Dyslipidemia 2016: Making Sense of the Guidelines and the New Drugs

Greenville Postgraduate Medical Assembly 2016
Embassy Suites Hotel
Greenville, South Carolina
Wednesday, April 20, 2016
8:00-9:00 AM

Jan Basile, MD
Seinsheimer Cardiovascular Health Program
Professor of Medicine
Medical University of South Carolina
Charleston, South Carolina
DISCLOSURE OF FINANCIAL RELATIONSHIPS

Jan N. Basile, MD

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Consultant: Amgen, Allergan, Janssen, Novartis
Speakers Bureau: Amgen, Arbor, Janssen
Major stock shareholder: None
Other: None
Learning Objectives:

Upon completion of this lecture, learners should be better prepared to:

1) Recognize the 4 patient populations who benefit most from statin-based therapy according to the ACC/AHA 2014 guidelines and the controversies surrounding targeting LDL-C as a treatment goal

2) Define the population where additional lipid-lowering agents w/or w/o a background of statin-therapy have further improved cardiovascular (CV) outcomes

3) Define the role of the PCSK9 inhibitors to further lower LDL-cholesterol in the hopes of improving CV outcome
Pre-test Question

On a scale of 1 to 5, please rate how confident you would be in treating your patients with Hypercholesterolemia?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Statin Evidence: Landmark Statin Trials
The Greater the Risk The Greater the Benefit
The Lower the LDL-C, The Greater the Benefit

*Extrapolated to 5 years

Adapted from Kastelein JP. Atherosclerosis. 1999;143(suppl 1):S17-S21.
Relationship Between LDL-C Levels and CHD Events in Secondary Prevention Statin Trials: The Lower the LDL-C, the Fewer the Events

**Primary Endpoint-Composite of CV death, MI, coronary revascularization, hospitalization for UA, or UA.**

Based on this, the LDL-C goal was lowered in the highest risk group to < 70 mg/dL.

Wiviott SD et al., J Am Coll Cardiol 2005: 1411-1416.

Meta-Analysis: 90,056 Individuals in 14 Randomized Clinical Trials of Statins

423,000 Patient Years of Follow-up

Per a 39 mg/dL (1 mmol/L) absolute reduction in LDL with Statin Rx

- 23% reduction in major cardiac events
- 20% reduction in CHD mortality
- 22% reduction in ischemic strokes
- Benefit entirely in proportion to LDL reduction
- No influence of baseline LDL on level of benefit
- No effect of sex, age, or other risk factors on benefit
- Similar relative risk reduction in all subgroups
- No increase in non-cardiovascular mortality

CTT Lancet 2005;366:1266-1278
## Effects on MAJOR VASCULAR EVENTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4.4)</td>
<td>2769 (6.2)</td>
<td>0.74 (0.70 – 0.79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3.4)</td>
<td>1960 (4.4)</td>
<td>0.81 (0.75 – 0.87)</td>
</tr>
<tr>
<td><strong>Any major coronary event</strong></td>
<td>3337 (7.4)</td>
<td>4420 (9.8)</td>
<td>0.77 (0.74 – 0.80)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (3.3)</td>
<td>1006 (4.7)</td>
<td>0.75 (0.69 – 0.82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (2.4)</td>
<td>658 (3.1)</td>
<td>0.79 (0.69 – 0.90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3.1)</td>
<td>1770 (3.9)</td>
<td>0.76 (0.69 – 0.84)</td>
</tr>
<tr>
<td><strong>Any coronary revascularization</strong></td>
<td>2620 (5.8)</td>
<td>3434 (7.6)</td>
<td>0.76 (0.73 – 0.80)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>105 (0.2)</td>
<td>99 (0.2)</td>
<td>1.05 (0.78 – 1.41)</td>
</tr>
<tr>
<td>Presumed ischemic stroke</td>
<td>1235 (2.8)</td>
<td>1518 (3.4)</td>
<td>0.81 (0.74 – 0.89)</td>
</tr>
<tr>
<td><strong>Any stroke</strong></td>
<td>1340 (3.0)</td>
<td>1617 (3.7)</td>
<td>0.83 (0.78 – 0.88)</td>
</tr>
<tr>
<td><strong>Any major vascular event</strong></td>
<td>6354 (14.1)</td>
<td>7994 (17.8)</td>
<td>0.79 (0.77 – 0.81)</td>
</tr>
</tbody>
</table>
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Neil J. Stone, MD, MACP, FAHA, FACC, Chair
Jennifer Robinson, D, MPH, FAHA, Vice Chair
Alice H. Lichtenstein, DSc, FAHA, Vice Chair

Anne C. Goldberg, MD, FACP, FAHA
Conrad B. Blum, MD, FAHA
Robert H. Eckel, MD, FAHA
Daniel Levy, MD*
David Gordon, MD*
C. Noel Bairey Merz, MD, FAHA, FACC

Donald M. Lloyd-Jones, MD, ScM, FACC, FAHA
J. Sanford Schwartz, MD
Patrick McBride, MD, MPH, FAHA
Sidney C. Smith, Jr, MD, FACC, FAHA
Karol Watson, MD, PhD, FACC, FAHA
Susan T. Shero, MS, RN*
Peter W.F. Wilson, MD, FAHA

**LDL-C Goals for High-Risk Patients Have Become More Intensive Over Time**

- As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time.

