</th>
<th>Clinical Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH(^1,2,3)</td>
<td>2032</td>
<td>Premature, occlusive CAD</td>
</tr>
<tr>
<td>MPS-II (Hunter syndrome)(^4)</td>
<td>500</td>
<td>Severe mental impairment</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria(^5,6)</td>
<td>5,000</td>
<td>Vascular thrombosis</td>
</tr>
<tr>
<td>MPS-IV (Morquio syndrome)(^7)</td>
<td>8,750</td>
<td>Extreme skeletal abnormalities</td>
</tr>
<tr>
<td>Hereditary angioedema(^8)</td>
<td>6,800-34,000</td>
<td>Swelling of SC tissue</td>
</tr>
</tbody>
</table>

Estimated US Prevalence of apheresis eligible patients with or without CHD

On the basis of this prevalence calculation and on post treatment LDL-C levels, these patients with severe FH and LDL-C levels \( \geq 300 \text{ mg/dL} \) \((\geq 7.76 \text{ mmol/L})\) bear phenotypic resemblance to patients with HoFH and may be considered the functional equivalents of homozygous patients.

HoFH is Caused by Genetic Mutations that Affect the Clearance of Atherogenic Lipoproteins

HoFH is typically caused by mutations in LDLR, Apo B, PCSK9, LDLRAP1, or other as-yet-unidentified genes

HoFH & Inheritance of Mutations

- HoFH may be caused by ~1, 700 mutations\(^1\)

- HoFH includes both “pure” HoFH & Compound HeFH\(^2\)
  - **Pure HoFH\(^2\)**: Inherited the same mutation from both parents
  - **Compound HeFH\(^2\)**: Inherited different mutations from each parent

---

### HoFH Mutation Inheritance: An Illustration

<table>
<thead>
<tr>
<th>Individual</th>
<th>Mother</th>
<th>Father</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unaffected</strong></td>
<td>• No FH Mutation</td>
<td>• No FH Mutation</td>
</tr>
<tr>
<td><strong>HeFH</strong> (1 FH Mutation)</td>
<td>• FH Mutation 1</td>
<td>• No FH Mutation</td>
</tr>
<tr>
<td></td>
<td>• No FH Mutation</td>
<td>• FH Mutation 1</td>
</tr>
<tr>
<td><strong>HoFH</strong> (2 FH Mutations)</td>
<td>2 different FH mutations (Compound HeFH)</td>
<td>• FH Mutation 1</td>
</tr>
<tr>
<td></td>
<td>2 of the same FH mutations (“Pure” HoFH)</td>
<td>• FH Mutation 1</td>
</tr>
</tbody>
</table>

---

1. LDLR Locus - Mutation List. Available at: [http://www.ucl.ac.uk/fhold/muttab.html](http://www.ucl.ac.uk/fhold/muttab.html).
HoFH: Rare, but Potentially Under-recognized

- HoFH is extremely rare. It is believed to occur in only 6.25 out of every one million persons - or 42,880 people globally.¹

- As with other rare diseases, the true prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis.²

- Although it may be diagnosed in childhood, HoFH may also go undiagnosed into adulthood.³

HoFH & Genetic Analysis

• There are ~1,700 mutations recognized to cause HoFH\(^1\)

• However, genetic testing is generally not needed for diagnosis
  
  – Genetic analysis does not generally affect management or treatment decisions\(^2\)

  – Additional mutations remain unknown, making results non-definitive\(^3\)

Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain.

Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.

Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods.

NLA = National Lipid Association.
HoFH May be Recognized Clinically

- Multiple clinical definitions exist for HoFH
- Diagnostic criteria may include one or more of the following factors:
  - **Lipid parameters**, e.g. elevations measured by
    - Total-C and/or LDL-C
    - Levels may be untreated and/or treated
  - Presence of **premature** CHD (age <55 for men, age <65 for women)
  - **Family history** of premature CHD or hypercholesterolemia
  - **Physical findings** if present (e.g. planar xanthomas)

