Moving Beyond Statins for the Management of Hypercholesterolemia
Evaluating Novel Therapies that Target Lipoprotein Synthesis, Transport, and Regulation

Learning Objectives

• Identify and overcome low-density lipoprotein cholesterol (LDL-C) treatment shortfalls of statin therapy
• Outline the mechanisms of action of emerging hypercholesterolemia agents targeting lipoprotein synthesis, transport, and regulation
• Summarize clinical trial data on the benefits and limitations of novel agents for hypercholesterolemia management
**Key Lesson from Statin Trials**

<table>
<thead>
<tr>
<th>Event</th>
<th>Statin/more statin</th>
<th>Control/less statin</th>
<th>RR (CI) per 1 mmol LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>3485 (1.0)</td>
<td>4593 (1.3)</td>
<td>0.73 (0.69 - 0.78)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1887 (0.5)</td>
<td>2281 (0.6)</td>
<td>0.80 (0.74 - 0.87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>5105 (1.4)</td>
<td>6512 (1.9)</td>
<td><strong>0.76 (0.73 - 0.78)</strong></td>
</tr>
<tr>
<td>CABG</td>
<td>1453 (0.4)</td>
<td>1857 (0.5)</td>
<td>0.75 (0.69 - 0.82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>1767 (0.5)</td>
<td>2283 (0.7)</td>
<td>0.72 (0.65 - 0.80)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>2133 (0.6)</td>
<td>2667 (0.8)</td>
<td>0.76 (0.70 - 0.82)</td>
</tr>
<tr>
<td>Any coronary revasc</td>
<td>5353 (1.5)</td>
<td>6807 (2.0)</td>
<td><strong>0.75 (0.72 - 0.78)</strong></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1427 (0.4)</td>
<td>1751 (0.5)</td>
<td>0.79 (0.72 - 0.87)</td>
</tr>
<tr>
<td>Hamorrhagic stroke</td>
<td>257 (0.1)</td>
<td>220 (0.1)</td>
<td>1.12 (0.88 - 1.43)</td>
</tr>
</tbody>
</table>

**LOWERING LDL-C REDUCES CV EVENTS**

- 99% or 95% CI
- Statin/more statin better
- Control/less statin better

RR = relative risk; CI = confidence interval; MI = myocardial infarction; CHD = coronary heart disease; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; CV = cardiovascular.


**How Low Should We Go in Secondary Prevention?**

HPS = Heart Protection Study; 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; P = placebo; S = statin; PR = pravastatin; AT = atorvastatin

PROVE IT–TIMI 22
4162 patients hospitalized within prior 10 days for ACS

PROVE IT = Pravastatin or Atorvastatin in Evaluation and Infection Therapy; TIMI = Thrombolysis in Myocardial Infarction; ACS = acute coronary syndrome.


How Low Should We Go in Secondary Prevention?

HPS = Heart Protection Study; 4S = Scandanavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; P = placebo; S = statin; PR = pravastatin; AT = atorvastatin.

Meta-Analysis Supporting Benefit of Lowering LDL-C, Even When Starting “Low”

<table>
<thead>
<tr>
<th>Baseline LDL-C</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>More vs less statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>704 (4.6%)</td>
<td>795(5.2%)</td>
<td>0.71 (0.52-0.98)</td>
</tr>
<tr>
<td>≥2 to &lt;3 mmol/L</td>
<td>1189 (4.2%)</td>
<td>1317 (4.8%)</td>
<td>0.77 (0.64-0.94)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>1065 (4.5%)</td>
<td>1203 (5.0%)</td>
<td>0.81 (0.67-0.97)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>517 (4.5%)</td>
<td>633 (5.5%)</td>
<td>0.61 (0.46-0.81)</td>
</tr>
<tr>
<td>Total</td>
<td>3837 (4.5%)</td>
<td>4416 (5.3%)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
<tr>
<td>Statin vs control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>206 (2.9%)</td>
<td>217 (3.2%)</td>
<td>0.87 (0.60-1.28)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>339 (2.4%)</td>
<td>412 (2.9%)</td>
<td>0.77 (0.62-0.97)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3 mmol/L</td>
<td>861 (2.5%)</td>
<td>1022 (3.2%)</td>
<td>0.76 (0.67-0.86)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>1460 (2.9%)</td>
<td>1821 (3.6%)</td>
<td>0.77 (0.71-0.84)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4205 (2.9%)</td>
<td>5338 (3.7%)</td>
<td>0.80 (0.77-0.84)</td>
</tr>
<tr>
<td>Total</td>
<td>7136 (3.8%)</td>
<td>8934 (3.6%)</td>
<td>0.79 (0.77-0.81)</td>
</tr>
</tbody>
</table>

Benefit similar even if starting with LDL-C <77 mg/dL


Risk Reduction in JUPITER by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline LDL-C</th>
<th>n</th>
<th>HR (95% CI) for Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤130 mg/dL</td>
<td>17,802</td>
<td></td>
</tr>
<tr>
<td>≤120 mg/dL</td>
<td>13,972</td>
<td></td>
</tr>
<tr>
<td>≤110 mg/dL</td>
<td>9734</td>
<td></td>
</tr>
<tr>
<td>≤100 mg/dL</td>
<td>6269</td>
<td></td>
</tr>
<tr>
<td>≤90 mg/dL</td>
<td>3687</td>
<td></td>
</tr>
<tr>
<td>≤80 mg/dL</td>
<td>2033</td>
<td></td>
</tr>
<tr>
<td>≤70 mg/dL</td>
<td>1022</td>
<td></td>
</tr>
<tr>
<td>≤80 mg/dL</td>
<td>511</td>
<td></td>
</tr>
</tbody>
</table>