<table>
<thead>
<tr>
<th>Year</th>
<th>ATP I</th>
<th>ATP II</th>
<th>ATP III</th>
<th>ATP III Update</th>
<th>2° AHA/ACC</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>Goal: &lt;130 mg/dL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>1993</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>2001</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>2004</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>2006</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>2010</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Goal: &lt;100 mg/dL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Definition of high-risk or highest-risk patient:**

- ATP I: definite CHD or 2 other CHD risk factors<sup>1</sup>
- ATP II: prior CHD or other atherosclerotic disease<sup>2</sup>
- ATP III and the 2004 update: CHD or CHD risk equivalents<sup>3,4</sup>
- 2° AHA/ACC 2006: established coronary and other atherosclerotic disease<sup>5</sup>
- ADA 2010: overt CVD<sup>6</sup>

<sup>a</sup>Factors that place a patient at very high risk are multiple components of the metabolic syndrome, established CVD plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (e.g., cigarette smoking), multiple components of the metabolic syndrome (especially TG ≥200 mg/dL + non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL), and recent acute coronary syndromes.<sup>4</sup>

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2013 ACC/AHA Expert Panel

Recommendation

A New Perspective on LDL-C and/or non-HDL Goals

- There is no RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.

- The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.

• Non-statin therapies, whether used alone or in addition to statins, do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.

### 2013 ACC/AHA Expert Panel

<table>
<thead>
<tr>
<th>TLC</th>
<th>Still an Integral part of CHD risk management</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>No longer a primary target of lipid-modifying therapy</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>No longer a secondary target of therapy in patients with hypertriglyceridemia (≥200 mg/dL)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>No treatment goals are identified for HDL-C</td>
</tr>
<tr>
<td></td>
<td>- Low HDL-C (&lt;40 mg/dL) as positive CHD risk factor</td>
</tr>
<tr>
<td></td>
<td>- High HDL-C (≥60 mg/dL) as negative CHD risk factor</td>
</tr>
<tr>
<td>TG</td>
<td>No treatment goals are identified for TG</td>
</tr>
<tr>
<td></td>
<td>Treat if levels &gt;500 mg/dL where risk of pancreatitis is still high</td>
</tr>
</tbody>
</table>

TLC = Therapeutic Lifestyle Change
NCEP Guidelines Identify TG and Non-HDL-C As Important Parameters for Lipid Management

Treatment Objectives for Elevated Triglycerides

- **Very High**
  - TG ≥500
  - **Primary Objective**: TG reduction
  - **Secondary Objective**: LDL-C and non-HDL-C reduction

- **High**
  - TG 200-499
  - **Primary Objective**: LDL-C goal
  - **Secondary Objective**: non-HDL-C reduction (VLDL-C and LDL-C)

* VLDL-C levels are influenced by triglyceride levels.

HDL-C=high-density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; NCEP=National Cholesterol Education Program; TG=triglyceride; VLDL-C=very low-density lipoprotein cholesterol.

LDL-C Reduction Remains Fundamental to Major Cholesterol Treatment Guidelines

Recommendations for Patients With Clinical ASCVD

ASCVD = atherosclerotic cardiovascular disease; ACC = American College of Cardiology; AHA = American Heart Association; ADA = American Diabetes Association; NLA = National Lipid Association; AACE = American Association of Clinical Endocrinologists; IAS = International Atherosclerosis Society; ESC = European Society of Cardiology; EAS = European Atherosclerosis Society.

*Percent LDL-C reduction defines treatment intensity and assesses adherence; †also includes percent LDL-C reduction as an efficacy metric.

### ADA: Recommendations for Statin And Combination Treatment in People with Diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Statin Intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high (C)</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate (A)</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High (B)</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe (A)</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate (B)</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>Moderate or high (B)</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe (A)</td>
</tr>
</tbody>
</table>

* In addition to lifestyle therapy.

** LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight or obesity, and family hx of premature ASCVD.

American Diabetes Association Standards of Medical Care in Diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71
# 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 by $\geq 50%$</td>
<td>Lowers LDL by 30 - &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 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>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

* Once-daily dosing

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American Diabetes Association Standards of Medical Care in Diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71
## 2014 National Lipid Association Guidelines: Criteria for ASCVD Risk Assessment, LDL-C Treatment Goals, and When to Consider Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HDL-C mg/dL, LDL-C mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>▪ 0-1 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥190</td>
</tr>
<tr>
<td></td>
<td>▪ Consider other risk indicators, if known</td>
<td>&lt;100</td>
<td>≥160</td>
</tr>
<tr>
<td>Moderate</td>
<td>▪ 2 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥160</td>
</tr>
<tr>
<td></td>
<td>▪ Consider quantitative risk scoring</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>▪ Consider other risk indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>▪ ≥3 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>▪ Diabetes mellitus* (Type 1 or 2)</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>▪ 0-1 other major ASCVD risk factors, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ No evidence of end organ damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Chronic kidney disease stage 3B or 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Quantitative risk score reaching the high-risk threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>▪ ASCVD*</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>▪ Diabetes mellitus* (Type 1 or 2)</td>
<td>&lt;70</td>
<td>≥70</td>
</tr>
<tr>
<td></td>
<td>▪ ≥2 other major ASCVD risk factors or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Evidence of end organ damage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.*

Despite Treatment Many US Adults With CHD* Are Not Achieving Prespecified LDL-C Levels

Treated Patients From NHANES 2007-2008

72% Not achieving LDL-C < 70 mg/dL

28% Achieving LDL-C < 70 mg/dL

NHANES = National Health and Nutrition Examination Survey.
*NHANES defined CHD based on answers to questions about CHD, angina, and MI (patient survey).

