Wise Lipid Management: State of the Art 2013

ACP Utah Chapter Annual Meeting
University of Utah Alumni Hall
September 27, 2013

Eliot A. Brinton, MD, FAHA, FNLA
President, American Board of Clinical Lipidology
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
President, Utah Lipid Center
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Management of Common Dyslipidemias for Practicing Internists

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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, Atherotech, Daiichi-Sankyo, Essentialis, Kowa, Merck, Novartis, Takeda
- Honoraria as **speaker:** Abbott, Amarin, Daiichi-Sankyo, Kowa, Merck, Takeda

**Talk Outline**

- **LDL/Non-HDL Lowering**
  - Statins
    - adverse effects (myopathy & DM)
    - compliance
    - “ATP-IV” Guidelines—when?
- **HDL Raising**
  - Clinical trial data
  - HDL hypothesis update
  - Fibrates vs Niacin vs Omega-3
- **TG (& Non-HDL) Lowering**
  - Clinical trial data
  - Fibrates vs Niacin vs Omega-3
Management of High LDL/Non-HDL


<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Factors</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>CVD/DM+MRF?</td>
<td>&lt;70*</td>
</tr>
<tr>
<td>High</td>
<td>CHD RE;FRS&gt;20%</td>
<td>&lt;100*</td>
</tr>
<tr>
<td>Moderate</td>
<td>FRS 10-20%</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Lower</td>
<td>0-1 Risk Factors</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

• In High and Very High Risk categories
  – Consider statin Rx even if already at goal
  – Consider combination Rx—statin + fibrate or niacin—if TG>200+NHDL-C>130 or if HDL-C<40

• Statin Rx for 30-40% ↓ LDL-C (R-5, A-10, S-20, F,L,P-40) in ≥ mod. high risk vs. don’t use lower doses
• 65-80 yo: 2° prev as younger; 1° prev+DM=high risk; other, use clinical judgment

• Non-HDL-C: use if TG>200; goal as LDL-C+30

*Therapeutic option: use clinical judgment (‘04)/Reasonable target (‘06)

Statin-Based LDL-C Lowering

Mean baseline LDL-C: 187 mg/dL to 194 mg/dL

*P<0.001 rosuvastatin vs atorvastatin 10 mg; simvastatin 10 mg, 20 mg, 40 mg; pravastatin 10 mg, 20 mg, 40 mg.
†P<0.002 rosuvastatin vs atorvastatin 20 mg, 40 mg; simvastatin 20 mg, 40 mg, 80 mg; pravastatin 20 mg, 40 mg.
‡P<0.001 rosuvastatin vs atorvastatin 40 mg; simvastatin 40 mg, 80 mg; pravastatin 40 mg.


Generics adequate for ~all cases
Statin Update

• Myopathy:
  – New internet-based survey
  – Continued work on causes & Rx (high-dose CoQ 10?)
• 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%

Do Statins Increase New-Onset DM-2?

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

**But Favorable Risk/Benefit Ratio**
- 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 new DM (>3:1 hi v low-dose)

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


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New Cholesterol Guidelines

- NCEP ATP-III 2001 & ’04 (9-12 years old); many new studies/approved agents since
- Update effort:
  - NHLBI directed multi-yr panel, re-branded as “evidence review”
  - NHLBI-AHA-ACC guideline partnership likely similar to/update of ATP-III
- Predictions
  - Lifetime risk (over 10-y Framingham Risk Score)
  - Increased emphasis on Non-HDL-C
  - Subclinical athero imaging? (separate guidelines)
  - Release late 2014?
Non-HDL Includes All Atherogenic Lipoprotein Classes

- **Very low-density lipoprotein**
  - Made in the liver
  - TG >> CE
  - Carries lipids from the liver to peripheral tissues

- **Intermediate-density lipoprotein**
  - Formed from VLDL due to loss of TG
  - Also known as a VLDL remnant

