Dyslipidemia Management: State of the Art 2013

Cardiovascular Health Summit, 2013
Crowne Plaza, Billings, MT
April 12, 2013
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Speaker Disclosures

Dr. Brinton has received:

- Research funding: Amarin, Health Diagnostic Laboratory, Merck, Roche
- Honoraria as consultant/advisor: Abbott, Aegerion, Amarin, Arisaph, Atherotech, Daiichi-Sankyo, Essentialis, Genzyme, Kowa, Merck, Novartis, Regeneron, Sanofi-Aventis, Takeda
- Honoraria as speaker: Abbott, Amarin, Daiichi-Sankyo, Janssen, Kowa, Merck, Takeda

Learning Objectives

- At the end of this learning activity, participants should be able to:
  - Discuss new developments in LDL-C lowering agents
  - Evaluate new and controversial data in management of patients with low HDL-C
  - Consider the impact of new medications and ongoing trials in management of high TG
Talk Outline

• LDL/Non-HDL Lowering
  – Statin adverse effects (myopathy & DM)
  – Lomitapide and Mipomersen approval—for HoFH only
  – PCSK9 mAb in development
  – “ATP-IV” Guidelines—when?
• HDL Raising
  – Observational Data
  – Clinical Trial data
    • AIM-HIGH sub-analysis
    • HPS-2 ACC presentation
    • CETP-I update
• TG/Non-HDL Lowering
  – Icosapent-ethyl approval, REDUCE-IT study
  – Epanova in development

Management of High LDL/Non-HDL

Statin Update

• Statin Myopathy:
  – New internet-based data (USAGE study)
  – Continued work on causes & Rx
• New-onset DM: FDA-mandated label update (all but pravastatin)
• Cognitive dysfunction: no solid data, but FDA-mandated label update
• Liver transaminase testing removed
Statin Side Effects (esp. Myopathy): Most Common Reason to Discontinue (but also common in pts who continued)

**USAGE:** Internet survey, 10,138 US adults w/ prior statin Rx (2000-2011)

**Among the 12% who discontinued**
- Reasons for discontinuing:
  - Side-effects—62% (86% w/ muscle pain/weakness = 53% of total)
  - Cost—17% (despite many inexpensive generics now available)
  - Lack of cholesterol lowering efficacy—12%
- When/how they stopped:
  - 57% stopped promptly after a side effect (no further Rx fill)
  - One-third stopped w/o asking or telling their health-care provider

**Among the 88% current users**
- Muscle pain or weakness reported by 25%


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Do Statins Increase New-Onset DM-2?

**Yes, Modest Increase w/ Certain Statins**
- ~ 9-25% ↑ DM risk
- Higher w/ increased age (+other DM RFs)
- Maybe no ↑ w/ pravastatin or lovastatin?
- Few data w/ fluvastatin or pitavastatin

**But Favorable Risk/Benefit Ratio Remains**
- NNH = 1 case of DM per 225 pts Rx’d x 4y
- NNT = 1 MACE per 31 pts Rx’d x 4y*
- Prevent >7 MACE:1 DM case (>3:1 at hi-dose)

No need to avoid statin in med- to high-risk pts


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New LDL-C-Lowering Drugs
Lomitapide Lowers LDL-C in HoFH (N=29 no ctrls)

LDL-C Reduced by 40% at Week 26 in Phase 3
(ITT with LOCF, N=29) — Includes data from 6 dropouts —

↓HDL-C 10-20% at 26 wks, gone at 56 wks
↓Lp(a) 21% (sig at 56 wks only)

— Includes data from 6 dropouts —

Lomitapide (Juxtapid—Aegerion): Update

• MoA: MTP-inhib, blocks VLDL/chylo assembly
• What clinical impact in the “statin world”?  
  – Approved December 2012, available 1/13  
  – For “HoFH”: how many in US? how to Dx?  
    • N=300 (?) per genetic studies, vs  
    • N=600 (?) LDL-apheresis (LDL-C >200 on-Rx), vs  
    • N=3000 (?) by study criteria (TC >500 pre-Rx)  
  – Concurrent LDL apheresis studied/allowed  
  – Cost: $225-295K/yr (!) vs LDL-apher $50-$125K/year

Lomitapide (Juxtapid—Aegerion): Update—cont.