Overall in trial, rosuvastatin reduced LDL-C by 50%, suggesting achieved LDL-C of ≤30 mg/dL in this subgroup

JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; HR = hazard ratio.
Achieved LDL-C <50 mg/dL Subgroup From JUPITER

N = 4154; median LDL-C = 44 mg/dL

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Rate</th>
<th>Adjusted HR (95% CI)</th>
<th>P for trend</th>
<th>P vs LDL-C not &lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin LDL-C not &lt;50 mg/dL</td>
<td>0.86 vs placebo</td>
<td>0.78(0.57-1.00)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin LDL-C &lt;50 mg/dL</td>
<td>0.44 vs placebo</td>
<td>0.35(0.25-0.49)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin LDL-C &lt;50 mg/dL vs not &lt;50 mg/dL</td>
<td>0.39(0.28-0.59)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>


Dual Inhibition Approach: Attacking Cholesterol Production (statin) and Absorption (ezetimibe)

- Inhibit cholesterol production with a statin
  - Reduce cholesterol synthesis
  - Increase clearance of LDL-C from the blood via upregulation of LDL receptors
- Inhibit intestinal cholesterol absorption with ezetimibe
  - Ezetimibe localizes and appears to act at the brush border of the small intestine
  - 54% less cholesterol was absorbed compared with placebo in a clinical study
  - This action led to a reduction in hepatic cholesterol stores, increasing clearance of cholesterol from the blood
Ezetimibe + Simvastatin
Greater LDL-C Reduction at Each Dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean Change in LDL-C From Untreated Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 10 mg (n=76)</td>
<td>-33%</td>
</tr>
<tr>
<td>Ezetimibe + Simvastatin 10 mg (n=67)</td>
<td>-45%</td>
</tr>
<tr>
<td>Simvastatin 20 mg (n=65)</td>
<td>-41%</td>
</tr>
<tr>
<td>Ezetimibe + Simvastatin 20 mg (n=48)</td>
<td>-52%</td>
</tr>
<tr>
<td>Simvastatin 40 mg (n=65)</td>
<td>-49%</td>
</tr>
<tr>
<td>Ezetimibe + Simvastatin 40 mg (n=73)</td>
<td>-55%</td>
</tr>
<tr>
<td>Simvastatin 80 mg (n=67)</td>
<td>-41%</td>
</tr>
<tr>
<td>Ezetimibe + Simvastatin 80 mg (n=65)</td>
<td>-60%</td>
</tr>
</tbody>
</table>

P<0.01 for ezetimibe/simvastatin vs simvastatin for each comparison.

**IMPROVE-IT: Study Design**

18,057 patients stabilized post ACS ≤10 days
LDL-C ≤125 mg/dL* (or ≤100 mg/dL† if prior lipid-lowering therapy)

Double-blind

ASA + standard medical therapy

Simvastatin 40 mg

Ezetimibe/simvastatin 10 mg/40 mg

Follow-up visit day 30, every 4 months

Duration: minimum 2.5-year follow-up (5250 events)

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

*3.2 mM. †2.6 mM
ASA = acetylsalicylic acid; UA = unstable angina.
Anticipated Achieved LDL-C in IMPROVE-IT

IMPROVE-IT = Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

Doses of Simvastatin

LDL-C (mg/dL)

Target: ≤79 mg/dL

40 mg

68

54

80 mg

62

48

Simvastatin
Ezetimibe/Simvastatin

Dose-Responsive LDL-C Reductions

Lipoprotein Classes

HDL-C = high-density lipoprotein cholesterol; LPL = lipoprotein lipase; IDL = intermediate-density lipoprotein; HL = hepatic lipase; VLDL = very low-density lipoprotein; CETP = cholesteryl ester transfer protein; LDLr = low-density lipoprotein receptor; SR-B1 = scavenger receptor class B, type 1; TG = triglycerides; CD36 = cluster of differentiation 36; SR-A = scavenger receptor class A; LCAT = lecithin-cholesterol acyltransferase; ABCA1 = ATP-binding cassette transporter 1.
**VA-HIT Trial**

- 2531 men with CHD
- HDL-C ≤ 40 mg/dL, LDL-C ≤ 140 mg/dL, TG ≤ 300 mg/dL
- Gemfibrozil 1200 mg/day vs placebo
- Results: TG 115 mg/dL vs 166 mg/dL; HDL 34 mg/dL vs 32 mg/dL; LDL 113 mg/dL in both

![Graph showing death from CHD or non-fatal MI (%) over years for VA-HIT trial](image)

- 22% RRR (95% CI 7%–35%)
- \( P = 0.006 \)

