CVD Risk Reduction with Lipid-Lowering Medications: Statins and Beyond

Lynne T Braun, PhD, CNP, FAHA, FAAN
Lynne_t_braun@rush.edu
Professor of Nursing, Nurse Practitioner
Rush University Medical Center
Disclosures

• NIH grant support
• UpToDate author and advisory board
Objectives

• Discuss the epidemiology and pathophysiology of hypercholesterolemia.
• Review the disorders that contribute to hypercholesterolemia and other lipid disorders.
• Discuss current treatment strategies to lower cholesterol and TG.
• Identify new treatment strategies for hypercholesterolemia.
Dyslipidemia

• Circulating levels of lipid or lipoprotein particles are abnormal because of genetic and/or environmental conditions that alter their production, catabolism, or clearance from circulation
Epidemiological Investigations of Cholesterol and CHD

• Positive relationship between cholesterol and initial or subsequent CHD events is observed over a broad range of LDL-cholesterol levels; the higher the LDL level, the greater the risk (Stamler et al., 1986)

• Populations with low total and LDL cholesterol levels have a near-absence of clinical CHD (Keys et al., 1980; Grundy et al., 1990; Law et al., 1994; Law, 1999)
Genetic Studies

- Elevated LDL linked to CHD in persons with genetic forms of hypercholesterolemia (Brown and Goldstein, 1986)

- Decreased LDL removal related to defective or reduced number of LDL receptors

- FH $\rightarrow$ significant atherosclerosis and premature CAD in the absence of other risk factors
Familial Hypercholesterolemia (FH)

- Autosomal dominant disorder associated with mutations of hepatocyte apo-B receptors resulting in decreased LDL removal by the liver
  - Common inherited disorder; 10,000,000 people worldwide (mainly heterozygous)
- Homozygotes (1:1,000,000):
  - TC 650-1000 mg/dL
  - Xanthoma by age 4
  - Death from CHD by age 20
- Heterozygotes (1:500):
  - TC 250-550 mg/dL
  - Xanthoma by age 20
  - Atherosclerosis by age 30
A RECEPTOR-MEDIATED PATHWAY FOR CHOLESTEROL HOMEOSTASIS

Nobel lecture, 9 December, 1985

by

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

Department of Molecular Genetics, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Blvd. Dallas, Texas, U.S.A.
Homozygous FH

Six year-old girl with homozygous Familial Hypercholesterolemia. Bumps on skin are deposits of cholesterol derived from LDL.

http://www4.utsouthwestern.edu/moleculargenetics/pages/gold/past.html
Xanthomas:
Signs of Hypercholesterolemia

Tendon Xanthomas

Corneal Arcus and Xanthelasma
Lipoproteins

- Chylomicrons
- Very-low-density lipoproteins (VLDLs)
- Intermediate-density lipoproteins (IDLs)
- Low-density lipoproteins (LDLs)
- High-density lipoproteins (HDLs)
Atherogenic Particles
Each Particle Contains a Single Apolipoprotein B Molecule

www.lipidsonline.com
### ATP III

**Lipid and Lipoprotein Classification**

<table>
<thead>
<tr>
<th>LDL Cholesterol (mg/dL)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Optimal</td>
</tr>
<tr>
<td>100–129</td>
<td>Near optimal/above optimal</td>
</tr>
<tr>
<td>130–159</td>
<td>Borderline high</td>
</tr>
<tr>
<td>160–189</td>
<td>High</td>
</tr>
<tr>
<td>≥190</td>
<td>Very high</td>
</tr>
</tbody>
</table>
Secondary Causes of Elevated LDL-C

• Diet: Saturated or trans fats, weight gain, anorexia
• Drugs: Diuretics, cyclosporine, glucocorticoids, amiodarone
• Diseases: Biliary obstruction, nephrotic syndrome, hypothyroidism
• Conditions: Obesity, pregnancy

Stone NJ et al., Circulation 2013, DOI: 10.1161/01.cir.0000437738.63853.7a
Secondary Causes of Elevated Triglycerides

- Diet: Weight gain, very low fat diets, high intake of refined carbs, excessive ETOH intake
- Drugs: Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
- Diseases: Nephrotic syndrome, chronic renal disease, lipodystrophies; diabetes (poorly controlled), hypothyroidism
- Conditions: Obesity, pregnancy

Stone NJ et al., Circulation 2013, DOI: 10.1161/01.cir.0000437738.63853.7a


Circulation. published online November 12, 2013;
What’s New in the Guideline?

• Focus on ASCVD risk reduction: 4 statin benefit groups
  – Goal is to reduce ASCVD events in secondary and primary prevention
  – High-intensity and moderate-intensity statin use

• A new perspective on LDL-C and/or non-HDL-C treatment goals
  – No evidence to support LDL-C and/or non-HDL-C treatment targets
  – Appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit

Stone NJ et al., Circulation 2013, DOI: 10.1161/01.cir.0000437738.63853.7a
What’s New in the Guideline?