- **Low-density lipoprotein**
  - Formed from IDL due to loss of TG
  - CE >> TG

- **Lipoprotein (a)**
  - Formed from LDL w/ addition of apo (a)?
  - Very atherogenic

- **High-density lipoprotein**
  - Removes cholesterol from peripheral tissues
**LDL-C Doubly Underestimates CVD Risk in Cases of Small, Dense LDL**

Large LDL
- Apo B
- Cholesterol Ester (CE)
- Fewer Particles & Less Risk/Particle

Small, Dense LDL
- More Apo B
- Less CE/particle so more particles

Lipid profile:
- TC: 198 mg/dL
- LDL-C: 130 mg/dL
- TG: 90 mg/dL
- HDL-C: 50 mg/dL
- Non–HDL-C: 148 mg/dL

Lipid profile:
- TC: 210 mg/dL
- LDL-C: 130 mg/dL
- TG: 250 mg/dL
- HDL-C: 30 mg/dL
- Non–HDL-C: 180 mg/dL

*After Otvos JD, et al. Am J Cardiol. 2002;90:22i-29i*

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**Coronary Heart Disease Risk by Non-HDL-C Quintiles**

Hazard Ratio

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

Non-HDL-C by levels of HDL-C

Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk


CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; NEPTUNE=National Cholesterol Education Program Evaluation ProjecT Utilizing Novel E-Technology; RE=risk equivalent.


Half of Patients Below LDL-C Goal are Above Non-HDL-C Goal

Percentage of patients with triglyceride levels of ≥200 mg/dL achieving treatment goals

- Achieved LDL-C Goal
- Achieved LDL-C and Non–HDL-C Goal

<table>
<thead>
<tr>
<th>Category</th>
<th>LDL-C Goal</th>
<th>Non–HDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 Risk Factor (n=163)</td>
<td>78%</td>
<td>64%</td>
</tr>
<tr>
<td>≥2 Risk Factors (n=340)</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>CHD + CHD RE (n=728)</td>
<td>52%</td>
<td>52%</td>
</tr>
<tr>
<td>CHD (n=320)</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Diabetes (no CHD) (n=308)</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Other CHD RE (no CHD) (n=100)</td>
<td>25%</td>
<td>44%</td>
</tr>
<tr>
<td>CHD + CHD RE (n=728)</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>Achieved LDL-C Goal</td>
<td>78%</td>
<td>64%</td>
</tr>
<tr>
<td>Achieved LDL-C and Non–HDL-C Goal</td>
<td>71%</td>
<td>71%</td>
</tr>
</tbody>
</table>
Non-HDL-C: A Neglected CVD Risk Factor/Rx Goal

Whenever TG > 200 mg/dL:
1. Non-HDL-C = Total C – HDL-C (all atherogenic lip)
2. Non-HDL-C goal = LDL-C goal + 30:

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Non–HDL-C Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD/DM+MRF?</td>
<td>&lt;70</td>
<td>&lt;100</td>
</tr>
<tr>
<td>FRS &gt;20%, CHD-RE</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>FRS 5-20, 2+ RFs</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>No CHD, 0-1 risk factors</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>

Rx to lower Non–HDL-C:
- TG >500: fibr, P-Om3, NA, statin
- TG 200-500: statin, ezet, Fibr, P-Om3, NA, BAS
- TG < 200: statin, ezet, BAS


LDL-C vs. Non-HDL-C

<table>
<thead>
<tr>
<th>Favoring LDL-C</th>
<th>Favoring Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus of most research</td>
<td>Always measured in lipid profile (free)</td>
</tr>
<tr>
<td>Focus of current guidelines</td>
<td>Avoids artifact of Friedewald calculation</td>
</tr>
<tr>
<td>Always reported in lipid profile</td>
<td>Mechanistically better (all pro-athero lipos)</td>
</tr>
<tr>
<td></td>
<td>Stronger CVD factor</td>
</tr>
<tr>
<td></td>
<td>Valid in HTG</td>
</tr>
<tr>
<td></td>
<td>Valid non-fasting</td>
</tr>
</tbody>
</table>