## Multiple Diagnostic Criteria, Lack of Consensus in Medical Literature for HoFH:

<table>
<thead>
<tr>
<th>Publication</th>
<th>Diagnostic criteria for HoFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seftel et al. [4]</td>
<td>• Serum cholesterol concentration &gt;14.3 mmol/L (550 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>• Appearance of xanthomas during first decade of life</td>
</tr>
<tr>
<td></td>
<td>• Hypercholesterolemia or clinical signs of hypercholesterolemia in both parents</td>
</tr>
<tr>
<td>Moorjani et al. [5]</td>
<td>• Plasma cholesterol levels &gt;550 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Appearance of xanthomas at an early age</td>
</tr>
<tr>
<td></td>
<td>• Detection of hypercholesterolemia in both parents</td>
</tr>
<tr>
<td>Haitas et al. [8]</td>
<td>• Hypercholesterolemia in both parents (when available)</td>
</tr>
<tr>
<td></td>
<td>• Total serum cholesterol &gt;13 mmol/L (500 mg/dL) + presence of xanthomas in first decade of life</td>
</tr>
<tr>
<td>Raal et al. [9,10]</td>
<td>• Untreated serum LDL consistently &gt;12 mmol/L (463 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>• Appearance of xanthomas in first decade of life</td>
</tr>
<tr>
<td></td>
<td>• Hypercholesterolemia, or its clinical features, documented in both parents</td>
</tr>
<tr>
<td></td>
<td>• Confirmation by DNA analysis for LDLR mutations</td>
</tr>
<tr>
<td>Goldstein [2]</td>
<td>• Unique yellow-orange cutaneous xanthomas (frequently present at birth)</td>
</tr>
<tr>
<td></td>
<td>• Tendon xanthomas, corneal arcus, generalized atherosclerosis during childhood</td>
</tr>
<tr>
<td></td>
<td>• Plasma cholesterol &gt;650 mg/dL in non-jaundiced child</td>
</tr>
<tr>
<td>Gagne et al. [11]</td>
<td>Two mutant alleles at LDLR confirmed by genetic testing or</td>
</tr>
<tr>
<td></td>
<td>• LDL-C ≥ 220 mg/dL (5.69 mmol/L) while receiving lipid-lowering therapy at the highest tolerated dose (&lt;15% response)</td>
</tr>
<tr>
<td></td>
<td>• LDL-C &gt; 90th percentile in ≥ 2 first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>• Presence of tendonous xanthomas and/or manifestations of premature coronary heart disease or corneal arcus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publication</th>
<th>Diagnostic criteria for HoFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marais et al. [12]</td>
<td>• Childhood cutaneous or tendinous xanthomata</td>
</tr>
<tr>
<td></td>
<td>• Total cholesterol &gt;15 mmol/L (600 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>• Both parents should have severe hypercholesterolemia (&gt;7.5 mmol/L or 300 mg/dL) or tendinous xanthomas</td>
</tr>
<tr>
<td></td>
<td>• Family history of premature ischemic heart disease</td>
</tr>
<tr>
<td>Kolansky et al. [13]</td>
<td>Total cholesterol &gt;500 mg/dL Xanthomas at an early age</td>
</tr>
<tr>
<td></td>
<td>Presence of hypercholesterolemia in proband’s parents or other first-degree relative</td>
</tr>
<tr>
<td>Marais et al. [14]</td>
<td>Clinical criteria: Fasting LDL &gt;500 mg/dL (12.9 mmol/L), triglycerides &lt; 600 mg/dL (6.8 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Either xanthomata before age 10 years or FH in both parents</td>
</tr>
<tr>
<td></td>
<td>Genetic criteria: identification of 2 LDLR gene mutations</td>
</tr>
<tr>
<td></td>
<td>Functional criteria: &lt;30% uptake compared to normal of LDL and up-regulated fibroblasts</td>
</tr>
<tr>
<td>Santos et al. [15]</td>
<td>Untreated LDL &gt;500 mg/dL Plus at least one:</td>
</tr>
<tr>
<td></td>
<td>• Genetic testing confirmation of 2 mutated LDL-R alleles</td>
</tr>
<tr>
<td></td>
<td>• Tendonous and/or tuberous xanthoma prior to age 10 years</td>
</tr>
<tr>
<td></td>
<td>• Documented elevated LDL and both parents consistent with HeFH (LDL &gt;200 mg/dL). If parent unavailable, history of CAD in first-degree relative (male &lt;55 years or female &lt;60 years of age)</td>
</tr>
<tr>
<td>Raal et al. [16]</td>
<td>Untreated LDL cholesterol &gt;13 mmol/L</td>
</tr>
<tr>
<td></td>
<td>And either appearance of xanthomas before age 10 years or familial hypercholesterolemia in both parents</td>
</tr>
<tr>
<td>Mabuchi et al. [7]</td>
<td>• Juvenile xanthomatosis with plasma cholesterol about 2 times that of parents or other family members with HeFH</td>
</tr>
<tr>
<td></td>
<td>• Genetic diagnostic criteria: true homozygosity, compound heterozygosity, or double heterozygosity for FH genes</td>
</tr>
</tbody>
</table>