• Global risk assessment for primary prevention
  – Use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both black and white men and women
    http://tools.cardiosource.org/ASCVD-Risk-Estimator/

• Safety recommendations
  – Used RCTs to identify important safety considerations of statins and provides expert guidance on management of adverse effects

• Role of biomarkers and noninvasive tests
  – Treatment decisions in selected individuals who are not in the 4 statin benefit groups may be informed by other factors
Lifestyle as the Foundation for Risk Reduction

Guideline on Lifestyle Management to Reduce Cardiovascular Risk

• A critical component of health promotion and ASCVD risk reduction
  – Heart-healthy diet
  – Regular exercise
  – Avoidance of tobacco products
  – Maintenance of a healthy weight

Eckel RH et al., Circulation 2013, DOI: 10.1161/01.cir.0000437740.48606.d1
4 Statin Benefit Groups

1. Individuals with clinical ASCVD, defined as the inclusion criteria for secondary prevention statin RCTs
   – Acute coronary syndromes
   – History of MI
   – Stable or unstable angina
   – Coronary or other arterial revascularization
   – Stroke or TIA
   – PAD
4 Statin Benefit Groups

2. Individuals with primary elevations of LDL-C $\geq 190$ mg/dL

3. Individuals with diabetes aged 40-75 years with LDL-C 70-189 mg/dL and without clinical ASCVD

4. Individuals without ASCVD or diabetes with LDL-C 70-189 mg/dL and estimated 10-year ASCVD risk $\geq 7.5\%$ (estimated using the Pooled Cohort Equations)
Use of Statins

• Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored.

• Statin therapy recommended for secondary and primary prevention of ASCVD

• Based on RCTs, statins reduce morbidity and mortality associated with ASCVD

• Cost-effective: many statins are now generic
Statin Therapy Provides Benefits For Primary and Secondary Prevention

Statins: Mechanism of Action

- Statins competitively inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.
- Statins increase LDL receptor activity as a result of lowering intracellular cholesterol in liver cells.
- Pleiotrophic effects (plaque stabilization, anti-inflammatory, anti-oxidative effects)
Reduce hepatic cholesterol synthesis, lowering intracellular cholesterol, which stimulates upregulation of LDL receptor and increases the uptake of non-HDL particles from the systemic circulation.
HMG-CoA Reductase Inhibitors (Statins)

• Reduce LDL 25-60%, reduce TG 10-30%, raise HDL 5-14%

• Proven to reduce coronary events and mortality in primary and secondary prevention trials

• First-line agents when LDL reduction is necessary

• Other effects: plaque stabilization, anti-inflammatory
HMG-CoA Reductase Inhibitors (Statins)

- Lovastatin (Mevacor)
- Pravastatin (Pravachol)
- Simvastatin (Zocor)
- Fluvastatin (Lescol)
- Atorvastatin (Lipitor)
- Lovastatin plus niacin (Advicor)
- Simvastatin plus niacin (Simcor)
- Rosuvastatin (Crestor)
- Simvastatin plus ezetimibe (Vytorin)
- Pitavastatin (Livalo)
ARS Question 1

According to the 2013 ACC/AHA cholesterol guidelines, which of the following is true for a 49-year-old male with diabetes and without ASCVD?

A. Diabetes is a CAD risk equivalent and this patient should receive a statin.

B. Whether or not to treat with a statin depends on the patient’s other risk factors.

C. If his ASCVD 10-year risk by Pooled Cohort Equations is ≥ 7.5%, he should receive a high-intensity statin.

D. An anatomic imaging test should be performed before prescribing a statin.
HEALTH STATUS OF ADULT CANDIDATE FOR STATIN THERAPY

**Clinical ASCVD**
- Yes
- LDL-C ≥190 mg/dL
- No
- Diabetes
- Yes
- No

**Primary Prevention**
- No diabetes, LDL-C 70–189 mg/dL and not receiving statin therapy.
- Estimate 10-yr ASCVD risk every 4–6 yrs using Pooled Cohort Equations

**<5% 10-year ASCVD risk**
- Age <40 or >75
- LDL-C <70 mg/dL

**≥7.5% 10-year ASCVD risk**
- Age <40 or >75
- LDL-C <190 mg/dL
- Potential candidate for moderate- or high-intensity statin

**Age 40–75**
- LDL-C 70–189 mg/dL

**In selected individuals, additional factors may be considered to inform treatment decision making**

**Clinical-patient Discussion**
- Prior to initiating statin therapy, discuss:
  1. Potential for ASCVD risk-reduction benefits
  2. Potential for adverse effects and drug-drug interactions
  3. Heart-healthy lifestyle
  4. Management of other risk factors
  5. Patient preferences
  6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L

**High-intensity statin**
- For patients aged ≤75
- Moderate-intensity statin if not candidate for high-intensity statin
- *Daily dose lowers LDL-C by approx ≥50%*

**Moderate-intensity statin**
- For patients aged >75 or if not a candidate for high-intensity statin
- **Moderate-intensity statin** for patients with estimated 10-yr ASCVD risk ≥7.5%

**No to statin**
- Emphasize adherence to lifestyle
- Manage other risk factors
- Monitor adherence

**Yes to statin**
- Encourage adherence to lifestyle
- Manage other risk factors
- Monitor adherence
- Initiate statin at appropriate intensity

For all patients, heart healthy lifestyle habits are recommended as the foundation of Atherosclerotic Cardiovascular Disease (ASCVD) prevention

---

Smith and Grundy J A C C. V O L . 6 4 , NO. 6 , A U G U S T 2 , 2 0 1 4 : 6
0 1 – 1 2
Primary Prevention

• Use the new Pooled Cohort Equations to estimate 10-year ASCVD risk.