Bottom line: Non-HDL-C is much better; LDL-C w/o unique adv. but we are stuck with it!
LDL-Related Advanced Testing: Non-HDL-C vs. Apo B

Favoring Non-HDL-C
- Cholesterol content conceptually better (causal role)
- Free with lipid profile (no extra testing needed)
- Well standardized
- Already incorporated in guidelines

Favoring Apo B/LDL-P
- Apo B may play causal athero role
- Fairly well standardized
- Stronger CVD factor (some dyslipidemias)
- Complementary to non-HDL-C?

Bottom line: Non-HDL-C usually adequate
Apo B/LDL-P sometimes useful adjuncts

Isn’t Statin Monotherapy Enough?
High Residual CVD Risk w/ Statin MonoRx

Majority of CHD Events Still Occur in Patients Treated with Statins

![Graph showing the percentage of patients experiencing major CHD events with and without statin therapy.]


Intensive Statin Therapy:
Residual CVD Risk is less, but Still Too High

Statistically significant, but clinically inadequate CVD reduction

![Graph showing the percentage of patients experiencing major CVD events with standard and intensive statin therapy.]

- PROVE IT-TIMI 22: Statin 22.4% vs. Placebo 20.4%
- IDEAL: Statin 12.6% vs. Placebo 13.7%
- TNT: Statin 8.7% vs. Placebo 10.4%

*Mean or median LDL-C after treatment.

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Limitations of Statins in Dyslipidemia & Atheroprevention

Need for Statin Adjuncts
- Incomplete CVD prevention
- Residual dyslipidemia
  - Inadequate LDL-C lowering
  - Residual high TG, low HDL, etc)

Need for Statin Alternatives
- Statin intolerance
- Statin phobia
Which other Rx?
- Non-statin lipid agents (x 5 + 2)
- Other Rx (anti-plt good; BP? & DM?)

Statin Adjuncts/Alternatives: LDL/Non-HDL

- CAI
- BAS
- Niacin (much less practical)
- (Fenofibrate)
- Rx Omega-3 (only pure EPA)
**Trial of ↓CVD with Ezetimibe: IMPROVE-IT**

- N = ~18,000
- Rx: Statin alone vs Statin + ezetimibe
- On-Rx LDL-C: 66 vs 52 mg/dL
- Original CVD event goal: 5250
- Study end 2013 (per DSMB)
- Prolonged continuation of trial suggests
  - No overwhelming benefit, but also
  - No futility (obvious lack of benefit)
- Expected CVD endpoint results:
  - Statistically positive CVD benefit?
  - Beneficial trend but not statistically signif.?

**BAS vs CAI**

**Cons**
- Less ↓LDL-C/Non-HDL-C, and
- ↑TG, and
- Harder to take
  - GI Sx
  - More/larger tablets vs. suspension
  - Drug absorption issues, but

**Pros**
- ↓A1c
- ↓CVD evidence (old monoRx trial LRC-CPPT)
Statin Adjuncts/Alternatives:
for TG / HDL

• (CAI)
• (BAS—adverse for TG)
• Niacin
• Fenofibrate
• Rx Omega-3 (EPA poor for HDL)
• (Pioglitazone—best insulin sensitizer, PROactive suggests ↓CVD)*


CVD Effects of Low HDL-C, HDL-Raising Update
Low HDL-C Predicts Residual CVD Risk *After* Optimal Statin Rx

LDL-C ≤70 mg/dL on statin\(^a,b\) (Treating to New Targets (TNT) Study)

![Graph showing 5-Year Risk of Major CVD Events, % for different HDL-C Quintiles](image)