Multiple Contributors Exist for Failure to Achieve Desired LDL-C Level

- Subjects with Very High Baseline LDL-C
- Subjects with Difficulty Adhering to Therapy
- Subjects Unable to Tolerate Optimal Therapy
- Subjects with Limited Access to Optimal Therapy
- Subjects with Hypo-responsiveness to Therapy
Early Nonstatin Trials of Lowering Cholesterol Levels

LRC-CPPT\(^a\): 3806 asymptomatic men
Cholestyramine + diet vs diet alone
\(\Delta\) LDL-C: 23-40 mg/dL

Helsinki Heart\(^b\): 4081 asymptomatic men
Gemfibrozil vs placebo
\(\Delta\) LDL-C: 21 mg/dL

- Placebo
- Cholestyramine resin

19% reduction
\(P < .05\)

- Placebo
- Gemfibrozil

34% reduction
\(P < .02\)

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# Niacin as Monotherapy: Secondary Prevention Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design/ Duration</th>
<th>Drug(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project 1975</td>
<td>2° prevention 5 - 8yrs.</td>
<td>Niacin</td>
<td>5 yrs – nonfatal MI ↓ 27%; stroke/TIA ↓ 24%; 15 yrs – total mortality ↓ 11%</td>
</tr>
<tr>
<td>Stockholm IHD Study 1988</td>
<td>2° prevention 5 yrs.</td>
<td>Niacin, clofibrate</td>
<td>Total mortality ↓ 26%; Ischemic heart disease mortality ↓ 36%</td>
</tr>
</tbody>
</table>

*JAMA.* 1975;231:360-381.  
Fibrates: Cardiovascular Outcome Data Shows Mixed Results Based on Mono vs Additive Rx

<table>
<thead>
<tr>
<th>Trial</th>
<th>Fibrate</th>
<th>Follow-up yr</th>
<th>Patient Population</th>
<th>Primary End Point</th>
<th>Absolute Event Rate (%)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (1982)</td>
<td>Gemfibrozil, 1200 mg</td>
<td>5.0</td>
<td>4081 men with non-HDL cholesterol ≥200 mg/dl (primary prevention)</td>
<td>Fatal or nonfatal MI, or CAD death</td>
<td>84/2030 (4.1)</td>
<td>56/2051 (2.7)</td>
<td>0.66 (0.47–0.92)</td>
</tr>
<tr>
<td>VA-HIT (1991–1993)</td>
<td>Gemfibrozil, 1200 mg</td>
<td>5.1</td>
<td>2531 men with CAD and HDL cholesterol &lt;40 mg/dl (secondary prevention)</td>
<td>Nonfatal MI or CAD death</td>
<td>275/1267 (21.7)</td>
<td>219/1264 (17.3)</td>
<td>0.78 (0.65–0.95)</td>
</tr>
<tr>
<td>BIP (1990–1992)</td>
<td>Bezafrate, 400 mg</td>
<td>6.2</td>
<td>3090 men and women with previous MI or angina (secondary prevention)</td>
<td>Fatal or nonfatal MI or sudden death</td>
<td>232/1542 (15.1)</td>
<td>211/1548 (13.6)</td>
<td>0.91 (0.76–1.08)</td>
</tr>
<tr>
<td>FIELD (1998–2000)</td>
<td>Fenofibrate, 200 mg</td>
<td>5.0</td>
<td>9795 men and women with type 2 diabetes (primary and secondary prevention)</td>
<td>Nonfatal MI or CAD death</td>
<td>288/4900 (5.9)</td>
<td>256/4895 (5.2)</td>
<td>0.89 (0.75–1.05)</td>
</tr>
<tr>
<td>ACCORD (2001–2005)</td>
<td>Fenofibrate acid, 160 mg</td>
<td>4.7</td>
<td>5518 men and women with type 2 diabetes on statin therapy (primary and secondary prevention)</td>
<td>Nonfatal MI, nonfatal stroke, or death from cardiovascular causes</td>
<td>310/2765 (11.2)</td>
<td>291/2753 (10.6)</td>
<td>0.92 (0.79–1.08)</td>
</tr>
</tbody>
</table>

* ACCORD denotes Action to Control Cardiovascular Risk in Diabetes trial, BIP Bezafrate Infarction Prevention study, CAD coronary artery disease, FIELD Fenofibrate Intervention and Event Lowering in Diabetes study, HHS Helsinki Heart Study, MI myocardial infarction, and VA-HIT Veterans Affairs High-Density Lipoprotein Intervention Trial.
Figure 7. ACCORD Lipid Confirms CV Benefit of Fibrate Therapy in Patients with Elevated TG and Low HDL-C