• Safety and tolerability  
  – Oral qd, but  
  – Fatty intest/abd Sx in ~all  
  – Fatty liver/↑transaminases in ~all  
• Rx requirements:  
  – REMS for Rx-ing MD, pt registry  
  – Dose titration up and down,  
  – Supplements (vit E, ALA, EPA, DHA)  
  – Contraindications: pregnancy, strong CYP inhib, hepatic insufficiency, intestinal disease  
  – Precautions: warfarin, simvastatin  
  – Paperwork: Rx forms, mail-order pharmacy, insurance pre-auth (!)
Mipomersen (Kynamro—Isis): Update

- MoA: Apo B anti-sense oligonucleotide (blocks apo B-100 synth & hep VLDL prod)
- What clinical impact in the “statin world”? 
  - Approved by FDA 1/29/13, available 2/13
  - For “HoFH”: how many in US? how to Dx?
    - N=300 (?) per genetic studies, vs
    - N=600 (?) LDL-apheresis (LDL-C >200 on-Rx), vs
    - N=3000 (?) by study criteria (TC >500 pre-Rx)
  - ↓Apo C-III 45% (non FH pts)
  - Concurrent LDL apheresis “not recommended” (not studied, but no other rationale)
  - Cost $176K/yr (vs $225-295K/yr, or $50-125K/yr)

Mipomersen (Kynamro—Isis): Update—cont.

- Safety and tolerability
  - Once-weekly but req. sc shot
  - Fatty liver/↑transaminase (flu-like Sx in ~30%)
  - Injection site rxn (~76-84%, recur at old sites)
  - Rejected by EMEA (d/c’s; liver, skin & CV tox)
  - New Rx category: safety? immune effects?
- Rx requirements:
  - REMS for Rx-ing MD, pt registry
  - Contraindic: mod-severe hepatic impairment
  - Precautions: flu-like (30%; fever, myalg), pregnancy category B
  - Rx forms, mail-order pharmacy, and insurance pre-auth (!)

Mipomersen →↓LDL-C 21% in HoFH (N=34)

Raal, FJ. Lancet 2010;375:998-1006
**New Cholesterol Guidelines**

- NCEP ATP-III 2001 (12 years old); many new studies/approved agents since
- New effort:
  - NCEP discontinued, *not* "ATP-IV"
  - NHLBI requested "evidence based", *not* an update of ATP-III—likely *very* different
  - Few/no studies *directly* tested ATP-III goals
  - May delete lipid Rx goals, like anti-plt Rx?
  - Will use lifetime risk (not 10-y Framingham)

**Relationship between HDL-C and CVD Risk:**

*General Population vs. Monogenic Disorders*
Coronary Heart Disease Risk by Non-HDL-C and HDL-C Quintiles

Hazard Ratio

Usual Mean Non-HDL-C Level, mg/dL

Usual Mean HDL-C Level, mg/dL

Non-HDL-C by levels of HDL-C

HDL-C by levels of Non-HDL-C


High CVD Risk in Patients with Low HDL-C

- Average HDL-C in CCU is 38 mg/dL (vs TG 167, LDL-C 103)\(^1\)
- Post-PCI, low HDL-C predicts 3 x ↑mort.\(^2\)
- Statin Rx→LDL-C <70 + HDL-C <mid 30s:
  - CVD in TNT: 1.5-1.9%/yr\(^3\)
  - CVD in AIM-HIGH: 5.4%/yr\(^4\)


Potential Antiatherogenic Actions of HDL

- Antioxidative Activity
- Antithrombotic Activity
- Anti-infectious Activity
- Endothelial Repair
- Vasodilatory Activity
- Anti-inflammatory Activity
- Reverse Cholesterol Transport
- Cellular Cholesterol Efflux
- Antiapoptotic Activity
- Apo A-I
- Apo A-II