- **HR vs Q1\(^*\)**: 0.85, 0.57, 0.55, 0.61

\(^a\)On-treatment level (3 months statin therapy); \(n = 2661\)

\(^b\)Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL

\(^*\)\(P=0.03\) for differences among quintiles of HDL-C


Coronary Heart Disease Risk by Non-HDL-C and HDL-C Quintiles

![Graph showing Hazard Ratio and Usual Mean Non-HDL-C Level, mg/dL](image)

High CVD Risk in Patients with Low HDL-C

- Average HDL-C in CCU pts 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\(^4\)


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?)
- Hypothesis: low-HDL-C ≈↑CVD only when ↑TG/remnants?
Clinical Trials of HDL-Raising Medications: Update

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment nN</th>
<th>Control nN</th>
<th>Peto OR 95% CI</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER-6-HALTS</td>
<td>2/187</td>
<td>9/176</td>
<td>0.25 [0.08, 0.94]</td>
<td></td>
</tr>
<tr>
<td>Guyton JR et al</td>
<td>1/676</td>
<td>2/272</td>
<td>0.16 [0.01, 1.90]</td>
<td></td>
</tr>
<tr>
<td>AFREGS</td>
<td>1/71</td>
<td>2/72</td>
<td>0.52 [0.05, 5.04]</td>
<td></td>
</tr>
<tr>
<td>ARBITER-2</td>
<td>3/87</td>
<td>7/80</td>
<td>0.39 [0.11, 1.40]</td>
<td></td>
</tr>
<tr>
<td>HATS</td>
<td>1/38</td>
<td>12/38</td>
<td>0.13 [0.04, 0.44]</td>
<td></td>
</tr>
<tr>
<td>UCSF_SCOR</td>
<td>0/48</td>
<td>1/49</td>
<td>0.14 [0.00, 6.96]</td>
<td></td>
</tr>
<tr>
<td>FATS</td>
<td>2/48</td>
<td>10/52</td>
<td>0.24 [0.07, 0.81]</td>
<td></td>
</tr>
<tr>
<td>STOCKHOLM</td>
<td>72/279</td>
<td>104/276</td>
<td>0.59 [0.41, 0.84]</td>
<td></td>
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<tr>
<td>CLAS</td>
<td>17/94</td>
<td>21/94</td>
<td>0.77 [0.38, 1.56]</td>
<td></td>
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<tr>
<td>CDP</td>
<td>914/1119</td>
<td>2333/2789</td>
<td>0.87 [0.72, 1.05]</td>
<td></td>
</tr>
</tbody>
</table>

Total
Test for heterogeneity: P = 0.009, I² = 59.2%
Test for overall effect: P < 0.0001

Subtotal excluding CDP

0.49 [0.37, 0.65]

AIM-HIGH — Results
Primary Outcome

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

- Risk ratio 0.96 (95% CI 0.90 – 1.03)
- Logrank P = 0.29

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P = 0.29

Placebo
ERN/LRPT
### Major Vascular Events by Age, Sex, Region and Statin-Based Therapy