Elevated TG and Low HDL-C

- HHS
- VA-HIT
- BIP
- FIELD
- ACCORD Lipid

Summary

Odds ratio (95% CI)

- 0.65 (0.55, 0.77) - Fibrate better
- 0.93 (0.85, 1.01) - Control better

All Others

Odds ratio (95% CI)

- Fibrate better
- Control better

Source: FDA Advisory Committee Briefing Document Trilipix® (Fenofibric Acid) Delayed Release Capsules. Endocrinologic and Metabolic Drugs Advisory Committee Meeting 19 April 2011
Recommendations: Lipid Management (5)

- Combination therapy (statin/fibrate) doesn’t improve ASCVD outcomes and is generally not recommended. Consider therapy with statin and fenofibrate for men with both trigs $\geq 204$ mg/dL (2.3 mmol/L) and HDL $\leq 34$ mg/dL (0.9 mmol/L).

- Combination therapy (statin/niacin) hasn’t demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended.

- Statin therapy is contraindicated in pregnancy.

American Diabetes Association Standards of Medical Care in Diabetes. Diabetes Care 2016; 39 (Suppl. 1): S60-S71
When to Consider Statins in Combination with:

Niacin  No use: AIM HIGH, HPS THRIVE-2

Fenofibrate  No use: FIELD, ACCORD

Fish Oil  No use: NO STUDIES

Ezetimibe  No use: NO STUDIES

Bile Acid Resin  No use: NO STUDIES

CLINICAL PEARL

Addition of non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.


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Print ISSN: 0009-7322. Online ISSN: 1524-4539
The 4 Statin Benefit Groups

• Clinical ASCVD*

• LDL-C $\geq 190$ mg/dL, Age $\geq 21$ years

• Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL

• Primary prevention - No Diabetes†: $\geq 7.5\%$‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease
†Requires risk discussion between clinician and patient before statin initiation
‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

Adults >20 years of age and a candidate for statin therapy

**Clinical ASCVD and Age ≤75**
- **YES**: High-intensity statin (Moderate intensity if not a candidate for high-intensity) Grade A
- **NO**

**LDL–C ≥190 mg/dL**
- **YES**: High-intensity statin (Moderate intensity if not a candidate for high-intensity) Grade B
- **NO**

**Diabetes type 1 or 2 and age 40-75**
- **YES**: Moderate intensity statin 5-7.4% Grade A
- **NO**

**≥7.5 % 10-year ASCVD risk and age 40 to 75**
- **YES**: Moderate- to high-intensity statin Grade A
- **NO**

Measure risk factors every 4-6 years and recalculate 10-year ASCVD risk in those without ASCVD, diabetes, and with LDL-C <190 mg/dl

New ACC/AHA 2013 Cholesterol Guidelines
No Definitive Guidelines

- Age greater than 75 years w/o ASCVD or with LDL-C < 190 mg/dl
- DM ages 20-39
- Age 20-39 w/o ASCVD and LDL-C < 190 mg/dl
- LDL-C and non-HDL-C goals
- Triglycerides, including “Severe”
- Non-Statin medications

IMPROVE-IT Study Design

Patients stabilized post ACS ≤ 10 days:

- LDL-C 50 – 125 mg/dL (or 50-100 mg/dL if prior lipid-lowering Rx)
- 34% on statins upon entering trial
- Mean age 64, 1147 sites in 39 countries

Standard Medical & Intervventional Therapy

N= 18,144

Simvastatin
40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)
-27% mono, 6% combo

Ezetimibe / Simvastatin
10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32
Improving IT (IMPROVE-IT)

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


CTT Collaboration. 
Lancet 2005; 366:1267-78; 
Lancet 2010;376;1670-81.
IMPROVE-IT (cont)

Safety of Very Low Achieved LDL-C Levels

- AE rates similar with very low, low, medium, and higher achieved LDL-C levels in patients treated with simvastatin/ezetimibe

<table>
<thead>
<tr>
<th>Adverse Event Categories</th>
<th>&lt; 30 mg/dL</th>
<th>30- &lt; 50 mg/dL</th>
<th>50- &lt; 70 mg/dL</th>
<th>≥ 70 mg/dL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE Leading to Discontinuation</td>
<td>6.9%</td>
<td>4.6%</td>
<td>9.7%</td>
<td>6.5%</td>
<td>.38</td>
</tr>
<tr>
<td>AST or ALT ≥ 3x ULN</td>
<td>4.6%</td>
<td>4.5%</td>
<td>8.8%</td>
<td>4.8%</td>
<td>.68</td>
</tr>
<tr>
<td>Myalgia with CK Elevation per Investigator</td>
<td>4.6%</td>
<td>4.5%</td>
<td>8.8%</td>
<td>4.8%</td>
<td>.90</td>
</tr>
<tr>
<td>Myopathy per CEC</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>.41</td>
</tr>
<tr>
<td>Rhabdomyolysis per CEC</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>.16</td>
</tr>
<tr>
<td>Memory Impairment or Altered Mental Status</td>
<td>2.1%</td>
<td>2.5%</td>
<td>2.9%</td>
<td>2.3%</td>
<td>.97</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.3%</td>
<td>0.8%</td>
<td>0.4%</td>
<td>0.6%</td>
<td>.57</td>
</tr>
</tbody>
</table>