Reconciling Observational Data Re: Low HDL-C

- Low HDL-C ≈ ↑ CVD
  - In general populations
  - In ACS
- Low vs high HDL-C (isolated) ≠ ↑ vs ↓ CVD
  - Certain gene variants (LIPG + 14—HDL-C only, ↓ LCAT?)
- Hypotheses:
  - Low-HDL-C ≈ ↑ CVD only when ↑ TG?
  - Related to TG-rich remnant lipids

Clinical Trials of HDL-Raising Medications: Recent CVD Results
Available Agents for HDL-Raising (& ↓TG)

<table>
<thead>
<tr>
<th>Agent</th>
<th>HDL-C ↑</th>
<th>Primary Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic acid</td>
<td>15-35%</td>
<td>HDL ↑</td>
</tr>
<tr>
<td>Fibrates</td>
<td>5-20%</td>
<td>TG ↓</td>
</tr>
<tr>
<td>Statins</td>
<td>5-15%</td>
<td>LDL ↓</td>
</tr>
<tr>
<td>Presc. Om-3*</td>
<td>2-10%</td>
<td>TG ↓</td>
</tr>
<tr>
<td>Bile-acid resins*</td>
<td>2-5%</td>
<td>LDL ↓</td>
</tr>
<tr>
<td>Ezetimibe*</td>
<td>1-3%</td>
<td>LDL ↓</td>
</tr>
<tr>
<td>Pioglitazone*</td>
<td>5-20%</td>
<td>Glucose ↓</td>
</tr>
<tr>
<td>Estrogens*</td>
<td>10-25%</td>
<td>Hot flashes</td>
</tr>
<tr>
<td>α-blockers*</td>
<td>10-20%</td>
<td>BPH</td>
</tr>
<tr>
<td>Alcohol*</td>
<td>5-15%</td>
<td>Social, etc.</td>
</tr>
</tbody>
</table>

* Lacking FDA-approved indication for HDL-raising.


Niacin Reduces Total CVD (CHD + CVA): Pre-AIM-HIGH Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate/Off Rate</th>
<th>Rate/Off Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM-HIGH</td>
<td>3/2173</td>
<td>3/2173</td>
<td>0.05 (0.00, 0.00)</td>
<td>0.05 (0.00, 0.00)</td>
</tr>
<tr>
<td>Quantin et al</td>
<td>1/276</td>
<td>1/272</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>ARCADIS2</td>
<td>1/73</td>
<td>1/72</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>HAT5</td>
<td>1/79</td>
<td>1/79</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>UXOP_SOKK</td>
<td>1/46</td>
<td>1/44</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>FATS6</td>
<td>1/48</td>
<td>1/48</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>STOOGT5H</td>
<td>1/275</td>
<td>1/275</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>CLAS</td>
<td>1/394</td>
<td>1/394</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
<tr>
<td>DOP</td>
<td>151/1121</td>
<td>2333/2790</td>
<td>0.06 (0.00, 0.00)</td>
<td>0.06 (0.00, 0.00)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: P = 0.003, I² = 58.3%
Test for overall effect: P = 0.0001


AIM-HIGH — Results

Primary Outcome

Data: WE Boden, JAMA 2011; 305:2073-2083.

AIM-HIGH: Niaspan beats Control in HTG/low HDL-C pts

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>ERN Better</th>
<th>ERN Worse</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-val.** Int.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≥ 190 and HDL &lt; 33</td>
<td>58 (22.4)</td>
<td>48 (17.8)</td>
<td></td>
<td>0.74 (0.50, 1.09)</td>
<td>0.073</td>
</tr>
<tr>
<td>No</td>
<td>220 (15.1)</td>
<td>234 (16.3)</td>
<td></td>
<td>1.09 (0.91, 1.31)</td>
<td></td>
</tr>
<tr>
<td>TG ≥ 200 and HDL &lt; 32</td>
<td>50 (25.0)</td>
<td>49 (19.7)</td>
<td></td>
<td>0.63 (0.40, 0.98)</td>
<td>0.017</td>
</tr>
<tr>
<td>No</td>
<td>224 (15.8)</td>
<td>242 (16.2)</td>
<td></td>
<td>1.11 (0.93, 1.33)</td>
<td></td>
</tr>
</tbody>
</table>