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt; 65</th>
<th>≥ 65 &lt; 70</th>
<th>≥ 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>786</td>
<td>367</td>
<td>605</td>
</tr>
<tr>
<td>ERN/LRPT</td>
<td>740</td>
<td>392</td>
<td>564</td>
</tr>
<tr>
<td>Risk ratio</td>
<td>1.14</td>
<td>1.09</td>
<td>1.10</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.94, 1.37)</td>
<td>(0.89, 1.31)</td>
<td>(1.00, 1.26)</td>
</tr>
<tr>
<td>Het or trend</td>
<td>χ² (uncorrected p value)</td>
<td>0.00 (p = 0.98)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1397</td>
<td>299</td>
</tr>
<tr>
<td>ERN/LRPT</td>
<td>1397</td>
<td>299</td>
</tr>
<tr>
<td>Risk ratio</td>
<td>1.15</td>
<td>1.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.94, 1.39)</td>
<td>(0.91, 1.54)</td>
</tr>
<tr>
<td>Het or trend</td>
<td>χ² (uncorrected p value)</td>
<td>0.21 (p = 0.68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Europe</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>813</td>
<td>845</td>
</tr>
<tr>
<td>ERN/LRPT</td>
<td>832</td>
<td>864</td>
</tr>
<tr>
<td>Risk ratio</td>
<td>1.03</td>
<td>1.06</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.86, 1.23)</td>
<td>(0.92, 1.22)</td>
</tr>
<tr>
<td>Het or trend</td>
<td>χ² (uncorrected p value)</td>
<td>0.07 (p = 0.07)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statin-based therapy</th>
<th>Simvastatin 40mg</th>
<th>Ezetimibe/simvastatin</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>949</td>
<td>809</td>
<td>1758</td>
</tr>
<tr>
<td>ERN/LRPT</td>
<td>945</td>
<td>813</td>
<td>1696</td>
</tr>
<tr>
<td>Risk ratio</td>
<td>0.97</td>
<td>1.28</td>
<td>1.04</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.80, 1.17)</td>
<td>(0.91, 1.47)</td>
<td>(1.00, 1.09)</td>
</tr>
<tr>
<td>Het or trend</td>
<td>χ² (uncorrected p value)</td>
<td>0.26 (p = 0.66)</td>
<td></td>
</tr>
</tbody>
</table>

### Major Vascular Events by Baseline Lipids

<table>
<thead>
<tr>
<th>mg/dL (mmol/L)</th>
<th>HDL cholesterol</th>
<th>LDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 (0.9)</td>
<td>388 (15.8%)</td>
<td>724 (14.7%)</td>
<td>541 (13.2%)</td>
</tr>
<tr>
<td>≥35 &lt;43</td>
<td>560 (13.7%)</td>
<td>685 (12.4%)</td>
<td>694 (12.8%)</td>
</tr>
<tr>
<td>≥43 (1.1)</td>
<td>748 (11.9%)</td>
<td>287 (12.0%)</td>
<td>461 (13.9%)</td>
</tr>
</tbody>
</table>

**HDL cholesterol**

- <35 (0.9) | 388 (15.8%) | 399 (16.3%) | 0.20 (p = 0.66)
- ≥35 <43 | 560 (13.7%) | 546 (13.5%) |
- ≥43 (1.1) | 748 (11.9%) | 813 (12.8%) |

**LDL cholesterol**

- <58 (1.5) | 724 (14.7%) | 679 (13.8%) | 5.91 (p = 0.02)
- ≥58 <77 | 685 (12.4%) | 761 (13.7%) |
- ≥77 (2.0) | 287 (12.0%) | 318 (13.5%) |

**Triglycerides**

- <89 (1.0) | 541 (13.2%) | 563 (13.4%) | 0.66 (p = 0.42)
- ≥89 <151 | 694 (12.8%) | 712 (13.2%) |
- ≥151 (1.7) | 461 (13.9%) | 483 (14.8%) |

**All** | 1696 (13.2%) | 1758 (13.7%) | 3.5% SE 3.3 reduction
Niacin and CVD: Summary

- Monotherapy benefit *not* proven as statin adjunct, *but*:
- AIM-HIGH: ↓CVD in HTG/low HDL-C(?)
- HPS-2/THRIVE:
  - Benefit if given longer than ~4 years?
  - Benefit in Caucasians?
  - Benefit if LDL-C > 58?
  - Benefit in HTG/low HDL-C???
  - Harm mainly related to laropiprant?
- Re-consider diet-supplement niacin?
  - IR if flushing tolerated
  - SR if no ↑ALT

Revisiting the HDL Hypothesis

**Con**
- Recent trials of HDL-raising have been neutral
- Genetic isolated ∆HDL-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
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) in
Revisiting the HDL Hypothesis