**FIELD Trial**

- 9795 patients with diabetes mellitus not on a statin
- TC 3 mmol/L-6.5 mmol/L (116 mg/dL-251 mg/dL) + either TC/HDL ratio ≥ 4 or triglycerides 1 mmol/L-5 mmol/L (89 mg/dL-443 mg/dL)
- Fenofibrate 200 mg/day vs placebo
- Lipids effects at 4 months: TG ↓ 28.6%, HDL-C ↑ 5.1%, LDL-C ↓ 12%

![Graph showing cumulative risk (%) for FIELD trial](image)

- More "drop in" of statin therapy in placebo arm (17% vs 8%)
- 11% ↓ in total coronary events (ie, including stroke and revascularization)

**VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; RRR = relative risk reduction.**


**FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; TC = total cholesterol.**

Elevated HDL-C Levels and CHD Incidence
Adjusted for Age and Race, 12-Year Follow-Up; N=12,339

ARIC = Atherosclerosis Risk in Communities.

Is HDL-C Simply a Marker of Increased CV Risk?

Low HDL-C levels are commonly found in patients who:

- Smoke
- Are sedentary
- Are obese
- Are insulin resistant or diabetic
- Have hypertriglyceridemia
- Have chronic inflammatory disorders
HDL-C Mendelian Randomization Studies

- Identify a genetic variant purely associated with HDL-C levels
  - SNP in endothelial lipase gene (LIPG Asn396Ser) in 2.6% of population
  - Associated with a 5.4-mg/dL increase in HDL-C
- From observational cohorts, estimate what association of genetic variant and MI should be if HDL-C is a true risk factor
  - In observational studies, 1 mg/dL ↑ HDL-C along with ~2% ↓ in odds of MI
  - ∴ Expect carriers of SNP to have 13% ↓ in odds of MI
- Determine association of genetic variant with outcomes
  - No association between SNP and MI (OR 0.99, 95% CI 0.88-1.11)
- Repeat using multi-SNP genetic risk score

<table>
<thead>
<tr>
<th></th>
<th>Observational Epidemiology</th>
<th>Genetic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>1.54 (1.45-1.63)</td>
<td>2.13 (1.69-2.69), P=2x10^{-10}</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.62 (0.58-0.66)</td>
<td>0.93 (0.68-1.26), P=0.63</td>
</tr>
</tbody>
</table>

OR (95% CI) per 1-SD increase in plasma lipid

SNP = single nucleotide polymorphism; OR = odds ratio; SD = standard deviation.

Coronary Drug Project

- 1966-1969: randomized 3908 patients with prior MI to immediate-release niacin (3 g/day) or placebo
- 5 year follow-up
- Efficacy: ↓ nonfatal MI by 26%, ↓ stroke/TIA by 24%
- Caveats:
  - No effect on mortality (primary endpoint), although 11% ↓ seen ~9 years after termination of trial
  - No statins
  - Baseline TC ~250 mg/dL
  - Niacin known to ↓ LDL-C (↓ TC by 9.9% in trial)

TIA = transient ischemic attack.
AIM-HIGH Trial: Design and Baseline

- 3414 patients with established CV disease, HDL-C <40 mg/dL (men) or <50 mg/dL (women)
- Extended-release niacin with open-label, run-in titration from 0.5 g/day to 2 g/day
- Simvastatin in all patients titrated to LDL-C 40 mg/dL-80 mg/dL
- Baseline lipids (median)
  - HDL-C: 35 mg/dL
  - LDL-C: 71 mg/dL
- Planned mean follow-up of 4.6 years
- Stopped early for futility

AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes.

AIM-HIGH Trial: Results

Achieved Lipid Levels at 2 Years

Primary endpoint:
CHD death, MI, stroke, hospitalization for ACS, symptom-driven coronary/cerebrovascular revascularization

Simvastatin Alone

Achieved Lipid Levels at 2 Years

Primary endpoint:
CHD death, MI, stroke, hospitalization for ACS, symptom-driven coronary/cerebrovascular revascularization

Niacin plus statin

Placebo plus statin

P=0.79 by log-rank test

HPS2-THRIVE: Eligibility

- Men and women
- Aged 50-80 years
- Prior history of:
  - MI
  - Ischemic stroke or TIA
  - Peripheral arterial disease
  - Diabetes with other CHD
- No contraindication to study treatments
- No significant liver, kidney, or muscle disease

HPS2-THRIVE = Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events.

HPS2-THRIVE: Active Prerandomization Run-In

- Screened (51,698) High CV risk patients screened in 245 sites within 6 countries
- LDL-lowering phase (36,059) Standardize background LDL-lowering therapy with simvastatin 40 mg (+/- ezetimibe) daily (to TC target of 135 mg/dL)
- Active ER niacin plus laropiprant (38,369) Test compliance with ER niacin 2 g plus laropiprant 40 mg daily for 1 month
- Randomization (25,673) ER niacin 2 g plus laropiprant 40 mg daily vs matching placebo tablets

ER = extended release.
**Effects of ER Niacin/Laropiprant on Lipids**

<table>
<thead>
<tr>
<th>Year of Follow-Up</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-12</td>
<td>6</td>
<td>-35</td>
</tr>
<tr>
<td>4</td>
<td>-7</td>
<td>6</td>
<td>-31</td>
</tr>
<tr>
<td>Study average</td>
<td>-10</td>
<td>6</td>
<td>-33</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>(-0.25)</td>
<td>(0.16)</td>
<td>(-0.37)</td>
</tr>
</tbody>
</table>

"Based on previous observational studies and randomized trials, it was anticipated such lipid differences might translate into a 10-15% reduction in vascular events."

—European Heart Journal, 2013


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**Effect of ER Niacin Plus Laropiprant on Major Vascular Events**

Risk ratio: 0.96 (95% CI 0.90-1.03)

Log rank $P=0.29$

## Major Vascular Events by Baseline Lipids

<table>
<thead>
<tr>
<th>mg/dL (mmol/L)</th>
<th>Randomized allocation</th>
<th>Risk ratio and 95% CI</th>
<th>Het or trend $X^2$ (uncorrected $P$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER niacin + laropiprant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 (0.9)</td>
<td>(12,838)</td>
<td>388 (15.8%)</td>
<td>399 (16.3%)</td>
</tr>
<tr>
<td>≥35 &lt;43</td>
<td>(12,835)</td>
<td>560 (13.7%)</td>
<td>546 (13.5%)</td>
</tr>
<tr>
<td>≥43 (1.1)</td>
<td></td>
<td>748 (11.9%)</td>
<td>813 (12.8%)</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58 (1.5)</td>
<td>(12,838)</td>
<td>724 (14.7%)</td>
<td>679 (13.8%)</td>
</tr>
<tr>
<td>≥58 &lt;77</td>
<td>(12,835)</td>
<td>685 (12.4%)</td>
<td>761 (13.7%)</td>
</tr>
<tr>
<td>≥77 (2.0)</td>
<td></td>
<td>287 (12.0%)</td>
<td>318 (13.5%)</td>
</tr>
<tr>
<td>TG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;89 (1.0)</td>
<td></td>
<td>541 (13.2%)</td>
<td>563 (13.4%)</td>
</tr>
<tr>
<td>≥89 &lt;151</td>
<td></td>
<td>694 (12.8%)</td>
<td>712 (13.2%)</td>
</tr>
<tr>
<td>≥151 (1.7)</td>
<td></td>
<td>461 (13.9%)</td>
<td>485 (14.8%)</td>
</tr>
<tr>
<td>All</td>
<td>1696 (13.2%)</td>
<td>1758 (13.7%)</td>
<td>3.5% SE 3.3 reduction</td>
</tr>
</tbody>
</table>

SE = standard error.

## CETP Inhibition

CETP is a plasma protein that catalyzes transfer of CE from HDL to apoB-containing lipoproteins (VLDL and LDL-C) in exchange for triglycerides.

CE = cholesteryl ester; FC = free cholesterol. 
ILLUMINATE: Torcetrapib

- 15,067 patients with vascular disease
- Atorvastatin titrated to achieve LDL-C <100 mg/dL
- Intervention: torcetrapib 60 mg once daily vs placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Torcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>2%↑</td>
<td>72%↑</td>
</tr>
<tr>
<td>Achieved (mg/dL)</td>
<td>49</td>
<td>83</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>3%↑</td>
<td>25%↓</td>
</tr>
<tr>
<td>Achieved (mg/dL)</td>
<td>81</td>
<td>58</td>
</tr>
</tbody>
</table>

All-cause mortality: HR 1.58 (95% CI 1.14-2.19), P=0.006

Major CV events: HR 1.25 (95% CI 1.09-1.44), P=0.001

HDLC (mg/dl)
- Placebo: 50
- Dalcetrapib: 70

LDL-C (mg/dl)
- Placebo: 100
- Dalcetrapib: 80

P D SBP (mmHg) +0.9 +5.4 <.001
P D DBP (mmHg) -0.1 +2.0 <.001

ILLUMINATE = Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Dal-OUTCOMES: Dalcetrapib

- 15,871 patients with ACS
- Target LDL-C <100 mg/dL and preferably <70 mg/dL, but not mandated or managed
- >97% on statins

HDL-C (mg/dl)
- Placebo: 40
- Dalcetrapib: 60

LDL-C (mg/dl)
- Placebo: 120
- Dalcetrapib: 90

**dal-OUTCOMES: Primary Endpoint**

Stopped early for futility . . .

CRP = C-reactive protein.

**CETP Inhibitors: Lipid Effects**

<table>
<thead>
<tr>
<th></th>
<th>Torcetrapib (60 mg daily)</th>
<th>Dalcetrapib (600 mg daily)</th>
<th>Anacetrapib (100 mg daily)</th>
<th>Evacetrapib (130 mg daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>+4%</td>
<td>N/A</td>
<td>+16%</td>
<td>N/A</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-24%</td>
<td>-4%</td>
<td>~ -30%</td>
<td>? -30%</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>-12%</td>
<td>N/A</td>
<td>-21%</td>
<td>N/A</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+61%</td>
<td>+25%</td>
<td>+140%</td>
<td>? +130%</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>+25%</td>
<td>+10%</td>
<td>+45%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = not available.
## Adjudicated CV Events and Death

<table>
<thead>
<tr>
<th></th>
<th>Anacetrapib N=808</th>
<th>Placebo N=804</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prespecified adjudicated CV safety endpoint</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>16 (2.0)</td>
<td>21 (2.6)</td>
<td>0.76 (0.39, 1.45)</td>
<td>0.40</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>6 (0.7)</td>
<td>9 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>1 (0.1)</td>
<td>6 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>5 (0.6)</td>
<td>5 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>11 (1.4)</td>
<td>8 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>8 (1.0)</td>
<td>28 (3.5)</td>
<td>0.29 (0.13, 0.64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Death or major CV event</td>
<td>27 (3.3)</td>
<td>43 (5.3)</td>
<td>0.62 (0.38, 1.01)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*Post hoc analysis.

## HPS3-TIMI55 REVEAL

- 30,000 patients with occlusive arterial disease in North America, Europe, and Asia
- Background LDL lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs placebo
- Scheduled follow-up: 4 years
- Primary outcome: coronary death, MI, or coronary revascularization

REVEAL = Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification.
PCSK9 Inhibition with a Monoclonal Antibody

PCSK9 = proprotein convertase subtilisin-like/kexin type 9.

PCSK9 Loss-of-Function Mutations: Effect of Lifelong Low LDL-C on CHD

### PCSK9 Directed Therapy in Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug (Alternate Name)</th>
<th>Agent</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Regeneron</td>
<td>SAR236553/REGN727 (SAR236553)</td>
<td>Human monoclonal antibody</td>
<td>3</td>
</tr>
<tr>
<td>Amgen</td>
<td>AMG-145</td>
<td>Human monoclonal antibody</td>
<td>3</td>
</tr>
<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>2</td>
</tr>
<tr>
<td>Pfizer/Rinat</td>
<td>RN316 (PF-04950615)</td>
<td>Monoclonal antibody</td>
<td>2</td>
</tr>
<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>2</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals</td>
<td>ALN-PCS02</td>
<td>siRNA oligonucleotide</td>
<td>1</td>
</tr>
<tr>
<td>Adnexus Therapeutics/BMS</td>
<td>BMS-962476</td>
<td>Fusion protein using Adnectin technology</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Small peptide mimetic; LDLR antagonist</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Shifa Biomedical Corp</td>
<td>TBD</td>
<td>Small molecule PCSK9 modulator</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

### LAPLACE-TIMI 57

- **102 centers**
- **5 countries**
- **Screening and placebo run-in period**
- **SC injection of 6-mL placebo**
- **Fasting LDL-C 5-10 days before randomization**

End of study: 4 weeks after last dose

Primary endpoint assessed

934 screened → 631 randomized → 629 treated

LAPLACE = LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy; SC = subcutaneous; Q2W = every other week; Q4W = every 4 weeks.

Primary Endpoint:
AMG 145 Reduced LDL-C at 12 Weeks

<table>
<thead>
<tr>
<th>LDL-C measured using ultracentrifugation</th>
<th>AMG 145 Q2W</th>
<th>AMG 145 Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg</td>
<td>-41.8</td>
<td>-41.8</td>
</tr>
<tr>
<td>n = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105 mg</td>
<td>-60.2</td>
<td>-61.6</td>
</tr>
<tr>
<td>n = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>140 mg</td>
<td>-66.1</td>
<td>-50.0</td>
</tr>
<tr>
<td>n = 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>280 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>420 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.0001 for each dose vs placebo

LDL-C at 12 weeks
Mean (mg/dL) (SD)
73 (25)
53 (21)
44 (25)
69 (28)
60 (23)
58 (26)


Secondary Results at 12 Weeks with Top 2 AMG 145 Doses

Treatment Effect vs. Placebo*

TC
140 mg Q2W 420 mg Q4W
140 mg Q2W 420 mg Q4W
-43%  -48%
-33%  -48%

Non-HDL-C
140 mg Q2W 420 mg Q4W
140 mg Q2W 420 mg Q4W
-41%  -48%
-37%  -48%

VLDL-C
140 mg Q2W 420 mg Q4W
140 mg Q2W 420 mg Q4W
-46%  -52%
-46%  -53%

TCHDL-C Ratio
140 mg Q2W 420 mg Q4W
140 mg Q2W 420 mg Q4W
-48%  -56%
-48%  -42%

ApoB
140 mg Q2W 420 mg Q4W
140 mg Q2W 420 mg Q4W
-64%  -62%
-66%  -62%

ApoB/ApoA1 Ratio
140 mg Q2W 420 mg Q4W
140 mg Q2W 420 mg Q4W
-53%  -53%
-43%  -43%

*P<0.0001 versus placebo for all parameters.
Results: Mean % Change in Lp(a) at Week 12 with AMG 145 vs Placebo

Week 12

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Mean % Change in Lp(a) Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG 145 Q2W</td>
<td>-18, -32.1, -32.3 (P&lt;0.001 for each dose vs placebo)</td>
</tr>
<tr>
<td>AMG 145 Q4W</td>
<td>-18.2, -22.8, -23.1 (P&lt;0.001 for each dose vs placebo)</td>
</tr>
</tbody>
</table>

Achieved Lp(a) at week 12, nmol/L, median (IQR)

- AMG 145 Q2W:
  - 70 mg (n=75): 30.0 (9-116)
  - 105 mg (n=79): 27.0 (7-148)
  - 140 mg (n=73): 29.0 (7-97)
- AMG 145 Q4W:
  - 280 mg (n=78): 21.5 (7-125)
  - 350 mg (n=79): 17.0 (7-155)
  - 420 mg (n=80): 40.0 (9-167)

Lp(a) = lipoprotein (a); IQR = interquartile range.


Safety

<table>
<thead>
<tr>
<th>Q2W Dose Groups</th>
<th>Q4W Dose Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG 145</td>
<td>AMG 145</td>
</tr>
<tr>
<td>Placebo 41</td>
<td>Placebo 48</td>
</tr>
<tr>
<td>70 mg 41</td>
<td>70 mg 48</td>
</tr>
<tr>
<td>105 mg 52</td>
<td>105 mg 48</td>
</tr>
<tr>
<td>140 mg 43</td>
<td>140 mg 48</td>
</tr>
<tr>
<td>n=79</td>
<td>n=79</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>Any adverse event</td>
</tr>
<tr>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Serious AE</td>
<td>Serious AE</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Lead to drug DC</td>
<td>Lead to drug DC</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug related AEs</td>
<td>Drug related AEs</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Lead to drug DC</td>
<td>Lead to drug DC</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>Injection site reaction</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>AST or ALT &gt;3 x ULN</td>
<td>AST or ALT &gt;3 x ULN</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CKP &gt;5 x ULN</td>
<td>CKP &gt;5 x ULN</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CV events§</td>
<td>CV events§</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Both events were reported as non-serious by the investigators. †All 50 were reported as non-serious by the investigator and none led to discontinuation of drug. ‡All 50 were reported as non-serious by the investigator and none led to discontinuation of drug. §ACS, coronary revascularization, TIA, congestive heart failure requiring hospitalization, or death.

AE = adverse event; DC = discontinuation; AST = aspartate transaminase; ALT = alanine aminotransferase; ULN = upper limit of normal; CPK = creatinine phosphokinase.

Subjects Reaching LDL-C <70 mg/dL
Among High-Risk Subjects on Intensive Lipid-Lowering Therapy (N=115)

- AMG 145 Dose Q2W
- AMG 145 Dose Q4W

P<0.001 for each AMG 145 dose vs placebo


GAUSS: Study Design and Entry Criteria

- Statin intolerant because of intolerable myalgias
- Elevated LDL-C: ≥100 mg/dL if CHD or risk equivalent; ≥130 mg/dL without CHD but with ≥2 risk factors; or ≥160 mg/dL with ≤1 risk factor

GAUSS = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects; IP = intraperitoneal.
GAUSS: % Change in LDL-C by Ultracentrifugation, from Baseline at Week 12

AMG 145 Q4W

- 280mg N=32
- 350mg N=30
- 420mg N=31

Placebo Q4W + Ezetimibe N=30

Change from Baseline (SE) at week 12 (%)

-41%*
-43%*
-51%*
-63%*

*P<0.001 vs placebo Q4W + ezetimibe

LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.


RUTHERFORD: Study Design

Primary endpoint: % change in LDL-C, measured by ultracentrifugation, from baseline at 12 weeks

population

- 18–75 years of age, with a diagnosis of HeFH by Simon Broome criteria
- LDL-C ≥100 mg/dL and TG ≤400 mg/dL
- At least 4 weeks of stable lipid-lowering therapy (eg, statin, ezetimibe, bile-acid sequestrants, niacin)

RUTHERFORD = Reduction of LDL-C with PCSK9 Inhibition in Heterzygous Familial Hypercholesterolemia Disorder Study; HeFH = heterozygous familial hypercholesterolemia.

**RUTHERFORD: % Change in LDL-C, by UC, from Baseline to Week 12**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C Change from Baseline (SE) at Week 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 56)</td>
<td>0% (±1%)</td>
</tr>
<tr>
<td>350 mg Q4W (n = 55)</td>
<td>-43% (±1%)</td>
</tr>
<tr>
<td>420 mg Q4W (n = 56)</td>
<td>-55% (±1%)</td>
</tr>
</tbody>
</table>

*P<0.001 vs. placebo

LDL-C values at baseline and week 12 were measured using preparative UC. Least square means are presented from the ANCOVA model including treatment and stratification factors as covariates. Missing UC LDL-C values at week 12 were imputed using last observation carried forward and calculated LDL-C. A Hochberg adjustment was used to control the family wise error rate at ≤0.05.

ANCOVA = analysis of covariance.


---

**SAR236553 Add-on to Atorvastatin**

- **Screening Period** (7 weeks)
- **Treatment Period** (12 weeks)
- **Follow-up Period** (8 weeks)

<table>
<thead>
<tr>
<th>Diet*</th>
<th>Placebo Q2W</th>
<th>SAR236553 50 mg Q2W</th>
<th>SAR236553 100 mg Q2W</th>
<th>SAR236553 150 mg Q2W</th>
<th>SAR236553 200 mg Q4W alternating with placebo</th>
<th>SAR236553 300 mg Q4W alternating with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 31</td>
<td>n = 30</td>
<td>n = 31</td>
<td>n = 31</td>
<td>n = 31</td>
<td>n = 30</td>
<td>n = 30</td>
</tr>
</tbody>
</table>

**Primary Endpoint**

% Δ calculated LDL-C from baseline to week 12

**Secondary Endpoints**

% Δ in other lipoproteins and apolipoproteins and % patients reaching pre-specified LDL-C levels

*National Cholesterol Education Program Adult Treatment Panel-III Therapeutic Lifestyle Changes or equivalent diet.

SAR236553 Phase 2: Change in LDL-C at 4-Week Dosing Intervals on Atorvastatin*

*On stable-dose atorvastatin 10 mg, 20 mg, or 40 mg; 80-mg dose not studied.

Attainment of Treatment Targets for LDL-C, Non-HDL-C, and ApoB With SAR236553

SAR236553 on Top of Atorvastatin in Primary Hypercholesterolemia: Phase 2

- **MTP Inhibition**
  - MTP involved in assembly and secretion of apoB
  - Inhibition ↓ production of apoB-containing lipoproteins
  - Result is to ↓ LDL-C synthesis

**Graph:**
- Atorvastatin 80 mg, plus placebo
- Atorvastatin 10 mg, plus SAR236553
- Atorvastatin 80 mg, plus SAR236553

**Table:**
<table>
<thead>
<tr>
<th>Week</th>
<th>LDL-C</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**References:**
Lomitapide Efficacy Results

- Single-arm, open-label study
- 23 patients with HoFH
- Mean age 31 years; 93% on statin therapy; 62% had undergone apheresis
- LDL-C at enrollment: 336±114 mg/dL
- Lomitapide escalated Q4W up to 60 mg or maximum tolerated dose (median 40 mg/day)

![Graph showing change in LDL-C over study weeks.]

LDL-C at enrollment: 336±114 mg/dL

50% ↓ in LDL-C

P<0.0001

HoHF = homozygous familial hypercholesterolemia.


Lomitapide Safety Results

<table>
<thead>
<tr>
<th>LFTs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 × ULN</td>
<td>10 (34)</td>
</tr>
<tr>
<td>≥5 × ULN</td>
<td>4 (14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GI</td>
<td>27 (93)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (79)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (66)</td>
</tr>
</tbody>
</table>

LFT = liver function test; GI = gastrointestinal.

ApoB Antisense Oligonucleotide

- Mipomersen is an antisense oligonucleotide that is complementary to coding region of mRNA for apo B-100
- Binding of mipomersen results in RNase H1-mediated degradation of mRNA leading to ↓ synthesis of apo B
- Apo B required for production of VLDL by the liver

Mipomersen Efficacy Results

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>n</th>
<th>Baseline</th>
<th>LDL-C</th>
<th>LDL-C</th>
<th>Lp(a)</th>
<th>TG</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH</td>
<td>51</td>
<td>439</td>
<td>-25%</td>
<td>-32%</td>
<td>N/A</td>
<td>+15%</td>
<td></td>
</tr>
<tr>
<td>Severe HeFH</td>
<td>58</td>
<td>276</td>
<td>-36%</td>
<td>-39%</td>
<td>N/A</td>
<td>+6%</td>
<td></td>
</tr>
<tr>
<td>HeFH with CAD</td>
<td>124</td>
<td>153</td>
<td>-28%</td>
<td>-21%</td>
<td>-14%</td>
<td>+3%</td>
<td></td>
</tr>
<tr>
<td>HC, high CAD risk</td>
<td>157</td>
<td>123</td>
<td>-37%</td>
<td>-24%</td>
<td>-26%</td>
<td>+2%</td>
<td></td>
</tr>
</tbody>
</table>

All changes statistically significant

QW = every week; CAD = coronary artery disease; HC = hypercholesterolemia.
Mipomersen Safety Results

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo (n = 129)</th>
<th>Mipomersen (n = 261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI disorder</td>
<td>28.7%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>16.3%</td>
<td>56.3%</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>6.2%</td>
<td>58.6%</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>0%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3.1%</td>
<td>13.0%</td>
</tr>
<tr>
<td>ALT ≥2 x and 3 x ULN</td>
<td>4.7%</td>
<td>23.4%</td>
</tr>
<tr>
<td>ALT ≥3 x and &lt;5 x ULN</td>
<td>0.8%</td>
<td>11.9%</td>
</tr>
<tr>
<td>ALT ≥5 x ULN</td>
<td>0%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>1.6%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>


REMS Restrictions

- Lomitapide and mipomersen are restricted under REMS due to the risk of hepatotoxicity
  - Available through a restricted program
  - Only certified healthcare providers and pharmacies may prescribe and distribute lomitapide

REMS = Risk Evaluation and Mitigation Strategies.
Summary

• Statins remain the cornerstone of lipid-lowering therapy
• For high-risk patients, optional goal of <70 mg/dL and perhaps should target even lower
• Ezetimibe under study
• No clinical benefit to raising HDL with niacin or certain CETP inhibitors; other CETP inhibitors (that also lower LDL-C) under study
• PCSK9 inhibitors robustly lower LDL; outcomes trials underway
• New treatments for familial hypercholesterolemia: MTP inhibitors and antisense oligonucleotide
NACCME would appreciate your feedback on the quality and impact of this activity. Please answer the following questions, some of which are rated on a 5-point Likert scale (1 = strongly disagree/poor; 5 = strongly agree/excellent).

1. Did this activity
   Meet your educational needs? □ Yes □ No
   Increase your knowledge? □ Yes □ No
   Increase your competence? □ Yes □ No
   Increase your confidence? □ Yes □ No

2. How much did you learn as a result of this CE program (1 = very little; 5 = great deal)?
   1 2 3 4 5

3. To what extent were you able to achieve each of the following learning objectives?
   Identify and overcome low-density-lipoprotein (LDL) treatment shortfalls of statin therapy
   1 2 3 4 5
   Outline the mechanisms-of-action of emerging hypercholesterolemia agents targeting lipoprotein synthesis, transport, and regulation
   1 2 3 4 5
   Summarize clinical trial data on the benefits and limitations of novel agents for hypercholesterolemia management
   1 2 3 4 5

4. Please rate the faculty on the following:
   SERGIO FAZIO, MD, PHD
   Knowledge and Expertise
   1 2 3 4 5
   Teaching Ability
   1 2 3 4 5
5. Please rate the following components relating to this activity:

<table>
<thead>
<tr>
<th>Component</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevance to your practice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational format</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audience-participation portions (eg, Q&amp;A, pre/post-testing)</td>
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<td>Handouts and/or other materials supporting the activity?</td>
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<td>Overall</td>
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6. The therapeutic recommendations presented in this activity did not encourage inappropriate or excessive use of products/devices.

☐ Agree  ☐ Disagree

7. The information presented in this activity did not serve to advance a proprietary interest of any commercial entity.

☐ Agree  ☐ Disagree

8. Of the patients you see on a weekly basis, how many will benefit from the information you learned today?

☐ 10 or fewer  ☐ 20  ☐ 30  ☐ 40  ☐ 50 or more

9. Naturally occurring mutations that lead to a loss of function of the PCSK9 gene are associated with:
   a. An increase in LDL-C and coronary heart disease
   b. A decrease in LDL-C and coronary heart disease
   c. An increase in HDL-C and increase in coronary heart disease
   d. A decrease in HDL-C and increase in coronary heart disease

10. How confident are you in your understanding of the LDL treatment shortfalls of statin therapy?
    a. Very confident
    b. Confident
    c. Somewhat confident
    d. Not confident

11. How would you rate your understanding of the mechanisms-of-action of emerging hypercholesterolemia agents designed to target lipoprotein synthesis, transport, and regulation?
    a. Excellent
    b. Good
    c. Fair
    d. Poor

12. How frequently do you intend to recommend alternate or add-on therapy in patients on statin therapy with an LDL > 100 mg/dL?
    a. Always
    b. Often
    c. Rarely
    d. Never
13. What factors do you intend to consider when developing treatment strategies for LDL management (select all that apply)?
   a. Adherence
   b. Cost
   c. Efficacy
   d. Tolerance

14. Do you intend to make any changes to your practice?
   □ Yes, please specify: _______________________________________________________________
   □ No

15. What barriers outside of your control prevent you from changing your practice and/or optimizing patient outcomes (check all that apply)?
   □ Lack of available guidelines for LDL-C management
   □ Formulary placement
   □ Affordability concerns on the part of the patient
   □ Patient adherence
   □ Lack of patient education regarding disease/treatment
   □ Adverse effects of LDL-lowering therapies
   □ Lack of influence over treatment selection
   □ Other: _______________________________________________________________

16. How might future activities help you address those barriers?
    ____________________________________________________________________________
    ____________________________________________________________________________
    ____________________________________________________________________________

17. Would you be interested in additional educational activities within this therapeutic area?
   □ Yes         □ No
   If yes, what topics would you like to learn more about? ____________________________
18. In which of the following other therapeutic or practice areas do you have educational needs? (check all that apply)

- Acute Coronary Syndromes
- Alzheimer's Disease
- Anemia
- Anesthesia
- Bacterial Infections
- Breast Cancer
- Deep Vein Thrombosis
- Diabetes
- Fibromyalgia
- Fungal Infections
- Gastroenterology
- Glaucoma
- Hemostasis
- Hepatitis B or C
- HIV
- Hyperlipidemia
- Hypertension
- Hyponatremia
- Law
- Medication Errors/Safety
- Multiple Myeloma
- Multiple Sclerosis
- Oncology Supportive Care
- Osteoporosis
- Overactive Bladder
- Pain
- Parkinson's Disease
- Prostate Cancer
- Psoriasis
- Psychiatry
- Pulmonary Medicine
- Rheumatoid Arthritis
- Sleep
- Stroke
- Transition of Care
- Transplant Medicine
- Other

19. In which of the following formats do you prefer to receive education? (check all that apply)

- Live symposium
- Small-group meeting
- Phone teleconference
- Live web meeting
- On-demand web
- Handheld/mobile device
- Enduring print
- Other

20. How much time did you spend participating in this activity? ________________________________

REQUEST FOR CREDIT
Please complete all sections to be eligible for credit and return to course registrar at the meeting site.

E-mail [REQUIRED] _______________________________________________________________________

Grand Rounds Location _______________________________________________________________________

Name ___________________________________________ Degree _________________________

Title/Specialty __________________________________ Affiliation _________________________

Address _________________________________________________________________________________

City __________________ State __________ Zip __________ Phone___________________

REQUIRED FOR PHARMACISTS: Date of Birth (MM/DD) ______________ NABP ID _______________