*Highest tertile of TG and lowest tertile of HDL-C  **Heterogeneity by treatment

AIM-HIGH—New Subgroup Analysis Summary

Subjects w/ HDL-C <32 mg/dL & TG >200 mg/dL had 37% ↓ CVD w/ ERNA: HR 0.63 (95%CI 0.40-0.98, interaction p=.017)
[1st + 3rd HDL/TG tertile <33 & >198 had HR .74 p=.07]

Similar subpopulations showed 27-71% ↓ CVD with:
• Gemfibrozil: HHS*, VA-HIT*
• Fenofibrate: FIELD, ACCORD-Lipid
• Omega-3 (pure EPA): JELIS*

**Bottom Line: TG/HDL drugs work in ↑ TG/↓ HDL-C! (Need to check ↑ TG/↓ HDL-C pts in HPS2/THRIVE)


Niacin May Reduce CVD Better in Patients with Metabolic Syndrome

Patients With HDL-C at BL: N=354 (Placebo), 138 (Niacin)

<table>
<thead>
<tr>
<th>Relative Hazard</th>
<th>Placebo</th>
<th>Niacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS- (0–2 RF’s)</td>
<td>0.78</td>
<td>0.30</td>
</tr>
<tr>
<td>MS+ (3–5 RF’s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Z(int) = –1.78
HPS-2/THRIVE: The Promise

Appeared to avoid most AIM-HIGH problems
- ~True placebo-control: good test of niacin?
- Adequate duration (~5 yrs)
- Adequate N (~23,000 subjects)
- Little pre-study Rx "contamination" (vs. AIM-HIGH)

But might have kept two problems
- NO selection for either low HDL-C or high TG pts
- All niacin subjects also on laropiprant, so NOT a test of niacin alone!

HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease

Baseline Lipids on Statin-based Rx

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total chol</td>
<td>128 (22)</td>
<td></td>
</tr>
<tr>
<td>Direct-LDL</td>
<td>63 (17)</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>44 (11)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>125 (74)</td>
<td></td>
</tr>
</tbody>
</table>

Note: pts had NONE of the usual lipid indications for Niacin

Effect of ERN/LRPT on Major Vascular Events

<table>
<thead>
<tr>
<th></th>
<th>Effect of ERN/LRPT on Major Vascular Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk ratio</td>
<td>0.96 (95% CI 0.90 – 1.03)</td>
</tr>
<tr>
<td>Logrank P value</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Note: majority of excess SAEs in DM-2 were "minor hyperglycaemic problem"

Effect of ERN/LRPT on SERIOUS Adverse Events (median follow-up 3.9 years)

<table>
<thead>
<tr>
<th>Event</th>
<th>Excess</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic complication</td>
<td>3.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>1.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infection</td>
<td>1.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0.7%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.4%</td>
<td>0.05</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.7%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Skin</td>
<td>0.3%</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

Note: majority of excess SAEs in DM-2 were "minor hyperglycaemic problem"
**Trend Towards MVE Benefit Among European Patients**

<table>
<thead>
<tr>
<th>Age category</th>
<th>Randomized allocation</th>
<th>Risk ratio &amp; 95% CI</th>
<th>Het or trend χ² (uncorrected p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>ERN/LRPT (12,835)</td>
<td>0.99</td>
<td>0.06 (p=0.96)</td>
</tr>
<tr>
<td>≥65</td>
<td>Placebo (12,838)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>ERN/LRPT (12,835)</td>
<td>0.99</td>
<td>0.06 (p=0.96)</td>
</tr>
<tr>
<td>Female</td>
<td>Placebo (12,838)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>European</td>
<td>0.99</td>
<td>0.06 (p=0.96)</td>
</tr>
<tr>
<td>Asian</td>
<td>ERN/LRPT (12,835)</td>
<td>0.99</td>
<td>0.06 (p=0.96)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo (12,838)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HPS-2/THRIVE: The Reality**