**Con**
- Recent trials of HDL-raising have been neutral
- Genetic isolated ∆HDL-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) 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 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 ↑chylos not related to ↑CVD
- TG accumulation not seen in atherosclerotic plaque
- TG-lowering drugs not completely proven to ↓CVD

**Pro**
- TG-rich lipos are atherogenic (esp. chol-rich remnants)
- TG lipolysis by LPL → pro-inflammatory FFA (uptake by CD36 and FA binding proteins to nucleus)
- 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>Duration of Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 years</td>
<td>5902</td>
<td>1.72 (95% CI, 1.56-1.90)</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>4256</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7728</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Fasting Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>7484</td>
<td></td>
</tr>
<tr>
<td>Nonfasting</td>
<td>2674</td>
<td></td>
</tr>
<tr>
<td>Adjusted for HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4469</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5689</td>
<td>1.72 (95% CI, 1.56-1.90)</td>
</tr>
</tbody>
</table>

*Individuals in top vs bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and (in most studies) blood pressure.


N=262,525.

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.

N = 4162

Three Atherogenic Consequences of Hypertriglyceridemia

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

“Atherogenic Dyslip.”
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

<table>
<thead>
<tr>
<th>A Subjects with Dyslipidemia</th>
<th>B Subjects without Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>ACCORD</td>
<td></td>
</tr>
<tr>
<td>FIELD</td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td></td>
</tr>
<tr>
<td>VA–HIT</td>
<td></td>
</tr>
</tbody>
</table>

Summary: 0.65 (0.54–0.78)
Summary: 0.94 (0.84–1.05)

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

Fibrates and CVD: Summary

• Appear to decrease CVD in HTG/low HDL-C pts (VA-FIT study needed!)
• May bring microvascular benefit (↓ DM retinopathy and amputation)
• Don’t impair glucose metabolism
• Well-tolerated, safe (no renal harm)

Statin + EPA/DHA: COMBOS Lipid Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Non-HDL-C</th>
<th>TG</th>
<th>VLDL-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-OM3 4 g/d + simvastatin 40 mg/d</td>
<td>-9.0*</td>
<td>-29.5*</td>
<td>-27.5*</td>
<td>-2.8</td>
<td>-1.2</td>
<td>-4.2†</td>
</tr>
<tr>
<td>Placebo + simvastatin 40 mg/d</td>
<td>-2.2</td>
<td>-6.3</td>
<td>-7.2</td>
<td>0.7‡</td>
<td>-1.9</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

*P<0.0001 between groups; †P=0.0232 between groups; ‡P=0.0522 between groups.

TG 200-500 baseline on statin.

Omega-3 acid ethyl esters.

Statin + EPA:
ANCHOR Lipid Endpoints

<table>
<thead>
<tr>
<th>Medial Placebo-adjusted Change (%)</th>
<th>TG</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-21.5</strong>*</td>
<td>265</td>
<td>128</td>
<td>93</td>
<td>82</td>
<td>37</td>
<td>4 g/day</td>
</tr>
<tr>
<td><strong>-10.1</strong>*</td>
<td>254</td>
<td>128</td>
<td>91</td>
<td>82</td>
<td>38</td>
<td>2 g/day</td>
</tr>
<tr>
<td><strong>-13.6</strong>**</td>
<td>-10.1*</td>
<td>-5.5**</td>
<td>-3.8*</td>
<td>-2.2**</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>-9.3</strong>*</td>
<td></td>
<td>-13.6****</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>-6.2</strong></td>
<td></td>
<td></td>
<td><strong>-3.6</strong></td>
<td><strong>-4.5</strong></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>-3.8</strong></td>
<td></td>
<td></td>
<td><strong>-3.6</strong></td>
<td><strong>-4.5</strong></td>
<td>NS</td>
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<td>NS</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td></td>
<td></td>
<td><strong>-3.6</strong></td>
<td><strong>-4.5</strong></td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