• Guideline is “patient centered”
  – Potential for risk reduction benefit, adverse effects, and drug-drug interactions, along with patient preferences, must be considered before statins are prescribed for the primary prevention of ASCVD.

Stone NJ et al., *Circulation* 2013, DOI: 10.1161/01.cir.0000437738.63853.7a
Goff DC et al., *Circulation* 2013, DOI: 10.1161/01.cir.0000437741.48606.98
10-Year ASCVD Risk

• These individuals can be identified by using the new *Pooled Cohort Equations for ASCVD risk prediction*, developed by the Risk Assessment Work Group.
• Stroke now included in ASCVD risk assessment, in addition to myocardial infarction (MI)
• Separate equations for nonwhite populations

Goff et al., *Circulation* 2013, DOI:10.1161/01.cir0000437741.48606.98
Role of Biomarkers and Noninvasive Tests

• In select individuals who are not in 1 of 4 statin benefit groups, and for whom the decision to initiate statin therapy is unclear, additional factors may be used to inform treatment decisions.

• Factors include:
  – LDL-C ≥ 160 mg/dL
  – Family history of premature ASCVD
  – Hs-CRP ≥ 2 mg/L
  – CAC score ≥ 300 Agatston units or 75th percentile for age, sex, and ethnicity
  – ABI < 0.9
  – Elevated lifetime risk of ASCVD
ARS Question 2

Mr. Johnson is a 68-year-old white male with a total cholesterol of 150 mg/dL, HDL-C of 46 mg/dL, an untreated SBP of 120 mmHg, and no diabetes or smoking history. His 10-year ASCVD risk is 12.6%. What is your most appropriate course of action?

A. Prescribe a moderate-intensity statin.
B. Prescribe a high-intensity statin.
C. Tell him to continue his vegan diet.
D. Have a conversation about risk factors and benefit vs. risk of statin therapy.
Shared Decision-Making

• Engage in a clinician–patient discussion before initiating treatment, e.g., statin therapy for primary prevention in patients with lower ASCVD risk.

• The ACC/AHA cholesterol guidelines recommend not only the risk calculation, but also the clinician–patient review of risk and the decision to take a statin.

• The more empowered patients feel, the more likely they will be motivated to manage their condition and adhere to medications.
• Age is a major contributor to the ASCVD risk calculation.
• A 65-year-old man and a 71-year-old woman with optimal risk factors have a >7.5% 10-year risk.
• Clinical judgment, statin safety issues, and consideration of patient preferences inform the treatment plan.
• Prescription of a statin is not automatic.
• Treatment plan is a comprehensive approach to risk reduction that begins with the use of the ASCVD risk calculator and incorporates addressing all modifiable risk factors.
• 63 yo woman with rheumatoid arthritis; LDL-C is 120 mg/dl but hs-CRP is 5 mg/L
  – ASCVD risk by calculator is only 5%
  – Patient and clinician discussion reviews benefits/risks and decision made to treat with a statin
    • Increased risk of ASCVD in those with rheumatoid arthritis
    • Elevated hs CRP ≥ 2.0 is optional factor that can be used to inform the risk discussion
• 68 yo white man with ASCVD risk > 7.5%
  – Guidelines indicate risk discussion needed before automatic prescription of statin
  – Patient has excellent risk profile and parents who live to 90-100 years of age
  – Clinician points out that age is a surrogate for exposure to risk factors
  – In risk discussion that the guidelines recommend, patient and clinician decide to focus on lifestyle and forego statin therapy
Intensity of Statin Treatment

• High-intensity statin therapy is defined as a daily dose that lowers LDL-C by $\geq 50\%$

• Moderate-intensity statin therapy lowers LDL-C by 30% to $<50\%$. 
<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40 †)–80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td><strong>Simvastatin 10 mg</strong></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
<td><strong>Pravastatin 10–20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Simvastatin 20–40 mg ‡</strong></td>
<td><strong>Lovastatin 20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pravastatin 40 (80) mg</strong></td>
<td><strong>Fluvastatin 20–40 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lovastatin 40 mg</strong></td>
<td><strong>Pitavastatin 1 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin 40 mg bid</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pitavastatin 2–4 mg</strong></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 3. Initiating statin therapy in individuals with clinical ASCVD**

**Clinical ASCVD**
- Not currently on statin therapy
  - Initial evaluation prior to statin initiation
    - Fasting lipid panel*
    - ALT
    - CK (if indicated)
    - Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

**Evaluate and Treat Laboratory Abnormalities**
1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT >3X ULN

---

**Aged ≤75 y**
- **without** contraindications, conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance
  - Initiate **high-intensity** statin therapy
  - Counsel on healthy lifestyle habits