Patients by LDL-C Level at 1 mo

- Randomized to simvastatin + ezetimibe, %

85 | 72 | 44 | 22 | < .001

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial IMPROVE-IT

- Re-affirms the LDL hypothesis
- Lower LDL-C is Better (achieved mean LDL-C was 70 mg/dL vs 54 mg/dL at 1 year)
- Hs-CRP was 0.5 lower with combination Rx
- ITT [intention-to-treat] patients followed for 7 years all did better (pre-specified endpoint)
- All safety endpoints for cancer, myopathy, and liver side effects were met (not different from statin-alone Rx)

When to Consider Statins in Combination with:

**Niacin**  
*No use*: AIM HIGH, HPS THRIVE-2

**Fenofibrate**  
*No use*: FIELD, ACCORD

**Fish Oil**  
*No use*: NO STUDIES

**Ezetimibe**  
*Can use*: NOW PROOF:  
(The IMPROVE IT trial)

**Bile Acid Resin**  
*No use*: NO STUDIES
2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

Endorsed by the National Lipid Association

2016 Expert Consensus Decision Pathway
Non-Statin Therapies Considered

- Ezetimibe
- Bile-acid sequestrants (BAS)
- PCSK9 inhibitors
  - Alirocumab, evolocumab
- Mipomersen
- Lomitapide
- LDL apheresis
- Niacin NOT routinely recommended

For selected pts with FH under care of a lipid specialist
Global CV Risk Assessment Score

• 10-year ASCVD risk
  – Nonfatal or fatal MI; and nonfatal or fatal stroke

• [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)

• App-AHA CV Risk Calculator-Free download

### ACC AHA Risk Calculator

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Enter patient values in this column</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td>m</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>48</td>
</tr>
<tr>
<td>Race</td>
<td>AA (for African Americans) or WH (for whites or others)</td>
<td>aa</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td>160</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td>50</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>130</td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y (for yes) or N (for no)</td>
<td>y</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
<td>n</td>
</tr>
<tr>
<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td>n</td>
</tr>
</tbody>
</table>

#### Your 10-Year ASCVD Risk (%)
7.7

#### 10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)
3.5
Coronary Artery Calcium (CAC) Scores

On the basis of current guidelines from both NCEP and ACC/AHA:

• CAC scores < 75th percentile and < 300 are to be treated with low- to moderate-dose statins. ¹,²
• CAC scores > 75th percentile or ≥ 300 are to be treated with high-dose statins. ¹,²
• CAC score of zero should be considered for lifestyle modification, unless a compelling indication for statin already exists as CAC=0 resulted in the largest, most accurate downward risk reclassification of tests done³

Inter-individual variability in response to statins

Subjects participating in clinical trials of statin therapy, display impressive average reductions in LDL-C. An individual patient’s response to statin therapy, however, can be very variable. The graph below shows dramatic inter-individual variability in response to Atorvastatin 10 mg daily. This has also been observed with other statins.
Statin Intolerance (SI)

- An estimated 5–20% (5-10%) cannot tolerate statin treatment
- Statin intolerance (most commonly muscle pain, aching, and weakness) commonly leads to discontinuation
- Intolerance may be the result of perception or expectation (clipping the package insert on the Rx)
- Most statin-intolerant patients can be successfully re-challenged (occurs when patients are blinded in studies)
- A subset of patients are truly statin intolerant but it is much smaller than we believe it is with the exact number unclear.
- The FDA defines SI as patients who have either been optimized on a statin or unable to tolerate any statin type or dose

Abramson JD, et al. BMJ. 2013;347:f6123
De Vera MA, et al. BJCP. 2014;78(4):684-698
What Does the 2013 ACC/AHA Guideline Say? Monitoring Statin Therapy

- Initial fasting lipid panel
- Second panel 4-12 weeks later to determine adherence to therapy
- Every 3-12 months as clinically indicated

CASE PRESENTION

• 51 year-old male
  - at age 41 treated with PCI for LAD occlusion
  - at age 49 further development of coronary disease resulting in three-vessel CABG
• PMHx-hasn’t smoked in 20 years, drinks a couple of beers on the weekend
• No hx of diabetes, hypertension, thyroid or liver disease
CASE PRESENTATION

- Fam Hx: brother died of an MI at age 43
- sister had angioplasty at age 52.
- Meds: On atorvastatin 80 mg and ezetimibe 10 mg
- Did not tolerate bile acid sequestrants (constipation and bloating) or niacin (bad flushing)
- TC=276 mg/dL, LDL-201 mg/dL, TGs 125 mg/dL and HDL 45 mg/dL. Lp(a)-56 mg/dL.
- BMI 24.6 kg/m2, BP 126/74 mm Hg
- Corneal Arcus and Achilles xanthoma found on exam
2013 ACC/AHA Cholesterol Guidelines

Recommend high-intensity statin therapy for patients at high risk

- Age ≥ 21 years and a candidate for statin therapy

Definitions of High- and Moderate-Intensity Statin Therapy

- **High**
  - Daily dose lowers LDL-C by ~ ≥ 50%

- **Moderate**
  - Daily dose lowers LDL-C by ~ 30% to < 50%

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments

LDL-C ≥ 190 mg/dL

Clinical ASCVD

- Yes
  - Age ≤ 75 years
    - High-intensity statin
    - (Moderate-intensity statin if not candidate for high-intensity statin)

- No
  - Yes
    - Age ≤ 75 years
      - OR if not candidate for high-intensity statin
      - Moderate-intensity statin
  - No
    - Diabetes
      - LDL-C 70-189 mg/dL
      - Age 40-75 years
      - Estimated 10-y ASCVD risk ≥ 7.5%
      - High-intensity statin
      - (Moderate-intensity statin if not candidate for high-intensity statin)
    - Moderate-intensity statin

FH: Most Common Inherited Disorder

Heterozygous FH is found in 1:250-300 patients

- FH: Most Common Inherited Disorder
- PCKD = polycystic kidney disease.