1. Adapted from Raal FJ, Santos RD. Atherosclerosis. 2012;223:262-268
Illustration of LDL-C Levels in HoFH

Untreated LDL >500 mg/dL

Diet and Exercise
<-10-20%

Statins,
Cholesterol Absorption Inhibitors
Bile Acid Sequestrants
-10-20%

LDL >300 mg/dL on max-
tolerated drug therapy

In HoFH, Lifelong Exposure to Extreme Levels of LDL-C Leads to Early CHD

The safety and effectiveness of KYNAMRO® ( mipomersen sodium) injection have not been established in pediatric patients.

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; CHD = coronary heart disease

Coronary arteries and the aortic root, including the valve, are known to be the affected site of atherosclerosis in HoFH.

HoFH patients are more likely to present with severe aortic valvular and supravalvular stenosis of the ascending aorta.


Fig (a) Unenhanced 3-dimensional computed tomography (CT) showed supravalvular stenosis (arrow), funneling of ascending aorta and calcification of the entire aorta. (b and c) Preoperative 2-dimensional CT. (d) Postoperative enhanced CT.
In some cases, HoFH patients may present with xanthomas or Corneal Arcus

• Xanthomas of the Achilles tendon occur with the more severe forms of FH and are associated with pain¹

• Studies have demonstrated skin disorders can greatly affect QoL, and are strongly linked to emotional stress

• Corneal Arcus

---

Genetic Disorders, Premature CHD, and HoFH are Associated with Emotional Impact on QoL

- Genetic diseases have a recognized emotional impact.
- HoFH patients have been associated with emotional impact on QoL:
  - Even when treated effectively, significant anxiety about developing CHD\(^4\)
  - Increased anxiety about the anticipated CHD in a loved one
  - Worry about passing on ‘bad genes’\(^2\)
    - 80\% of parents of children with FH report suffering distress because of the child’s illness\(^3\)
    - 38\% of parents state that the disorder was an emotional burden on the family\(^3\)

Please Note: KYNAMRO® (mipomersen sodium) injection is not indicated to reduce anxiety or improve quality of life in patients with HoFH

Summary

- HoFH is a rare, genetic lipid disorder characterized by extreme hypercholesterolemia and early and/or progressive atherosclerosis.
- True prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis.
- Although HoFH may be diagnosed in childhood, it may also go undiagnosed into adulthood.
- Genetic testing is generally not needed for diagnosis.

- Multiple clinical diagnostic criteria exist for HoFH: There is a lack of consensus in medical literature.
- Clinical diagnostic criteria may include factors such as: very high lipid levels, presence of premature CHD, family history of premature CHD or hypercholesterolemia, physical findings if present (e.g. planar xanthomas).
Understanding The Liver
The Liver and Its Functions

• Largest organ in the body
  – Weighs approximately 3 lbs.