**Aged >75 y†**
- **with** conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance
  - Initiate **moderate-intensity** statin therapy
  - Counsel on healthy lifestyle habits

**Monitor statin therapy**
  - (Figure 5)
Statin Safety Recommendations

• Use moderate-intensity statin therapy in patients who are predisposed to statin-associated adverse effects.
  – Multiple or serious comorbidities, including impaired renal or hepatic function
  – History of previous statin intolerance or muscle disorders
  – Unexplained ALT elevations > 3 times ULN
  – Concomitant use of drugs affecting statin metabolism
  – > 75 years of age
  – History of hemorrhagic stroke
  – Asian ancestry

• CK should not be routinely measured, although it is reasonable to measure baseline CK in persons at increased risk for adverse muscle events
<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP450</th>
<th>% Protein-binding</th>
<th>Lipophilic</th>
<th>Plasma Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>3A4</td>
<td>&gt; 95</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3A4</td>
<td>&gt; 95</td>
<td>Yes</td>
<td>1-2</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>None</td>
<td>~ 50</td>
<td>No</td>
<td>1-2</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>3A4</td>
<td>&gt; 95</td>
<td>Yes</td>
<td>14</td>
</tr>
<tr>
<td>Fluvastatin XL</td>
<td>2C9</td>
<td>&gt; 95</td>
<td>Yes</td>
<td>1-2</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>2C9</td>
<td>~ 88</td>
<td>No</td>
<td>19</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2C9</td>
<td>&gt;99</td>
<td>Yes</td>
<td>12</td>
</tr>
</tbody>
</table>
Statin Safety Recommendations

• During statin therapy, it is reasonable to measure CK for muscle symptoms (pain, stiffness, cramping, weakness)
• Baseline ALT should be performed before initiating statin therapy
• During statin therapy, it is reasonable to measure ALT if symptoms suggest hepatotoxicity (unusual fatigue, weakness, loss of appetite, abdominal pain, dark urine, jaundice)
• Decreasing the statin dose may be considered with 2 consecutive LDL-C levels < 40 mg/dL
• It may be harmful to initiate simvastatin at 80 mg daily or increase the dose to 80 mg daily
Statin Safety Recommendations

• Individuals on statin therapy should be evaluated for new onset DM.
  – Those who develop DM should be counseled on a heart-healthy diet, physical activity, healthy body weight, stopping tobacco use. Statin therapy should be continued to reduce their risk of ASCVD events.

• Use caution in individuals > 75 years of age, persons taking concomitant meds that alter drug metabolism, taking multiple drugs, taking drugs for conditions that required complex medication regimens (transplant patients or patients with HIV). Review prescribing information before initiating any cholesterol-lowering drug.
Statin Safety Recommendations

• If mild to moderate muscle symptoms develop during statin therapy:
  – Discontinue statin until muscle symptoms can be evaluated.
  – Evaluate for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders, steroid myopathy, vitamin D deficiency, primary muscle diseases).
  – If muscle symptoms resolve, and if no contraindications exist, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin.
  – If a causal relationship exists, discontinue the original statin, and once muscle symptoms resolve, use a low dose of a different statin.
  – Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
Monitoring Statin Therapy

• A baseline lipid panel should be obtained followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy to determine patient’s adherence.

• Thereafter, assessments should be every 3 to 12 months as clinically indicated.

• LDL-C levels and per cent reduction are to be used only to assess response to therapy and adherence.
# Statin Use in CKD and Transplant Patients

## CKD
- Crestor 5-10 mg
- Atorvastatin – no dose adjustment needed
- Simvastatin 5 mg (advanced CKD)
- Livalo – 1-2 mg
- Lescol XL – caution/monitor
- Pravastatin – caution/monitor
- Lovastatin 20 mg

## Cyclosporine
- Crestor 5 mg
- Atorvastatin 10 mg
- Simvastatin – contraindicated
- Livalo – contraindicated
- Pravastatin 20 mg
Insufficient Response to Statin Therapy

- In persons with a less-than-anticipated response to statin therapy or are intolerant to the recommended intensity of statin therapy:
  - Reinforce adherence to medication and lifestyle changes
  - Exclude secondary causes of hyperlipidemia
  - Investigate statin intolerance

- In persons at high ASCVD risk receiving the maximum tolerated statin who have a less-than-anticipated therapeutic response, addition of a nonstatin LDL lowering agent may be considered if the benefits outweigh the potential for adverse effects:
  - Individuals with clinical ASCVD < 75 years of age
  - Individuals with baseline LDL-C ≥ 190 mg/dL
  - Individuals 40 to 75 years of age with diabetes
Cholesterol Absorption Inhibitor

• Ezetimibe (Zetia)
• Reduces cholesterol by inhibiting cholesterol absorption at the brush border of the small intestine (inhibits Niemann-Pick C1-like 1 protein)
• One 10 mg tablet is effective and well-tolerated either alone or in combination with statin
• Zetia is metabolized in small intestine and liver; perform LFTs at initiation
• Lowers LDL 18% (alone) or an additional 25% with a statin
Cholesterol Absorption Inhibitor