**Why no benefit of ERNL added to statin?**

- Did not study pts with lipid indication for niacin!
- Avg. base: HDL-C 44 mg/dL, TG 125, LDL-C 63
- Benefit in pts w/ LDL-C >57 mg/dL? (sig trend)
- Benefit in low HDL-C/High TG? (analyses pend.)
- Benefit in Caucasians? (close to sig 9%↓)
- Harm from niacin (new DM-2, myopathy)
- Harm from laropiprant?
  - Pan-infections (anti-WBC effect?)
  - Hemorrhage (↑CVA due to ↑aneurysms vs anti-plt?)
HDL-Raising via CETP-Inhibition

CETP in HDL Metabolism and Atherosclerosis

• Human CETP deficiency: ↑↑HDL-C and ↓↓CVD
• Decreasing CETP in animals: ↑↑HDL-C and ↓↓athero


Lipid Effects of CETP Inhibitors
% Change from Baseline, added to statin Rx

<table>
<thead>
<tr>
<th>CETP Agent</th>
<th>Dose (mg/day)</th>
<th>HDL-C (%)</th>
<th>LDL-C (%)</th>
<th>TG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib</td>
<td>60</td>
<td>61</td>
<td>-24</td>
<td>-9</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>100</td>
<td>138</td>
<td>-40</td>
<td>-7</td>
</tr>
<tr>
<td>Evacetrapib*</td>
<td>100</td>
<td>82</td>
<td>-13</td>
<td>-4</td>
</tr>
<tr>
<td>Dalcetrapib</td>
<td>600</td>
<td>31</td>
<td>-2</td>
<td>-3</td>
</tr>
</tbody>
</table>

*Dose of evacetrapib in clinical endpoint trial is 130 mg/d.
CETP Inhibitors: 2 Down, 2 Remain

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Torcetrapib Caused Off-target Hyperaldosteronism (ILLUMINATE data)
- Torcetrapib arm of ILLUMINATE: 1
  - ↑ Systolic Blood Pressure:
    - Mean 15.4 mmHg
    - >15 mmHg SBP: 19.5% torcet (vs 9.4% placebo, P=0.001)
  - ↓ serum potassium
  - ↓ serum bicarbonate
  - ↓ serum sodium
  - ↓ serum aldosterone
- ↑ CVD in ILLUMINATE correlated with adrenal dysfunction
- Inverse relationship of CVD and on-Rx-HDL-C preserved
- Conclusion: ↑ CVD likely due to off-target actions of torcetrapib, not related to CETP inhibition 1,2


dal-OUTCOMES Results: No ↓ CVD


<table>
<thead>
<tr>
<th>Year</th>
<th>No. at risk</th>
<th>Placebo</th>
<th>Dalcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>7932</td>
<td>7937</td>
<td>7942</td>
</tr>
<tr>
<td>2013</td>
<td>7386</td>
<td>7372</td>
<td>7386</td>
</tr>
<tr>
<td>2014</td>
<td>6552</td>
<td>6495</td>
<td>6552</td>
</tr>
<tr>
<td>2015</td>
<td>1743</td>
<td>1736</td>
<td>1743</td>
</tr>
</tbody>
</table>

P=0.52 by log-rank test
Dal-OUTCOMES Results: HDL Was Likely Still Functional

**Graph:**
- **X-axis:** Quintiles of Change in HDL-C (mg/dL) Baseline to Month 1
- **Y-axis:** Annualized Event Rate (%)
- **Legend:**
  - Decalix
  - Placebo

**Small stat. sig. ↑BP (0.6 mm) suggested small adverse adrenal effect, which may have overcome small benefit from modest ↑HDL.**


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**Does Anacetrapib Reduce CVD Events? DEFINE Results**

**Cardiovascular Events During the Treatment Phase of the Study**

<table>
<thead>
<tr>
<th>Event</th>
<th>Anacetrapib (N = 808)</th>
<th>Placebo (N = 804)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respecified, adjudicated cardiovascular safety end point</td>
<td>14 (2.0%)</td>
<td>21 (2.6%)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>4 (0.5%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>6 (0.7%)</td>
<td>9 (1.1%)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>1 (0.1%)</td>
<td>6 (0.7%)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>5 (0.6%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>11 (1.4%)</td>
<td>8 (1.0%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (0.4%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>8 (1.0%)</td>
<td>28 (3.5%)</td>
</tr>
<tr>
<td>PCI</td>
<td>6 (0.7%)</td>
<td>25 (3.1%)</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (0.2%)</td>
<td>3 (0.4%)</td>
</tr>
</tbody>
</table>