- Dominant Otosclerosis
- Adult PCKD
- Sickle Cell Disease
- Multiple Exostoses
- Huntington's Disease
- Fragile X
- Neurofibromatosis
- Cystic Fibrosis
- Duchenne's Muscular Dystrophy

PCKD = polycystic kidney disease.

What Is Clinical ASCVD and FH?

### Clinical ASCVD

- Defined in 2013 ACC/AHA guidelines as one or more of the following: \(^1,2\)
  - **Coronary heart disease (CHD)**
    - Acute coronary syndrome
    - History of myocardial infarction (MI)
    - Stable or unstable angina (UA)
    - Coronary or other arterial revascularization
  - Stroke or transient ischemic attack
  - Peripheral arterial disease

### Familial Hypercholesterolemia (FH) \(^2-4\)

- Inherited conditions characterized by elevated LDL-C and mutations in genes involved in LDL metabolism \(^3\)

#### Heterozygous FH

- LDL-C \(\geq 190\) mg/dL \(^3,^*\)
- Identification \(^4\)
  - Elevated LDL-C with physical findings or family history of early MI
  - DNA-based evidence

#### Homozygous FH

- LDL-C > 500 mg/dL \(^5,^*^\)
- CVD diagnosis on average at 20 years \(^3\)

---

DNA = deoxyribonucleic acid.

*Typical levels when untreated; †LDL-C level indicative of HoFH, lower levels do not exclude HoFH.

\(^1\) LDL-C level indicative of HoFH, lower levels do not exclude HoFH.

\(^2\) Simon Broome criteria in adults include an LDL-C of > 190 mg/dL (without therapy) plus clinical criteria (including patient or family history of tendon xanthomas, family history of early CAD, or family history of TC > 290 mg/dL). \(^2,^3\)

## Currently Used Therapies for HoFH and HeFH

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Major Effect</th>
<th>LDL-lowering Response HoFH</th>
<th>LDL-lowering Response HeFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Chol Diet</td>
<td>↑ LDLR activity</td>
<td>&lt; 10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Statins</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>Resins</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓ chol adsorp + ↑ LDLRa</td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Stanol Esters</td>
<td>↓ chol adsorp + ↑ LDLRa</td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>↓ VLDL synthesis</td>
<td>&lt;10%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>LDL apheresis</td>
<td>Removes LDL-C</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
</tr>
</tbody>
</table>
Heterozygous Familial Hypercholesterolemia
Frequency: 1/200-300
USA: 600,000 patients

FINAL OPTION - LDL apheresis
↓LDL 75-80% acutely (50% over 2-week average)

FDA APPROVAL (HELP, LIPOSORBER)

- LDL > 200 mg/dL (with CHD)
- LDL > 300 mg/dL (no CHD)
New drugs for treatment of hypercholesterolemia
Novel Targets for Lipid Management

Drugs that block Lipoprotein Assembly

1. ApoB Antisense (Mipomersen)
   trade name KYNAMRO™

2. MTP Inhibition (Lomitapide)
   trade name JUXTAPID™

Both drugs are only available under a REMS program (Risk Evaluation & Mitigation Strategies)

Drugs that Increase Lipoprotein Clearance

1. PCSK9 Inhibitors (At least 8 in development, 2 Already FDA approved)
**Novel LDL-Lowering Approaches for Familial Homozygous Hypercholesterolemia**

<table>
<thead>
<tr>
<th></th>
<th>Mipomersan Kynamro™</th>
<th>Lomitapide Juxtapid™</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Antisense oligonucleotide</td>
<td>MTTP inhibitor</td>
</tr>
<tr>
<td>T 1/2</td>
<td>1-2 months</td>
<td>39.7 hours</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Injection, weekly</td>
<td>Oral, daily</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Tissues</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Approval</strong></td>
<td>January 2013</td>
<td>December 2012</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Black Box Warning for Risk of hepatotoxicity</td>
<td>Black Box Warning for Risk of Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Only certified HCPs and pharmacies may prescribe and distribute drug via a restricted REMS program</td>
<td>Only certified HCPs and pharmacies may prescribe and distribute drug via a restricted REMS program</td>
</tr>
</tbody>
</table>