Liver

- LDL apoB100
- VLDL apoB100
- CM Remnant apoB48
- CM apoB48

Duodenum
- Ezetimibe

Jejunum

Ileum

Colon
Improve-It Trial

- Evaluated the clinical efficacy of combination Ez/simva vs simvastatin alone in ACS patients ≥ 50 years of age and LDL-C 50-125 mg/dL (or 50-100 mg/dL if prior lipid-lowering treatment)

- Primary endpoint: CV death, MI, hospital admission for UA, coronary revascularization, or stroke

- Absolute RR over 7 years was 2% -- 32.7% in the Ez/simva arm experiencing a primary endpoint vs 34.7% in the simvastatin arm

Cannon C, AHA 2014.
**LDL-C and Lipid Changes**

<table>
<thead>
<tr>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Mean LDL-C (mg/dL)

- Median Time avg 69.5 vs. 53.7 mg/dL

Number at risk:

| EZ/Simva | 8990  | 8889  | 8230  | 7701  | 7264  | 6864  | 6583  | 6256  | 5734  | 5354  | 4508  | 3484  | 2608  | 1078  |
| Simva    | 9009  | 8921  | 8306  | 7843  | 7289  | 6939  | 6607  | 6192  | 5684  | 5267  | 4395  | 3387  | 2569  | 1068  |
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

NNT= 50

7-year event rates
Individual Cardiovascular Endpoints and CVD/MI/Stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.99</td>
<td>15.3</td>
<td>15.4</td>
<td>0.782</td>
</tr>
<tr>
<td>CVD</td>
<td>1.00</td>
<td>6.8</td>
<td>6.9</td>
<td>0.997</td>
</tr>
<tr>
<td>CHD</td>
<td>0.96</td>
<td>5.8</td>
<td>5.7</td>
<td>0.499</td>
</tr>
<tr>
<td>MI</td>
<td>0.87</td>
<td>14.8</td>
<td>13.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86</td>
<td>4.8</td>
<td>4.2</td>
<td>0.052</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.79</td>
<td>4.1</td>
<td>3.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Cor revasc ≥ 30d</td>
<td>0.95</td>
<td>23.4</td>
<td>21.8</td>
<td>0.107</td>
</tr>
<tr>
<td>UA</td>
<td>1.06</td>
<td>1.9</td>
<td>2.1</td>
<td>0.618</td>
</tr>
<tr>
<td>CVD/MI/stroke</td>
<td>0.90</td>
<td>22.2</td>
<td>20.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*7-year event rates (%)

Ezetimibe/Simva Better
Simva Better
Safety — ITT

No statistically significant differences in cancer or muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva n=9077 %</th>
<th>EZ/Simva n=9067 %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST≥3x ULN</td>
<td>2.3</td>
<td>2.5</td>
<td>0.43</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5</td>
<td>1.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>3.5</td>
<td>3.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2</td>
<td>0.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6</td>
<td>0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer* (7-yr KM %)</td>
<td>10.2</td>
<td>10.2</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Adjudicated by Clinical Events Committee

% = n/N for the trial duration
Conclusions

**IMPROVE-IT**: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES**: *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES**: Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES**: Confirms ezetimibe safety profile

- **Reaffirms the LDL hypothesis**, that reducing LDL-C prevents cardiovascular events
- **Results could be considered for future guidelines**
Bile Acid Sequestrants (Resins)

• Bind with negatively charged bile acids in the intestines
• Interrupt bile acid reabsorption into the enterohepatic circulation
• Decrease hepatic cholesterol pool → synthesis of new LDL receptors (improves LDL clearance from plasma)
Bile Acid Resins: **Mechanism of Action**

**Net Effect:** ↓ LDL-C

- **Gall Bladder**
  - ↑ LDL Receptors
  - ↑ VLDL and LDL removal
  - ↑ Cholesterol 7-α hydroxylase
  - ↑ Conversion of cholesterol to BA
  - ↑ BA Secretion

- **Liver**
  - ↑ BA Excretion
  - ↑ BA Secretion
  - ↑ LDL Receptors
  - ↑ VLDL and LDL removal

- **Terminal Ileum**
  - ↑ BA Excretion
  - Reabsorption of bile acids
Bile Acid Sequestrants

Demonstrated Therapeutic Benefits

• Reduce major coronary events
• Reduce CHD mortality
  – Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) cholestyramine reduced CHD risk and decreased LDL-C by 12% (1984)
Bile Acid Sequestrants

• Major actions
  – Reduce LDL-C 15–30%
  – Raise HDL-C 3–5%
  – May increase TG

• Side effects
  – GI distress/constipation
  – Decreased absorption of other drugs

• Contraindications
  – Dysbetalipoproteinemia - type III hyperlipoproteinemia (high cholesterol and TG)
  – Elevated TG (especially >400 mg/dL)
Bile Acid Sequestrants

- Colesevelam (Welchol) -- tablets
- Colestipol (Colestid) – tablets or powder
- Cholestyramine (Questran Light) -- resin
Bile Acid Sequestrants