---

**Ongoing Clinical Trials of CETP-Inhibitors**

**REVEAL**
- Anacetrapib 100mg/d
- N=30,000
- Stable CHD
- Background atorvastatin
- 1° endpoint: fatal CHD, MI, or coronary revascularization
- Start 6/11
- 4 yr min f/u
- End ~1/17

**ACCELERATE**
- Evacetrapib 130mg/d
- N=11,000
- ACS 30d-1y, or non-CHD, or DM+CAD
- Background statin
- 1° endpoint: fatal CHD, MI, CVA, or coronary revascularization, hosp for USA
- Start 2H12
- 1.5 yr min f/u
- End ~2H15
Revisiting the HDL Hypothesis

Con
- Recent trials of HDL-raising have been neutral
- Genetic isolated ΔHDL-C may not predict CVD

Pro
- CVD risk reduction only ~1/3 w/ statin monoRx, so
- Statin monoRx is not enough for high-risk patients
- Low HDL-C predicts high CVD risk, even w/ statin Rx
- HDL↑(+TG↓) Rx shows ↓CVD in ↓HDL/HTG pts

(My) Current Recommendation
- Consider HDL/TG meds (fibrate, Om-3, niacin)
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*(My)* Current Recommendation
- Consider HDL/TG meds (fibrate, Om-3, niacin) in
- New analyses and trials must address:
  - Does Rx with each particular HDL-raising med → ↓CVD?
  - Is HDL a causal factor or a biomarker of risk?

How Should We *Measure* HDL?

- Plasma concentration
  - HDL-C
  - Apo A-I
  - HDL-P—*independent* (not rel. to TG/LDL-P)
- HDL Composition/Structure—in devel.
  - HDL size (including pre-beta HDL)
  - HDL proteome, TG, other?
- HDL Function—in development
  - Cholesterol efflux
  - Inflammation, oxidation, etc.

*Bottom line:*
HDL metrics are a "moving target"
HDL-C is ok for routine clinical use for now

Update on Management of Hypertriglyceridemia
Can Hypertriglyceridemia Cause Atherosclerosis?

**Con**
- HTG assoc. w/ CVD weaker than LDL-C, partly HDL-C dependent
- Severe HTG from ↑ chylomicrons not related to ↑ CVD
- TG accumulation not seen in atherosclerotic plaque
- TG-lowering drugs not completely proven to ↓ CVD

**Pro**
- TG-rich lipoproteins are atherogenic (esp. chol-rich remnants)
- TG lipolysis by LPL → pro-inflammatory FFA (uptake by CD36 and FA binding proteins to nucleus)
- Apo C-III raises TG and is pro-inflammatory
- HTG causes atherogenic changes in LDL and HDL
- TG-lowering meds → ↓ CVD in HTG/low HDL-C pts
  - EPA → ↓ CVD in general population on-top of statin!

---

**TG Levels Predict CHD Risk: Meta-analysis of 29 Observational Studies**

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
<th>CHD Risk Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥10 years</td>
<td>&lt;10 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>5902</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>7728</td>
</tr>
<tr>
<td>Fasting Status</td>
<td>Fasting</td>
<td>7484</td>
</tr>
<tr>
<td></td>
<td>Nonfasting</td>
<td>2674</td>
</tr>
<tr>
<td>Adjusted for HDL-C</td>
<td>No</td>
<td>4469</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5689</td>
</tr>
</tbody>
</table>

- Overall CHD Risk Ratio* = 1.72 (95% CI, 1.56-1.90)

---

**Increased CHD Risk with TG >150 mg/dL (even w/ LDL-C < 70!)**

**PROVE IT-TIMI 22 Trial:**
- Patients w/ acute coronary syndrome (ACS)
- Rx atorvastatin 80 mg or pravastatin 40 mg
- Primary endpoint: death, MI, and recurrent ACS (adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment). Lipid values are in mg/dL.