REMS = Risk Evaluation Mitigation Strategy.
### Novel LDL-Lowering Approaches for Familial Homozygous Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Anti-Sense ApoB inhibitor Mipomersan (FDA: HoFH) (Injectable)</th>
<th>MTTP-inhibitor Lomitapide (FDA: HoFH) Less VLDL in liver and chlyomicron in gut (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expected LDL-C Reduction</strong></td>
<td>25%-37% on top of statins +/- other LLT</td>
<td>40-50% on top of statins +/- other LLT</td>
</tr>
<tr>
<td><strong>Lp(a) Reduction</strong></td>
<td>-20-30%</td>
<td>-1-19%</td>
</tr>
<tr>
<td><strong>GI Side Effects</strong></td>
<td>Mild</td>
<td>Moderate-to-severe</td>
</tr>
<tr>
<td><strong>Transaminitis</strong></td>
<td>Mild</td>
<td>Moderate-to-severe</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>80-90%</td>
<td>80-90%</td>
</tr>
<tr>
<td><strong>Long Term Safety</strong></td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>Fatty liver Injection reactions Flu-like symptoms</td>
<td>Fatty liver</td>
</tr>
</tbody>
</table>

**Cuchel M. et al. Curr Opin Lipidol 2013;24:246-250.**
Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

• A protein (serine protease) secreted by the liver which acts as a chaperone for the LDL receptor targeting the receptor for degradation.

• Patients with hyperactive PCSK9 (Gain of function mutations) have fewer LDL receptors and higher circulating LDL-C levels leading to premature atherosclerosis.

• Loss of function mutations assoc. with low LDL-C

• Monoclonal antibodies against the PCSK9 protein block this “vacuum effect” on the LDL receptor leading to expression of a greater number of LDL receptors thereby lowering LDL-C levels
PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation
Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR
PCSK9 Monoclonal Antibodies Have Been Studied in…

- Monotherapy
- Add on to Low or High-Dose Statin +/- Ezetimibe
- Statin Intolerance
- Familial Heterozygote Hypercholesterolemia
- Familial Homozygous Hypercholesterolemia (most variants)
- Long Term
### PCSK9-Directed Therapies Approved or In Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug (Alternate Name)</th>
<th>Agent</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Regeneron</td>
<td>Alirocumab Praluent®</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Amgen</td>
<td>Evolocumab Repatha®</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Pfizer/Rinat</td>
<td>Bococizumab</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>3</td>
</tr>
<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals</td>
<td>ALN-PCS02</td>
<td>siRNA oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>1</td>
</tr>
<tr>
<td>Adnexus Therapeutics/Bristol-Myers Squibb</td>
<td>BMS-962476</td>
<td>Fusion protein using Adnectin technology</td>
<td>Cardiovascular disease</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Small peptide mimic; LDLR antagonist</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Shifa Biomedical Corp.</td>
<td>TBD</td>
<td>Small molecule PCSK9 modulator</td>
<td>Metabolic disorders</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Adapted from Brautbar A, Ballantyne CM. Nat Rev Cardiol. 2011;8:253-265.
17 Phase 3 Studies of PCSK9 Inhibitors in > 10,000 Patients

Monotherapy:
- MENDEL-2
- ODYSSEY MONO

In combination with statin:
- LAPLACE-2
- ODYSSEY COMBO II
- ODYSSEY COMBO I
- YUKAWA-2

Statin intolerance:
- GAUSS-2
- ODYSSEY ALTERNATIVE
- ODYSSEY CHOICE II

Heterozygous FH:
- RUTHERFORD-2
- ODYSSEY FH I and II

Homozygous FH:
- TESLA Part B

Long-term extension studies:
- OSLER-1 and OSLER-2
- ODYSSEY LONG TERM

Clinical Trial Results for the Anti-PCSK9 Monoclonal Antibodies

• Results in LDL Cholesterol level Reductions 40-70%
• Results in triglycerides and Lp(a) Reductions of 30% in various patient populations
  - on or off statins (including intolerant) w or w/o ezetimibe
  - with or w/o Familial Hypercholesterolemia
  - with or w/o clinical ASCVD
• No dose-limiting toxicities have been seen with injection site reactions of 0-5%
• To date over 10,000 patients have received these drugs in clinical trials for up to 1 year
# Contrasting the PCSK9 Inhibitors

## Characteristic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Praluent™ Alirocumab</th>
<th>Repatha™ Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Approval</strong></td>
<td>July 2015</td>
<td>August 2015</td>
</tr>
<tr>
<td><strong>Indication:</strong> Adjunct to diet and maximally tolerated statin therapy* for Rx of:</td>
<td>Clinical ASCVD who require additional LDL-C reduction</td>
<td>Clinical ASCVD who require additional LDL-C reduction</td>
</tr>
<tr>
<td>*highest dose of Statin achieved or unable to tolerate any dose of statin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>-Heterozygous Hypercholesterolemia</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>-Homozygous Familial Hypercholesteolemia</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dosage (SQ)</strong></td>
<td>75 mg q 2 weeks. If inadequate LDL-C, increase to 150 mg</td>
<td>140 mg q 2 weeks 420 mg once monthly-FoH only</td>
</tr>
<tr>
<td><strong>Usage in Adolescents</strong></td>
<td>No</td>
<td>13-17 yrs old</td>
</tr>
<tr>
<td><strong>LDL-C Monitoring</strong></td>
<td>Measure w/in 4-8 weeks to measure response</td>
<td>Only 4-8 weeks post dose FoH</td>
</tr>
<tr>
<td><strong>Storage (time out of refrigerator)</strong></td>
<td>Max 24 hours</td>
<td>Max 30 days</td>
</tr>
</tbody>
</table>
ORIGINAL ARTICLE

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D.,
Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D.,
Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H.,
Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D.,
Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D.,
and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

ABSTRACT

BACKGROUND

Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9), significantly reduced low-density lipoprotein (LDL) cholesterol levels in short-term studies. We conducted two extension studies to obtain longer-term data.