• Take within 30 min. of meal
• Except for *colesevelam*, concomitant oral meds should be taken at least 1 hour before or 4 hours after bile acid sequestrant
• Bile acid sequestrants are not absorbed systemically
Nicotinic Acid

- Inhibits the hepatic production of VLDL and of its metabolite LDL
- Raises HDL by reducing VLDL synthesis
- Less circulating VLDL is available to receive cholesterol esters from HDL, thereby delaying the catabolism of HDL
Nicotinic Acid: Mechanism of Action

Mobilization of FFA

Liver

Hepatocyte

Systemic Circulation

Decreases hepatic production of VLDL and of apo B

VLDL

Apo B

TG synthesis

VLDL secretion

Serum LDL

Serum VLDL results in reduced lipolysis to LDL

HDL

LDL
Nicotinic Acid

• Major actions
  – Lowers LDL-C 5–25%
  – Lowers TG 20–50%
  – Raises HDL-C 15–35%
  – Lowers lipoprotein(a)

• Side effects: flushing (pretreat with aspirin or ibuprofen), hyperglycemia, hyperuricemia, upper GI distress (take with food), hepatotoxicity

• Contraindications: liver disease, severe gout, peptic ulcer
Nicotinic Acid

- Niacin – immediate-release, taken tid
- Niaspan – extended-release, taken once after dinner or at bedtime

- Combination of lovastatin and Niaspan – Advicor
- Combination of simvastatin and Niaspan -- Simcor
Nicotinic Acid

Demonstrated Therapeutic Benefits

• Reduces major coronary events
• Possible reduction in total mortality
  – Coronary Drug Project, 1975, 1986
HPS2-Thrive

• Designed to assess the effects of adding extended-release niacin in combination with laropiprant to effective statin-based LDL cholesterol–lowering treatment in 25,673 high-risk patients with prior vascular disease

• Primary outcome was the first major vascular event, defined as a major coronary event (nonfatal myocardial infarction or death from coronary causes), stroke of any type, or coronary or noncoronary revascularization

## Baseline Cholesterol Values

<table>
<thead>
<tr>
<th></th>
<th>Niacin–Laropiprant (N=12,838)</th>
<th>Placebo (N=12,835)</th>
<th>All Participants (N=25,673)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58 mg/dl</td>
<td>4,933 (38.4)</td>
<td>4,927 (38.4)</td>
<td>9,860 (38.4)</td>
</tr>
<tr>
<td>≥58 to &lt;77 mg/dl</td>
<td>5,505 (42.9)</td>
<td>5,549 (43.2)</td>
<td>11,054 (43.1)</td>
</tr>
<tr>
<td>≥77 mg/dl</td>
<td>2,400 (18.7)</td>
<td>2,359 (18.4)</td>
<td>4,759 (18.5)</td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>64±17</td>
<td>63±17</td>
<td>63±17</td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 mg/dl</td>
<td>2,459 (19.2)</td>
<td>2,441 (19.0)</td>
<td>4,900 (19.1)</td>
</tr>
<tr>
<td>≥35 to &lt;43 mg/dl</td>
<td>4,098 (31.9)</td>
<td>4,037 (31.5)</td>
<td>8,135 (31.7)</td>
</tr>
<tr>
<td>≥43 mg/dl</td>
<td>6,281 (48.9)</td>
<td>6,357 (49.5)</td>
<td>12,638 (49.2)</td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>43.9±11.2</td>
<td>44.0±11.2</td>
<td>43.9±11.2</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;116 mg/dl</td>
<td>3,547 (27.6)</td>
<td>3,582 (27.9)</td>
<td>7,129 (27.8)</td>
</tr>
<tr>
<td>≥116 to &lt;135 mg/dl</td>
<td>4,800 (37.4)</td>
<td>4,691 (36.5)</td>
<td>9,491 (37.0)</td>
</tr>
<tr>
<td>≥135 mg/dl</td>
<td>4,491 (35.0)</td>
<td>4,562 (35.5)</td>
<td>9,053 (35.3)</td>
</tr>
<tr>
<td>Mean — mg/dl</td>
<td>128±22</td>
<td>128±22</td>
<td>128±22</td>
</tr>
</tbody>
</table>
**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Niacin–laropiprant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>12,838</td>
<td>12,232</td>
<td>11,517</td>
</tr>
<tr>
<td>12,835</td>
<td>12,247</td>
<td>11,523</td>
</tr>
<tr>
<td>7672</td>
<td>7643</td>
<td>4978</td>
</tr>
<tr>
<td>4978</td>
<td>5036</td>
<td></td>
</tr>
<tr>
<td>Benefit per 1000 participants assigned to niacin–laropiprant</td>
<td>0±3</td>
<td>3±3</td>
</tr>
</tbody>
</table>