Reference:
Three Atherogenic Consequences of Hypertriglyceridemia

1. ↑TG/VLDL-C
2. SD LDL/LDL-P
3. ↓HDL-C & Apo A-I

Fatty Liver & ↑VLDL synthesis are key to ↑TG and consequences

Fibrates Reduce CHD Risk ~35% in Patients with High TG and Low HDL-C

A meta-analysis of randomized fibrate trials

A Subjects with Dyslipidemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td></td>
</tr>
<tr>
<td>FIELD</td>
<td></td>
</tr>
<tr>
<td>SPAR</td>
<td></td>
</tr>
<tr>
<td>SPRINT</td>
<td></td>
</tr>
</tbody>
</table>

Summary: OR 0.76 (0.54-1.08)

B Subjects without Dyslipidemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio [95% CI]</th>
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</tr>
<tr>
<td>SPRINT</td>
<td></td>
</tr>
</tbody>
</table>

Summary: OR 0.58 (0.38-0.89)

"With Dyslipidemia" = TG ≥ 204mg/dL and HDL-C ≤ 34mg/dL

EPA Reduces CVD in JELIS Subgroup: TG >150mg/dL and HDL <40mg/dL

HR: 0.47 (95% CI: 0.23-0.96) P=0.043

EPA reduces CVD by 57% vs 19% in total study population

Number of patients
Control: 479, 464, 432, 414, 406, 392
EPA: 402, 405, 443, 427, 412, 402

Adjusted for age, sex, smoking, diabetes, and hypertension.

**CVD with “TG/HDL Drugs” in High TG/Low HDL-C Subgroups**

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Lipid Subgroup Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-statin era HHS</td>
<td>-34% (0.02)</td>
<td>TG ≥ 254 mg/dl LDL-C/HDL-C ≥ 5.0</td>
</tr>
<tr>
<td>BIP (Bezafibrate)</td>
<td>-4.4% (0.36)</td>
<td>TG ≥ 250 mg/dl HCC &lt; 45 mg/dl</td>
</tr>
<tr>
<td>Same statin use</td>
<td>-11% (0.16)</td>
<td>TG ≥ 150 mg/dl</td>
</tr>
<tr>
<td>Statin addition</td>
<td>-9.4% (0.26)</td>
<td>HDL-C &lt; 35 mg/dl</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>-11% (0.16)</td>
<td>TG ≥ 150 mg/dl</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-11% (0.32)</td>
<td>HDL-C ≥ 40 mg/dl</td>
</tr>
<tr>
<td>JELIS (ethyl EPA)</td>
<td>-15% (0.011)</td>
<td>TG ≥ 150 mg/dl</td>
</tr>
</tbody>
</table>

**Gemfibrozil Reduces CVD In Patients w/ Average to Elevated Insulin Levels**

*Baseline Fasting Insulin Quartile*

- Quartile 1: 24-29
d- Quartile 2: 30-38
- Quartile 3: ≥ 39
- Quartile 4: ≤ 23

*Favors Gemfibrozil Favors Placebo CVD Risk Reduction, % P=.04 Versus Placebo*

*Fibrates reduce CVD best in Insulin Resistance*

**Statin + EPA/DHA (Lovaza): COMBOS Lipid Endpoints**

Additional changes to baseline simvastatin therapy

- Placebo + simvastatin 40 mg/d
- P-OM3 4 g/d + simvastatin 40 mg/d

TG 200-500 baseline on statin.
Statin + EPA (Vascepa): ANCHOR Lipid Endpoints

TG Non–HDL-C Apo B LDL-C HDL-C
Baseline (mg/dL)
265 254 128 128 93 91 82 82 37 38

**P<0.001; ***P<0.001; **P<0.01; *P<0.05;
NS = not significant (P ≥ 0.05), icosapent ethyl vs placebo

Icosapent Ethyl
- 4 g/day
- 2 g/day

TG Non–HDL-C Apo B LDL-C HDL-C
Median Placebo-adjusted Change (%)
-21.5 ****
-13.4 ****
-3.8 ****
-5.5 **
-9.3 ****
-3.6 ****
-6.2 ****
-3.8 ****
-6.2 ****
-4.5 NS
-2.2 NS

Bottom line: EPA/DHA better for ↓TG & ↑HDL-C. EPA better for ↓LDL-C, ↓Non-HDL-C, ↓Apo B (↓CVD?)