• Functions:
  – Filters blood coming from the digestive tract, before passing it to the rest of the body
  – Detoxifies chemicals and metabolizes drugs
  – Secretes bile that ends up back in the intestines
  – Makes proteins important for blood clotting and other functions

Image purchased from canstockphoto.com
Liver Function Panel and Tests (LFTs): Why and How They Are Done

- Liver function tests check the levels of certain enzymes and proteins in your blood\(^1\)

- Liver function tests can be used to:
  - Screen for liver infections\(^1\), gallbladder\(^2\), and biliary tract\(^2\) abnormalities
  - Monitor the progression of a disease, such as viral or alcoholic hepatitis, and determine how well a treatment is working\(^1\)
  - Measure the severity of a disease, particularly scarring of the liver (cirrhosis)\(^1\)
  - Monitor possible side effects of medications\(^1\)

- LFTs are performed via a blood draw. Blood samples are sent to a laboratory for testing.\(^3\)

Common Liver Function Panel and Tests (LFTs)

- Liver function panel checks how well the liver is working and consists of many different blood tests¹

<table>
<thead>
<tr>
<th>Liver Test</th>
<th>What Test Is Reporting¹</th>
<th>Normal Range²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Measures the amount of this enzyme in the blood; measured to see if the liver is damaged or diseased. Low levels of ALT are normally found in the blood. When the liver is damaged or diseased, it releases ALT into the bloodstream.</td>
<td>0 − 40 (IU/L)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>Measures the amount of this enzyme in the blood; when body tissue or an organ such as the heart or liver is diseased or damaged, additional AST is released into the bloodstream. The amount of AST in the blood is directly related to the extent of the tissue damage.</td>
<td>10 − 34 (IU/L)</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>Measures the amount of the enzyme ALP in the blood; made mostly in the liver and in bone; the amounts of different types of ALP in the blood may be measured and used to determine whether a high level is from the liver or bones.</td>
<td>44 − 147 IU/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Measures the amount of bilirubin in a blood sample; Produced when the liver breaks down old red blood cells; When bilirubin levels are high, the skin and whites of the eyes may appear yellow (jaundice).</td>
<td>Direct: 0 − 0.3 mg/dL</td>
</tr>
</tbody>
</table>

Common Causes of Elevated Liver Enzymes

- Certain prescription medications, including statins
- Drinking alcohol
- Heart failure
- Hepatitis A, B, C
- Biliary system abnormalities
- Nonalcoholic fatty liver disease - dysmetabolic syndrome (which includes diabetes mellitus, hypertension, hyperuricemia, hypertriglyceridemia, in women PCOS)
- Obesity
- Over-the-counter pain medications, including acetaminophen

## Important Terminology

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prothrombin time (PT)</strong></td>
<td>A test of the time it takes for a blood sample to clot, under specific conditions in a lab. If low levels of clotting factors are present, the prothrombin time is longer. PTT is partial thromboplastin time. A PT test evaluates the coagulation factors VII, X, V, II, and I (fibrinogen).</td>
</tr>
<tr>
<td><strong>Partial Thromboplastin Time (PTT)</strong></td>
<td>May be ordered along with a PT test to evaluate hemostasis, the process that the body uses to form blood clots to help stop bleeding. The PTT evaluates the coagulation factors XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen) as well as prekallikrein (PK) and high molecular weight kininogen (HK).</td>
</tr>
<tr>
<td><strong>International normalized ratio (INR)</strong></td>
<td>A standardized way for all labs to report PT, so their results can be compared accurately with each other.</td>
</tr>
<tr>
<td><strong>Childs Pugh</strong></td>
<td>A score that is used with the Model for End-Stage Liver Disease (MELD) to determine priority for liver transplantation.</td>
</tr>
</tbody>
</table>

- PT and INR rise in people with severe liver disease because the liver fails to make normal amounts of certain clotting factors.  

Hy’s Law

• Based on Hy Zimmerman’s inductive reasoning, term coined by Robert Temple in 1980s as a “biomarker” of drug hepatotoxicity, a signal for potential serious risk. Applied only to hepatocellular toxicity, not to cholestatic reactions or other liver diseases. Adapted from Hy’s conclusions.

Hepatocellular Injury
• Elevated aminotransferases (ATs), but at what level?
  – 2x Upper Limit of Normal (ULN), but too common and benign
  – 3x ULN
  – 8x ULN, 10x or greater ULN; what is signal: noise threshold?