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

**P<0.0001; ***P<0.001; **P<0.01; *P<0.05;
NS = not significant (P≥0.05), icosapent ethyl vs placebo

**Bottom line: EPA/DHA likely 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.

JELIS: 19% ↓Major Coronary Events with Om-3 Added to Statins

Control

EPA

Pure EPA 1.8 g/d

HR (95% CI): 0.81 (0.69–0.95)
P=0.011

-19%

No. at Risk
0 1 2 3 4 5 Years
Control 9319 8931 8671 8433 8192 7958
EPA 9326 8929 8658 8389 8153 7924
JELIS Patient Subgroup
TG >150 & HDL-C <40 mg/dL

Effects of EPA on CAD in HTG patients with multiple risk factors: Sub-analysis of primary prevention cases from the JELIS Study

Effects of EPA on the incidence of major coronary events for the high TG / low HDL-C group
HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

Selected Om-3 CVD Outcome Studies

<table>
<thead>
<tr>
<th>Om-3 Type/dose</th>
<th>GISSI-P1,2</th>
<th>ORIGIN3</th>
<th>JELIS4</th>
<th>REDUCE-IT5 (Ongoing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Italian</td>
<td>International</td>
<td>Japanese</td>
<td>International</td>
</tr>
<tr>
<td>N</td>
<td>11,324</td>
<td>12,536</td>
<td>18,645</td>
<td>~8,000</td>
</tr>
<tr>
<td>Gender</td>
<td>85% male</td>
<td>65% male</td>
<td>31% male</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>Risk Profile</td>
<td>Recent MI (≤3 mos; median 10 days)</td>
<td>High CV risk, and IFG, IGT, or T2DM</td>
<td>80% T1 prev; TC ≥6.5 mM; excl MI 1≤6 mos prior</td>
<td>TG &gt;150 mg/dL, +CHD or +GHD risk</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3.5 years</td>
<td>6.2 years (median)</td>
<td>4.6 years (mean)</td>
<td>4–6 years (planned)</td>
</tr>
<tr>
<td>Statin Use</td>
<td>Minimal</td>
<td>53% in n-3 FA arm, 55% in pbo arm</td>
<td>All on statins (simva or pravastatin)</td>
<td>All on background statins (LDL-&lt;2 goal)</td>
</tr>
<tr>
<td>Primary End Point</td>
<td>All-cause death, non-fatal MI, NF stroke</td>
<td>Death from CV causes</td>
<td>MACE</td>
<td>MACE</td>
</tr>
<tr>
<td>Result</td>
<td>RRR 10% (P=0.048)/15% (P=0.023)</td>
<td>HR=0.98 P=0.72</td>
<td>RRR 19% (no minimum TG level) P=0.011</td>
<td>Powered for 15% RRR</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↓2%–3% &gt;control groups</td>
<td>↓12% both arms</td>
<td>↓25% in both groups</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: Trial designs differ so results can not be directly compared.

excl=excluded; GISSI= Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocondrico; IFG= impaired fasting glucose; IGT= impaired glucose tolerance; MACE= major adverse cardiac event; mos=months; ORIGIN=Outcome Reduction with an Initial Glargine Intervention; pbo=placebo; prev=prevention; REDUCE-IT=Reduction of Cardiovascular Events with EPA-Intervention Trial; RR=relative risk; RRR=relative risk reduction.
Lipid Update 2013: Summary

• New concerns re: statins (but still v. good)
• New HDL controversies:
  – Relationship of HDL with athero & CVD
  – New observational and clinical trial data
• New TG developments:
  – Appreciation for High TG epi. & mech.
  – New TG-lowering medication
• Please “consider” Rx HTG/Low HDL-C
• Please refer (sooner) to a lipidologist for:
  – Severe hypercholesterol. (apher x2, meds x2)
  – Severe hypertriglyceridemia (new med x 1)