*P = 0.29 by log-rank test*
<table>
<thead>
<tr>
<th>Event Type</th>
<th>Niacin–Laropiprant (N=12,838)</th>
<th>Placebo (N=12,835)</th>
<th>Rate Ratio (95% CI)</th>
<th>Absolute Excess with Niacin–Laropiprant percentage points</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>620 (4.8)</td>
<td>491 (3.8)</td>
<td>1.28 (1.13–1.44)</td>
<td>1.0±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Musculoskeletal event</td>
<td>481 (3.7)</td>
<td>385 (3.0)</td>
<td>1.26 (1.10–1.44)</td>
<td>0.7±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin-related event</td>
<td>86 (0.7)</td>
<td>51 (0.4)</td>
<td>1.67 (1.20–2.34)</td>
<td>0.3±0.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Infection event</td>
<td>1031 (8.0)</td>
<td>853 (6.6)</td>
<td>1.22 (1.12–1.34)</td>
<td>1.4±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding event</td>
<td>326 (2.5)</td>
<td>238 (1.9)</td>
<td>1.38 (1.17–1.62)</td>
<td>0.7±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New-onset diabetes in participants</td>
<td>494/8704 (5.7)</td>
<td>376/8670 (4.3)</td>
<td>1.32 (1.16–1.51)</td>
<td>1.3±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>without diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disturbed diabetes control in</td>
<td>460/4134 (11.1)</td>
<td>311/4165 (7.5)</td>
<td>1.55 (1.34–1.78)</td>
<td>3.7±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>participants with diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fibric Acid Derivatives (Fibrates)

- Inhibit hepatic synthesis of VLDL and facilitate VLDL catabolism (increase LPL activity)
- Peroxisome proliferator receptor alpha (PPARα) activator
- Reduction in TG (35-50%) and increase in HDL (15-25%)
- Effective for treatment of hypertriglyceridemia with or without low HDL and primary hypoalphalipoproteinemia
Fibrates: Mechanisms of Action on Lipids

**Liver**
- Apo AI increase
- Apo AI increase
- ABCA1 increase
- Apo CIII decrease
- TG decrease
- FFA increase
- Acyl-CoA Synthase increase
- Acetyl CoA increase

**Circulation**
- HDL increase
- VLDL decrease
- LPL increase
- LDL decrease

**Results**
- Increased HDL production
- Decreased VLDL production
- Increased VLDL clearance
- Decreased LDL particles and increased particle size

---

Fibric Acids

• Major actions
  – Lower LDL-C 5–20% (with normal TG)
  – May raise LDL-C (with high TG)
  – Lower TG 20–50%
  – Raise HDL-C 10–20%

• Fibrates are metabolized by CYP3A4 pathway → concern with statin and fibrate combination → increased myositis

• Side effects: dyspepsia, gallstones, myopathy

• Contraindications: Severe renal or hepatic disease

• Obtain baseline chemistries, including creatinine, LFTs, CK
Fibric Acid Derivatives (Fibrates)

- Gemfibrozil is dosed 600 mg bid 30-60 min before meals
- Fenofibrate and fenofibric acid (Trilipix) are dosed 1 tab daily
### AHA Recommendations for Omega-3 FA Intake

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without documented CHD</td>
<td>Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts)</td>
</tr>
<tr>
<td>Patients with documented CHD</td>
<td>Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician.</td>
</tr>
<tr>
<td>Patients needing triglyceride lowering</td>
<td>2–4 grams of EPA+DHA per day provided as capsules under a physician’s care</td>
</tr>
</tbody>
</table>

# Omega-3 Fatty Acids (Fish Oils)

| **Indications:** | Adjunctive therapy to diet Hypertriglyceridermia (Type IV and V)  
| | With statins or other LDL-C-lowering drugs in mixed hyperlipidemia |
| **Efficacy:** | Decrease TG 30–40%  
| | LDL-C remains the same or increases  
| | No change in HDL-C |
| **Side Effects:** | GI upset and a “fish burp”  
| **Intervention Trials:** | Lyon Heart Study (dietary), GISSI Prevenzione Trial, others |
| **Prolongation of bleeding time** |
Essential Fatty Acid Families

**ω-6 family**
- **C18:2 ω-6** Linoleic
  - Corn Oil
  - Safflower Oil
  - Sunflower Oil
- **C20:4 ω-6** Arachidonic

More thrombotic and inflammatory metabolites

**ω-3 family**
- **C18:3 ω-3** α-Linolenic
  - Flaxseed Oil
  - Canola Oil
  - Soybean Oil
- **C20:5 ω-3** Eicosapentaenoic (EPA)
- **C22:6 ω-3** Docosahexaenoic (DHA)
  - Oily Fish
  - Fish Oil Capsules

Less thrombotic and inflammatory metabolites
Prescription Omega-3 (Fish Oil)

- Lovaza (DHA and EPA) and Vascepa (EPA only)
- Reduces hepatic VLDL synthesis and/or secretion and enhances TG clearance from circulating VLDL particles
- TG lowering dose is 2 gm BID
- Adverse effects: GI, arthralgia
- May prolong bleeding time
- Control medical problems that contribute to TG elevations, e.g., DM, excessive ETOH, hypothyroidism
## Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Triglyceride Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>30–50</td>
</tr>
<tr>
<td>Immediate-release niacin</td>
<td>20–50</td>
</tr>
<tr>
<td>Omega-3</td>
<td>20–50</td>
</tr>
<tr>
<td>Extended-release niacin</td>
<td>10–30</td>
</tr>
<tr>
<td>Statins</td>
<td>10–30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5–10</td>
</tr>
</tbody>
</table>