Plus Jaundice
• Implies injury that impairs bilirubin excretion, for which there is high capacity before accumulation occurs.
  – Bilirubin threshold 3 mg/dL for seeing jaundice but imprecise
  – Bilirubin 2 mg/dL, 2x ULN, still implies impaired liver function
Common Liver Diseases: A Brief Overview
Liver Disease and Potential Causes

• Any disturbance of liver function that causes illness (also referred to as hepatic disease)

• A broad term that covers all the potential problems that cause the liver to fail to perform its designated functions
  – Usually, more than 75% or three quarters of liver tissue needs to be affected before decrease in function occurs

Potential Causes of Liver Disease

• Cells can become inflamed
• Bile flow can be obstructed
• Cholesterol or triglycerides can accumulate
• Blood flow to the liver may be compromised
• Liver tissue can be damaged by chemicals and minerals, or infiltrated by abnormal cells

Common Types of Liver Disease

• Cirrhosis
• Hepatic steatosis (fatty liver)
• Non-alcoholic fatty liver disease (NAFLD)
• Non-alcoholic steatohepatitis (NASH)
Hepatic Steatosis (Fatty Liver)¹

- Characterized by the excessive accumulation of triglycerides in the form of lipid droplets in the liver
- Can be caused by chronic excessive alcohol intake (alcoholic steatosis) or obesity, excessive lipids in the diet (nonalcoholic steatohepatitis, NASH)
- Increases risk of developing hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Nutritional</th>
<th>Drugs</th>
<th>Metabolic or Genetic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-calorie Malnutrition</td>
<td>Glucocorticoids</td>
<td>Lipodystrophy</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Starvation</td>
<td>Dysbetalipoproteinemia and familial hypobetalipoproteinemia²</td>
<td>Small bowel overgrowth with bacterial overgrowth</td>
<td></td>
</tr>
<tr>
<td>Total Parenteral Nutrition (TPN)</td>
<td>Cholesterol ester storage</td>
<td>HIV infection</td>
<td></td>
</tr>
<tr>
<td>Rapid Weight Loss</td>
<td>Webe-Christian disease</td>
<td>Environmental hepatotoxins</td>
<td></td>
</tr>
<tr>
<td>GI Surgery for Obesity</td>
<td>Antiviral agents</td>
<td>Wolman’s disease</td>
<td>Bacillus cereus toxins</td>
</tr>
</tbody>
</table>

Hepatic Steatosis (Fatty Liver)

Large vacuoles of triglyceride fat accumulate in liver cells.
Non-alcoholic Fatty Liver Disease (NAFLD)

• Alcohol-like liver disease characterized by hepatic triglyceride accumulation in individuals who do not consume excessive alcohol

• Clinical course of NAFLD dictated by histopathology
  – NAFL – Simple steatosis - Benign
  – NASH – Steatosis + inflammation (steatohepatitis) - Aggressive
Non-alcoholic Fatty Liver (NAFL) Steatosis

Intracellular fat deposition

Simple Steatosis

www.gastroslides.org
Non-alcoholic Steatohepatitis (NASH)

• Often called “silent” liver disease  
  – Resembles alcoholic liver disease, but occurs in people who drink little or no alcohol

• Major feature: fat in the liver; inflammation and damage  
  – Can lead to cirrhosis

• Affects 2 to 5% of Americans

**Causes**

Still not clear; most often occurs in persons who are middle-aged and overweight or obese

**Symptoms**

Few or no symptoms; patients generally feel well in the early stages and only begin to have symptoms (i.e., fatigue, weight loss, and weakness) once disease is more advanced

Non-alcoholic Steatohepatitis (NASH)

Fat deposits
Inflammation

Intracellular fat deposition

Inflammation

www.gastro.org
Cirrhosis

- Slowly progressing disease in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly
  - Scar tissue blocks the flow of blood through the liver and slows the processing of nutrients, hormones, drugs, and naturally produced toxins
- 12th leading cause of death by disease

<table>
<thead>
<tr>
<th>Most Common Causes</th>
<th>Hepatitis C, fatty liver, and alcohol abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Loss of appetite, lack of energy (fatigue), which may be debilitating, weight loss or sudden weight gain, bruises, yellowing of skin or the whites of eyes (jaundice), itchy skin, fluid retention (edema) and swelling in the ankles, legs, and abdomen (often an early sign)</td>
</tr>
</tbody>
</table>

Cirrhosis

Formation of scar tissue
Summary