12-week trial in high-risk statin-treated patients (n = 702) with TG 200-500 and LDL-C 40-100.

Effect of Icosapent Ethyl on Inflammatory Markers

*P<0.01; †P<0.001; ‡P<0.0001 vs placebo. hs-CRP=high-sensitivity C-reactive protein; ICAM= intercellular adhesion molecule; Lp-PLA2=lipoprotein (a) phospholipase A2; Ox-LDL=oxidized LDL. Bays HE et al. Am J Cardiovasc Drugs. 2013;13:37-40.

Reduction of Cardiovascular Events with EPA – Intervention Trial: REDUCE-IT

- Randomized, double-blind, multinational
- 2 outcomes: individual CVD events, lipid/lipoprotein levels, safety, subgroup analyses (diabetics, etc.)
- Completion ~Nov 2016

Icosapent ethyl = Vascepa = AMR101


Primary endpoint: 1st major CV event composite

Icosapent ethyl 2g bid
Placebo
Study duration ~4–6 years

Icosapent ethyl = Vascepa = AMR101

N=8000 M&F ≥ 45 y/o
High CVD risk:
- Prior CHD (70% pts), or
- DM-2 + 2 RF
Dyslipidemic:
- H/O ↑Chol, but at LDL-C goal on statin, and
- TG 150-500 mg/dL

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Primary endpoint: 1st major CV event composite

Icosapent ethyl = Vascepa = AMR101

Omefas (Epanova) Update

• Omefas (omega-3 fatty acids—Epanova, Omthera) in phase III
• Plan to file NDA mid 2013
• Composition: EPA 50-60%, DHA 15-25%, + other om-3 FAs

ECLIPSE (Jan 2011)
  – Design: N=54, 4-way cross-over 24 h PK of EPA & DHA, 24 h post 4 g Omefas (Epanova) or O3AEE (Lovaza) on low- or high-fat diets.
  – Results:
    • Plasma EPA+DHA w/ Omefas 4x > vs O3AEE on low-fat diet (also > on high-fat)
    • EPA w/ Omefas 13x >:

Omefas (Epanova) Update—cont.

• EVOLVE (Nov 2012)
  – Design: N=399 TG 500-2000 mg/dL on 2, 3, or 4 g/d Omefas vs 4 g/d olive oil (control) x 12 wks
  – Results:
    • TG ↓26% at 2 g/d and ↓31% at 4 g/d
    • Non-HDL-C ↓8% at 2 g/d and ↓16% at 4 g/d
    • Apo C-III ↓11% at 2 g/d and ↓14% at 4 g/d
    • Some mild GI Sx

• ESPRIT
  – Design: N=647 “HTG” statin-Rx, Omefas 2 g/d vs 4 g/d vs Olive oil 4 g/d x 6 wks
  – Results:
    • TG ↓15% at 2 g/d, ↓21% at 4 g/d
    • Non-HDL-C ↓4% at 2 g/d, ↓7% at 4 g/d
    • LDL-C ↑5% at 2 g/d, ↑1% at 4 g/d
    • Apo C-III ↓8% at 2 g/d, ↓13% at 4 g/d

Lipid Update 2013: Summary

• New concerns re: statins
• New statin adjuncts/alternatives (to ↓LDL-C)
• New HDL controversies:
  – Relationship of HDL with athero & CVD
  – New observational and clinical trial data
  – Ongoing development of HDL-raising meds
• New TG developments:
  – Appreciation for High TG epi. & mech.
  – New omega-3 approved
  – Another omega-3 in late-stage phase 3
• Still OK to consider HDL & TG Rx as statin adjunct or alternative (statin intolerant)