METHODS

In two open-label, randomized trials, we enrolled 4465 patients who had completed 1 of 12 phase 2 or 3 studies (“parent trials”) of evolocumab. Regardless of study-group assignments in the parent trials, eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 months with assessment of lipid levels, safety, and (as a prespecified...

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women’s Hospital, and the Department of Medicine, Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W.); the Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.), and the Division of Lipidology, Department of Medicine, University of Cape Town, Cape Town (D.J.B.) — both in South Africa; the Departments of Epidemiology and Medicine, College of Public Health, University of Iowa, Iowa City (M.J.K.); and the Division of Lipidology, Department of Medicine, University of North Carolina, Chapel Hill (R.A.S.).
OSLER 1 & 2 Studies
Long Term Extension Studies Use of Evolocumab Or Standard Therapy
(Standard therapy in some cases included statin or ezetimibe)

Adverse Event rates similar in both groups except for neuro-cognitive complaints which were more frequent with evolocumab.
OSLER 1 & 2 Studies
Effect on CV Events
(Pre-specified Exploratory Analysis)

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempe, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

ABSTRACT

BACKGROUND
Alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9), has been shown to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are receiving statin therapy. Larger and longer-term studies are needed to establish safety and efficacy.

METHODS
We conducted a randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or more and were receiving treatment with statins at the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile), with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.
ODYSSEY LONG TERM: Alirocumab vs Placebo on LDL-C from Baseline to Week 78

2341 patients on background of high-dose or maximally-tolerated statin ± other lipid-lowering therapy randomized to placebo or 150 mg q 2 weeks for 78 weeks

Intent-to-treat analysis
ODYSSEY LONG TERM:
Post-hoc analysis of time to first adjudicated cardiovascular events

Endpoints: CHD death, MI, stroke, UA requiring hospitalization

**IMPROVE-IT vs. CTT:** Ezetimibe vs. Statin Beneficial

**OSLER 1 & 2**
- LDL-C ↓ 62%
- RRR 52%

**ODYSSEY LONG TERM**
- LDL-C ↓ 62%
- RRR 47%

**Reduction in LDL cholesterol (mmol/L)**

**Proportional reduction in event rate (SE)**


## PCSK9 Inhibitors Furthest along in Development

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Description</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>Fully human IgG1 mAb</td>
<td>3*</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Fully human IgG1 mAb</td>
<td>3*</td>
</tr>
<tr>
<td>Bococizumab</td>
<td>Humanized IgG1 mAb</td>
<td>3</td>
</tr>
</tbody>
</table>

* FDA approved
PCSFK9 Inhibition: Summary

- While early post-hoc data on CVD events is encouraging;
  - Full CVD Outcome trial results:
    - in late 2016-evolocumab (FOURIER=27,500)
    - early 2018-alirocumab (ODYSSEY OUTCOME=18,000)
    - 2019-bococizumab (SPIRE I= 12,000 and II=6,300).
- We anxiously await the results of these outcome trials
Conclusions

The ACC/AHA Blood Cholesterol Guidelines deemphasize LDL-C and non-HDL-C thresholds and risk stratified treatment targets and now recommend treating patient risk for CVD with statins of specific dose and potency.

National Lipid Association Recommendations offer an alternative goal directed strategy focusing on Non-HDL-C as the primary target.

There is some discretion for physicians to discern if LDL-C reduction is adequate. If not, or if the patient is statin intolerant or only tolerates a low dose of a statin, then adjuvant therapy can be used.

Mipomersen given weekly by SQ injection is an anti-sense molecule that increases degradation of the mRNA for apoB100.

Lomitapide, given daily, orally is a MTP inhibitor that reduces lipidation and maturation of apoB100 in the endoplasmic reticulum.

Mipomersen and lomitapide are only indicated for the treatment of HoFH and are available only through a REMS program.

REMS=Risk Evaluation Mitigation Strategy.
Conclusions

• Monoclonal antibodies directed against PCSK9 are a very promising new class of LDL-C lowering agent with 2 already FDA approved. These drugs are being tested in large-scale outcomes trials with and without a statin background in both patients who have stable ischemic heart disease and those who are status post acute coronary syndrome. These drugs reduce the total atherogenic lipoprotein burden by reducing serum LDL-C, VLDL-C, non-HDL-C, apo B, Lp(a), and remnant lipoproteins.

• Payment for these drugs continues to be an important issue.
Summary:

You should now be better able to:

1) Recognize the 4 patient populations who benefit most from statin-based therapy according to the ACC/AHA guidelines

2) Define the population where additional lipid-lowering agents w/or w/o a background of statin-therapy have further improved cardiovascular (CV) outcomes

3) Define the role of the PCSK9 inhibitors to further lower LDL-cholesterol in the hopes of improving CV outcome
Post-test Question

On a scale of 1 to 5, please rate how confident you would be in treating your patients with Hypercholesterolemia?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident