Dyslipidemia Management

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Disclosures:
Advisory for Aegerion, BASF, Kowa, Merck, Sanofi, and NHP.

Lipid Modulating Agents

- Statins (LDL, TG)
- Niacin (HDL, TG, LDL)
- Fibrates (TG, HDL)
- Resins (LDL)
- Ezetimibe (LDL)
- Omega 3 fats (TG)
- PCSK9 inhibitors (LDL)
2013: ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Identified four groups of patients with most extensive evidence of benefit of statin therapy for ASCVD prevention

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL-C ≥190 mg/dl
3. Individuals 40-75 years of age with diabetes and LDL-C 70-189 mg/dl
4. Individuals without ASCVD or diabetes, 40-75 years of age, with LDL-C 70-189 mg/dl and an estimated 10-year ASCVD risk of ≥ 7.5% by the Pooled Risk Equations

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease.


High, Moderate, and Low-intensity Statin Therapy Used in Clinical Trials

<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 approximately &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40*-80* mg Rosuvastatin 20*-40** mg</td>
<td>Atorvastatin 10* (20**) mg Rosuvastatin (5**) 10* mg Simvastatin 20* -40* mg Pravastatin 40* (80**) mg Lovastatin 40* mg Fluvastatin XL 80** mg Fluvastatin 40 mg BID* Pitavastatin 2-4** mg</td>
<td>Simvastatin 10** mg Pravastatin 10*-20* mg Lovastatin 20* mg Fluvastatin 20**-40** mg Pitavastatin 1** mg</td>
</tr>
</tbody>
</table>

*Statins demonstrated reduction in major CVD events.
**FDA approved doses not tested in clinical trials.

FDA = Food and Drug Administration.

Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at Which 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>Low</td>
<td>0-1 major ASCVD risk factors, Consider other risk indicators, if known</td>
<td>&lt;130</td>
<td>≥190</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;100</td>
<td>≥160</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors, Consider quantitative risk scoring</td>
<td>&lt;130</td>
<td>≥160</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td>High</td>
<td>≥3 major ASCVD risk factors, Diabetes mellitus* (Type 1 or 2), 0-1 other major ASCVD risk factors, and No evidence of end organ damage: Chronic kidney disease Stage 3B or 4, LDL-C ≥190 mg/dL (severe hypercholesterolemia), Quantitative risk score reaching the high risk threshold</td>
<td>&lt;130</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
<tr>
<td>Very High</td>
<td>ASCVD*, Diabetes mellitus* (Type 1 or 2), ≥2 other major ASCVD risk factors or Evidence of end organ damage</td>
<td>&lt;100</td>
<td>≥100</td>
</tr>
</tbody>
</table>

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

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT): Design

Patients stabilized post-ACS ≤ 10 days
LDL-C ≤ 125 mg/dL (or ≤ 100 mg/dL if prior statin)

Double-blind

<table>
<thead>
<tr>
<th>ASA + Standard Medical Therapy</th>
<th>Ezetimibe/ Simvastatin 10/40 mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 40 mg*</td>
<td>*(uptitrated to 80 mg if LDL-C &gt; 79 mg/dL)</td>
</tr>
</tbody>
</table>

Follow-up visit day 30, every 4 months
Duration: Minimum 2.5 year follow-up (5250 events)
Primary Endpoint: CV death, MI, Hospitalization for UA, Revascularization (> 30 days after randomization), or Stroke

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT)

<table>
<thead>
<tr>
<th>1 yr mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>hs-CRP</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>
</tbody>
</table>

Δ in mg/dL
-16.7 -19.3 -16.7 +0.6 -0.5

Mean LDL-C (mg/dL)

Median Time avg 69.5 vs. 53.7 mg/dL

Time since randomization (months)

Number at risk

Simva 9009 8921 8306 7843 7289 6939 6607 6192 5684 5267 4395 3387 2569 1068
EZ/Simva 8990 8899 8230 7701 7264 6664 6583 6256 5734 5354 4508 3484 2608 1078

Primary Endpoint - ITT

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva – 34.7%
2742 events
NNT = 50

EZ/Simva – 32.7%
2572 events

7-year event rates

IMProved Reduction of Outcomes: International Trial (IMPROVE IT)

Ezetimibe vs Statin Benefit

Proportional reduction in event rate (SE)

IMPROVE-IT


Lipid Lowering Agents for Orphan-status Hypercholesterolemia:

Blocking Lipoprotein Production
A Case of Homozygous FH

- 55 yo woman with history of multiple coronary stenting and two CABG surgeries
- On LDL apheresis for two years until AV fistula clogged
- On 3 medications, LDL around 650 mg/dl
- One affected child with a less severe hypercholesterolemia

TG = triglycerides; LDLR = low-density lipoprotein receptor; MTP = microsomal triglyceride transfer protein.
ApoB Antisense
Microsomal Triglyceride Transfer Protein Inhibition

Mipomersen: Mechanism of Action

Mipomersen (apoB) antisense strand:

G C C T C
A G T C T
G C T T C
T C

2′ MOE
Phosphorothioate backbone

Mipomersen crosses the hepatocyte and nuclear membranes to target apoB mRNA

RnaseH = Ribonuclease H.
Phase 2: Hypercholesterolemia, Monotherapy
Dose-dependent Reduction of LDL-C

Once Weekly Dosing

SE = standard error.

HoFH Phase 3 Study Design

- Open label, ascending dose of lomitapide
- Low fat diet
- Careful LFT monitoring
- Liver fat evaluation by MRI + spectroscopy

LFT = liver function test; MRI = magnetic resonance imaging.
Pharmacologic MTP Inhibition Reduces LDL-C Levels in HoFH

Data are mean, 95%CI (n=23).

HoFH Phase 3 Study: Hepatic Fat Content

*Fewer number of MRS reads due to patients with contraindication for MRI.
Newly approved PCSK9 Inhibitors

PCSK9 = Proprotein convertase subtilisin/kexin type 9.

Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles

PCSK9 Regulates the Surface Expression of LDLRs by Targeting for Lysosomal Degradation


Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels

PCSK9 Gain of Function = Less LDLRs       PCSK9 Loss of Function = More LDLRs

PCSK9 Loss-of-Function Mutations Resulted in Low LDL-C Levels and Reduced CHD Rates

- Wild-type PCSK9 degrades LDL receptors.1,2
- Loss-of-function mutations increase hepatic LDL receptor expression, reducing LDL-C levels by 15%-40%. 2,3
- CHD was reduced 47% to 88% in PCSK9 loss-of-function mutation carriers compared with normal individuals.3

Impact of a PCSK9 mAb on LDL Receptor Expression


Results: Single-Dose SQ Subcutaneous Administration

Mean Percent Change from Baseline in LDL Cholesterol Values among Healthy Volunteers in Single-Dose Studies

No. at Risk:

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
<th>150 mg</th>
<th>250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Subjects at Risk</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Among subjects receiving increasing single doses of REGN727, values are shown for subcutaneous administration. LDL cholesterol values were calculated with the use of the Friedwald formula. The I bars indicate standard errors. Stein EA, et al. N Engl J Med. 2012;366(12):1108-1118.

Change in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

LOCF = last observation carried forward.

McKenney JM. A Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, REGN727/SAR236553, in Patients with Primary Hypercholesterolemia (NCT: 01288443). American Cardiology Conference 2012, Chicago, IL.
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Summary of TEAEs (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>Q2W Dosing</th>
<th>Q4W Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>50mg</td>
</tr>
<tr>
<td>Overview of all TEAEs – no.</td>
<td>N=31</td>
<td>N=30</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Any treatment-emergent SAE</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Any TEAE leading to permanent treatment d/c</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs of special interest — no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt;3 x ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle (including pain, weakness)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CK &gt;10 x ULN</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Injection-site reactions occurred in the SAR236553 groups only and were generally mild and non-progressive.

TEAE = treatment-emergent adverse events; SAE = serious adverse event; AST = aspartate aminotransferase.

McKenney JM. A Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, REGN727/SAR236553, in Patients with Primary Hypercholesterolemia (NCT: 01288443). American Cardiology Conference 2012, Chicago, IL.
Change in Lipids/Lipoproteins from Baseline to Week 8 LOCF

*Percent change from baseline median data are reported. Clinicaltrials.gov no. NCT01288469.
†P<.001 vs Placebo + A80mg; †P=.051 vs Placebo + A80mg; †P=.0003 vs Placebo + A80mg; †P<.05 vs Placebo + A80mg.

McKenney JM. A Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, REGN727/SAR236553, in Patients with Primary Hypercholesterolemia (NCT: 01288443). American Cardiology Conference 2012, Chicago, IL.

GAUSS: Effect of Evolocumab on Percentage Change in LDL-C From Baseline

MENDEL: Effects of Evolocumab on LDL-C at Week 12
Relative Change in LDL-C from Baseline*

<table>
<thead>
<tr>
<th>Evolocumab</th>
<th>Placebo</th>
<th>70 mg</th>
<th>105 mg</th>
<th>140 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2W Dosing</td>
<td>-3.7</td>
<td>-41.0</td>
<td>-43.9</td>
<td>-50.9</td>
</tr>
<tr>
<td>Q4W Dosing</td>
<td>4.5</td>
<td>-39.0</td>
<td>-43.2</td>
<td>-48.0</td>
</tr>
</tbody>
</table>

*Primary endpoint; †P<.001 vs placebo.
MENDEL = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels; 2; LS = least squares.

OSLER Trial: Effect of Evolocumab on LDL Cholesterol

<table>
<thead>
<tr>
<th>Standard of care alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
</tr>
<tr>
<td>120</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

61% reduction (95% CI 59%-63%), P<0.0001
Absolute reduction: 73 mg/dL (95% CI 71-76%)

Evolocumab plus standard of care

OSLER Trial: Effect of Evolocumab on Cardiovascular Outcomes

Composite Endpoint: Death, MI, UA → hosp, coronary revasc, stroke, TIA, or CHF → hosp

Standard of care alone (n=1489)
HR 0.47
95% CI 0.28-0.78
P=0.003

Evolocumab plus standard of care (n=2976)
Cumulative incidence [%]

TIA = transient ischemic attack; CHF = congestive heart failure; MI = myocardial infarction; UA = unstable angina.

ODYSSEY Long Term: Study Design

Adults with HeFH or at high CV-risk
On maximally tolerated statin ± other LLT
LDL-C ≥70 mg/dL (1.81 m mol/L)

Double-blind treatment (18 months)
Placebo Q2W SC
Alirocumab 150 mg Q2W SC
(single 1 mL injection using prefilled syringe for self-administration)

Follow-up (8 weeks)
Assessments
Primary efficacy endpoint

SC = subcutaneous; W = week.
**Post hoc** Analysis of Adjudicated Major Adverse Cardiovascular Events*

Cox model analysis
HR = 0.52 (95% CI 0.31 to 0.90)
Nominal p-value = 0.02

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Placebo + maximally tolerated statin ± other LLT</th>
<th>Alirocumab + maximally tolerated statin ± other LLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>24</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>36</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>52</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>64</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>78</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>86</td>
<td>0.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Based on primary endpoint for the ODYSSEY OUTCOMES trial, including CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization. Unstable angina requiring hospitalization was considered based on strict criteria/clear progression of ischemia.


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**Treatment-Emergent General Allergic and Neurologic Serious Adverse Events**

<table>
<thead>
<tr>
<th>MedDRA query serious AEs</th>
<th>Alirocumab (n=1550)</th>
<th>Placebo (n=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Allergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>8 (0.5)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>3 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Dermatitis allergic</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Laryngeal oedema</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>5 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Demyelination</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Miller Fisher Syndrome</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>0</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

MedDRA = Medical Dictionary for Regulatory Activities.
# Cardiovascular Outcomes Trials of PCSK9 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Sanofi/Regeneron</td>
<td>Amgen</td>
<td>Pfizer</td>
</tr>
<tr>
<td><strong>Trial</strong></td>
<td>ODYSSEY Outcomes</td>
<td>FOURIER</td>
<td>SPIRE I</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>18,000</td>
<td>22,500</td>
<td>12,000</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>4-16 weeks post-ACS</td>
<td>MI, stroke, or PAD</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>Evidence-based Rx</td>
<td>Atorvastatin ≥20 mg or equivalent</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td>≥70 mg/dL</td>
<td>≥70 mg/dL</td>
<td>70-99 mg/dL</td>
</tr>
<tr>
<td><strong>PCSK9i Dosing</strong></td>
<td>Every 2 weeks</td>
<td>Every 2 or Every 4 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>CHD death, MI, ischemic stroke, or UA hospitalization</td>
<td>Primary: CV death, MI, stroke, UA hospitalization or coronary revascularization</td>
<td>Key Secondary: CV death, MI, or stroke</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>March 2018</td>
<td>December 2017</td>
<td>August 2017</td>
</tr>
</tbody>
</table>

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### Fibrates Reduce CHD Risk in Patients with HTG and Low HDL-C

A meta-analysis of randomized fibrate trials

**Subjects without Dyslipidemia**

<table>
<thead>
<tr>
<th>Study (treatment)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (simvastatin + fenofibrate)</td>
<td>0.94 (0.84-1.05)</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td></td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td></td>
</tr>
<tr>
<td>HHS (gemfibrozil)</td>
<td></td>
</tr>
<tr>
<td>VA-HIT (gemfibrozil)</td>
<td></td>
</tr>
</tbody>
</table>

**Subjects with Dyslipidemia**

<table>
<thead>
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<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (simvastatin + fenofibrate)</td>
<td>0.63 (0.54-0.78)</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td></td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td></td>
</tr>
<tr>
<td>HHS (gemfibrozil)</td>
<td></td>
</tr>
<tr>
<td>VA-HIT (gemfibrozil)</td>
<td></td>
</tr>
</tbody>
</table>

TG ≥204 mg/dL, HDL-C ≤34mg/dL

JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins

![Graph showing the reduction in cumulative incidence of major coronary events with EPA and statin combination compared to statin alone.](image)

N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin Rx. Baseline TG=153 mg/dL. Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

*Primary endpoint: sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.


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JELIS: Larger Decrease in MACE in those with TG >150 mg/dL & HDL-C <40 mg/dL*

![Graph showing the decrease in cumulative incidence of major coronary events with EPA 1.8 gm/day compared to control group.](image)

No. of patients

<table>
<thead>
<tr>
<th>Years</th>
<th>Control</th>
<th>EPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>475</td>
<td>482</td>
</tr>
<tr>
<td>1</td>
<td>444</td>
<td>455</td>
</tr>
<tr>
<td>2</td>
<td>432</td>
<td>443</td>
</tr>
<tr>
<td>3</td>
<td>414</td>
<td>427</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>413</td>
</tr>
<tr>
<td>5</td>
<td>392</td>
<td>403</td>
</tr>
</tbody>
</table>

HR: 0.47
95% CI: 0.23–0.98
P=0.043

HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

**AIM-HIGH Study Results**

**Primary Outcome**

Extended Release Niacin and Major Vascular Events

Risk ratio 0.96 (95% CI 0.90 – 1.03)

Logrank P=0.29

Placebo

ERN/LRPT

NEJM 2014
Raising HDL via CETP Inhibition

CETP = cholesterylester transfer protein.

Mechanism of Action of CETP

- Two hypotheses have been proposed for the mechanism by which CETP transfers neutral lipids between plasma lipoproteins
- (i) a shuttle mechanism that involves CETP collecting cholesteryl esters from one lipoprotein and delivering them through the aqueous phase to another lipoprotein.
- (ii) a tunnel mechanism in which CETP bridges two lipoproteins to form a ternary complex, with lipids flowing from the donor to acceptor lipoprotein through the CETP molecule

CETP Polymorphisms and Cardiovascular Risk in Humans

- A meta-analysis has been conducted of studies investigating relationships between CETP polymorphisms and cardiovascular disease in humans
- 46 studies had data on 27,196 coronary cases and 55,338 controls
- Those polymorphisms that were associated with lower CETP mass and lower CETP activity had higher levels of HDL-C and a significantly reduced coronary risk


CETP Inhibitors and Modulators

ILLUMINATE
Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

15,067 patients
- Men and women
- Aged 45-75 years
- 250 sites in 7 countries
- CHD or risk equivalent, any HDL-C level, statin eligible

Primary End Point
Composite of fatal CHD, nonfatal MI, stroke (fatal and non-fatal and unstable angina requiring hospitalization)


Torcetrapib: "Beneficial" Effects on Lipoproteins, but Increased Cardiovascular and Non-Cardiovascular Morbidity and Mortality

Was the toxicity of torcetrapib related to off-target effects specific to this molecule?

The dal-HEART Program tests a novel hypothesis that raising HDL through CETP inhibition will attenuate cardiovascular risk.

dal-OUTCOMES
A double-blind, randomized, placebo-controlled study in 15,600 patients recently hospitalized for ACS

**Goal:** To evaluate the effect of dalcetrapib on CV outcomes

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dal-VESEL
A double-blind, randomized, placebo-controlled study in 450 patients with CHD or CHD risk equivalent

**Goal:** To evaluate the effect of dalcetrapib on endothelial function and blood pressure, measured by FMD and ABPM

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dal-PLAQUE
A double-blind, randomized, placebo-controlled study in 130 patients with CHD

**Goal:** To evaluate the effect of dalcetrapib on inflammation, plaque size, and burden, measured by PET/CT and MRI

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dal-PLAQUE 2
A double-blind, randomized, placebo-controlled study in 900 patients with CAD

**Goal:** To evaluate the effect of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging.

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**dal-OUTCOMES Results:** No ↓CVD


ACCELERATE Trial of Evacetrapib

![Graph showing percent change in HDL-C levels during the trial.]

Mean HDL-C = 104 mg/dL
Mean difference = 130%

ACCELERATE Trial of Evacetrapib

![Graph showing percent change in LDL-C levels during the trial.]

Mean LDL-C = 84 mg/dL
Mean difference 37%
ACCELERATE Trial of Evacetrapib

Cumulative Incidence of Primary Efficacy Endpoint

- Evacetrapib, 774 events (12.8%)
- Placebo, 768 events (12.7%)

Log Rank Test

HR = 1.01
95% CI, 0.91-1.12
P=0.85

S. Nicholls, ACC 2016

Preliminary analysis prior to formal database lock
CETP Inhibitor Anacetrapib


REVEAL Trial

*Randomized Evaluation of the Effects of Anacetrapib through Lipid-Modification*

30,000 patients
aged > 50 with with occlusive arterial disease

Atorvastatin to achieve LDL-C target

Primary End Point
Coronary death, myocardial infarction or coronary revascularization

Sites in North America, Europe and Asia

Anacetrapib 100 mg

Placebo

4 year follow-up
Planned completion in 2017

Summary and Conclusions

• Statins as mainstay of cholesterol control.
• Additional agents as adjuvants in statin intolerant subjects or to achieve LDL goal.
• For TG control, fibrates and omega 3 fats have yet to produce evidence of CVD benefits.
• For HDL control, niacin has failed to produce evidence of CVD benefits.
• New agents available for management of orphan-status HoFH.
• PCSK9 inhibitors for common FH and to help CAD subjects reach LDL goal.
• Raising HDL does not help.