ARS Question 3

All of the following are non-statin LDL-lowering agents except:
A. Ezetimibe
B. Omega-3 (fish oil)
C. Niacin
D. Bile acid sequestrants
Lipid-altering Drugs

- HMG-CoA Reductase Inhibitors (Statins)
  Reduce LDL

- Bile Acid Sequestrants (colestipol, cholestyramine, colesevelam)
  Reduce LDL

- Nicotinic Acid (Niacin, Niaspan)
  Raises HDL, lowers TG, and lowers LDL
Lipid-altering Drugs (Con’t)

• Cholesterol absorption inhibitor (ezetimibe)
  *Lowers LDL*

• Fibric acid derivatives (gemfibrozil, fenofibrate, fenofibric acid)
  *Lower triglycerides*

• Fish oil (Lovaza, Vascepa)
  *Lowers triglycerides*
LDL Apheresis

Patients who after 6 mos do not have an adequate response to maximal drug therapy:

• Homozygous FH with LDL-C ≥ 300 mg/dL
• Heterozygous FH with LDL-C ≥ 300 mg/dL and 0-1 risk factors
• Heterozygous FH with LDL-C ≥ 200 mg/dL and high risk characteristics such as ≥ 2 risk factors or high lipoprotein (a) ≥ 50 mg/dL
• Heterozygotes with LDL-C ≥ 160 mg/dL and very high risk characteristics (established CHD, other CVD, or diabetes)

Goldberg et al., J Clin Lipidology 2011;5:S1-S8.
What is LDL-Apheresis?

Treatment to remove LDL cholesterol from the blood while keeping the good HDL cholesterol.

Extracorporeal, blood taken outside of the body, and returned to the patient without need for albumin or other blood products.

Ross, JL, MSN, CRNP 2012
Novel Therapies -- Why?

• Substantive LDL-C reductions are difficult to achieve with standard therapies
• Significant numbers of individuals are unable to tolerate currently available lipid-altering therapies
• Challenges associated with LDL apheresis
  – Limited availability of treatment centers
  – Difficulty with vascular access
  – Treatment sessions are time consuming
2 New Drugs: Homozygous FH

• HoFH is an inherited disorder caused by homozygous mutations in the LDL receptor gene
• Estimated to be 1 case per 1 million persons
• Clinical diagnosis: presence of xanthomas at an early age (< 10 years), untreated LDL > 500 mg/dL, treated LDL ≥ 300 mg/dL
Mipomersen (Kynamro)

- Antisense oligonucleotide inhibitor that targets apo B 100
- Injectable therapy as adjunct to lipid-lowering meds and diet
- Acts to reduce ApoB production, thus reducing VLDL production and therefore LDL-C
- Approved for patients with HoFH
Mipomersen (ApoB-100 antisense)

- Single stranded DNA, induced degradation of mRNA
- Administered via weekly subcutaneous injections
- Decreased secretion of Apo B containing lipoproteins from the liver
- Lowers LDL and Lp(a)
Lomitapide (Juxtapid)

- An MTP inhibitor
- MTP (microsomal triglyceride transfer protein) is necessary for formation of chylomicron and VLDL particles
- Lomitapide prevents the assembly of apoB containing lipoproteins in enterocytes and liver.
- Lowers LDL-C
Emerging Therapies: PCSK9 Inhibitors

- PCSK9 (Proprotein Convertase subtilisin/kexin type 9) is a protein secreted by the hepatocyte

- Loss of function mutations in PCSK9 decrease LDL-C and CV risk

- Ongoing clinical trials with monoclonal antibodies to PCSK9 demonstrate 60%-70% reduction in LDL-C and 26% reduction in Lp(a)
OSLER Trials

• Evolocumab, a fully human monoclonal Ab that typically achieves a 60% reduction in LDL-C
• Long-term extension of the parent trial → primary goal of gathering long-term data on safety, side effects, LDL-C reduction, and CV outcomes
• Evolocumab was administered to 4465 patients subcu either 420 mg once a month or 140 mg every 2 weeks
  – Mean age 58 years, at least 1 CV risk factor
  – 70.1% received statin therapy at start of OSLER trials

Sabatine MS et al., NEJM 2015; DOI: 10.1056/NEJMoa1500858
Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.
Figure 2. Cumulative Incidence of Cardiovascular Events.
Take Home Points

1. Encourage adherence to a healthy lifestyle.

2. Statins are recommended for people in groups with demonstrated benefit.

3. For primary prevention, use the pooled cohort equations for estimating 10-year ASCVD risk.

4. Engage in a clinician–patient discussion before initiating statin therapy, especially for primary prevention in patients with lower ASCVD risk.

5. Initiate the appropriate intensity of statin therapy.
6. Evidence is inadequate to support treatment to specific LDL-C or Non–HDL-C goals.

7. Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored.

8. Regularly monitor patients for adherence to lifestyle and statin therapy.

9. Currently, there is no evidence that niacin added to a statin improves outcomes.

10. When ezetimibe is added to a statin, a modest improvement in outcomes is seen.