Consensus and Controversy in Diabetes and Dyslipidemia

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CVD Outcomes in DM vs non-DM

102 Prospective studies, 698, 782 people, 8.5 million person-yr of follow-up

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>70 (5%)</td>
<td>23 (2%)</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>113 (9%)</td>
<td>56 (4%)</td>
</tr>
<tr>
<td>Stroke subtypes</td>
<td>47 (4%)</td>
<td>22 (2%)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>12 (1%)</td>
<td>6 (0.5%)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Undifferentiated stroke</td>
<td>15 (1%)</td>
<td>7 (0.6%)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>2 (0.2%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>


Supremacy of Statins in CVD Risk Reduction
HPS: Major Vascular Events by LDL Cholesterol

<table>
<thead>
<tr>
<th>Lipid Levels at Entry</th>
<th>Simvastatin (14,269)</th>
<th>Placebo (16,287)</th>
<th>STATIN Better</th>
<th>PLACEMBO Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>282 (16.4%)</td>
<td>358 (21.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100 &lt; 130</td>
<td>668 (18.9%)</td>
<td>871 (24.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 130</td>
<td>1083 (21.6%)</td>
<td>1356 (26.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


LDL-C : Less is More


CTT: Meta-analysis of 26 Statin Trials


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Is there a point of No-Return?

SHARP: Major Atherosclerotic Events by renal status at randomization

<table>
<thead>
<tr>
<th>Group</th>
<th>Eey/ine (n=3907)</th>
<th>Placebo (n=4020)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis (n=8247)</td>
<td>296 (9.5%)</td>
<td>379 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>529 (11.5%)</td>
<td>829 (13.4%)</td>
<td>16.9% Δ 5.4 reduction (p=0.0022)</td>
</tr>
</tbody>
</table>

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

23% had diabetes: same outcome

~ 10-15% of patients have significant myalgia with statins, most with dose escalation

Underlying Mechanism(s)?
**Simvastatin and Myopathy**

Simvastatin allocation (per 1000 person-years)

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>80 mg (6031)</th>
<th>20 mg (8033)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>25 (4.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>2-7</td>
<td>28 (0.8)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>3</td>
</tr>
</tbody>
</table>

Myopathy: New, unexplained muscle pain or weakness plus CK>15xULN (vs 0 developed rhabdomyolysis)

**AHA, 2008**

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**SLCO1B1 Variants and Statin-Induced Myopathy — A Genome-Wide Study**

Myopathy Associated with 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype

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**Auditon Response Question 1**

Recent meta-analysis of clinical trials have shown an increased risk of diabetes. How high is the approximate risk?

- A. 5%
- B. 10%
- C. 15%
- D. 20%
Statins and Incident diabetes

Significant correlation with age (p=0.02), not with BMI or LDL reduction

Sattar, N et al  Lancet 2010; 375: 735-742

To put it in Perspective:

- Incidence of Diabetes with statin therapy:
  ~1 new case per 200 persons treated over 5 years

- Incidence of Major Cardiovascular Event
  ~ 5 new events prevented per 200 persons treated over 5 years

LDL-C-Lowering Drugs

- Drugs reducing cholesterol synthesis
  - HMG CoA reductase inhibitors: statins (preferred)
    - LDL-C reduction up to 60%
    - Latest addition: pitavastatin

- Drugs reducing cholesterol absorption
  - Bile acid sequestrants (BAS)
    - Colesevelam, cholestyramine, colestipol
      - Bind to bile acids > increase excretion of cholesterol
      - LDL-C reduction 15-25%; TG may rise
    - Cholesterol transport inhibitor
      - Ezetimibe; binds to intestinal cholesterol transporter
      - LDL-C reduction ~15-20%
Potential LDL Lowering Agents

- Anti-sense apoB synthesis inhibitor: Mipomersen
  ~ 30% reduction in LDL-C in patients with FH
  (Baseline LDL-C: >300 mg/dl)
- MTP-1 Inhibitors: Lomitapide
  : Inhibits assembly of all Apo-B lipoproteins
- PCSK-9 Inhibitors: Several in trials
  : Prevents degradation of LDL receptors

PCSK9: A Novel Target for LDL

Effect of PCSK9 antibody (AMG-145), add-on to statin +/- Eze on LDL-C

Baseline LDL-C ~ 125 mg/dl

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How to deal with the Residual Risk of CVD after achieving LDL-C Goal?

Patients with Diabetes Have High Residual CVD Risk After Statin Treatment

<table>
<thead>
<tr>
<th>Event Rate (No Diabetes)</th>
<th>Event Rate (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Statin</td>
<td>On Placebo</td>
</tr>
<tr>
<td>HPS* (CHD patients)</td>
<td>19.8%</td>
</tr>
<tr>
<td>CARE†</td>
<td>19.4%</td>
</tr>
<tr>
<td>LIPID‡</td>
<td>11.7%</td>
</tr>
<tr>
<td>PROSPER§</td>
<td>13.1%</td>
</tr>
<tr>
<td>ASCOT-LLA¶</td>
<td>4.9%</td>
</tr>
<tr>
<td>TNT</td>
<td></td>
</tr>
</tbody>
</table>

* CHD death, nonfatal MI, stroke, revascularizations
† CHD death, nonfatal MI, CABG, PTCA
‡ CHD death and nonfatal MI
§ CHD death, nonfatal MI, stroke
¶ CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg vs 10 mg atorvastatin)

Mechanisms Relating Insulin Resistance and Dyslipidemia

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ATPIII: Recommendations for Non-HDL-C

If Triglyceride 200 -499 mg/dL:

Non-HDL-C (total C minus HDL) is a secondary target of therapy with a goal of 30 mg/dL higher than the LDL goal.


ADA/ACC Consensus Statement

"...In patients with Cardio-metabolic Risk, we recommend guiding therapy with apo-B measurements, and treatment to apo-B goals, in addition to LDL-C and non-HDL-C assessment.*

<table>
<thead>
<tr>
<th>TREATMENT GOALS</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-risk patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Including those with 1) Known CVD or 2) Diabetes plus one or more additional CVD risk factor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
<td></td>
</tr>
<tr>
<td>High-risk patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Including those with 1) No diabetes or known clinical CVD but 2 or more additional major CVD risk factors or 2) Diabetes but no other CVD risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
<td></td>
</tr>
</tbody>
</table>

*Smoking, HBP, f/h premature CHD


Discordance between non-HDL-C, and Apo-B

<table>
<thead>
<tr>
<th>Non-HDL-C</th>
<th>Apo-B &lt; 90 mg/dl</th>
<th>Apo-B ≥ 90 mg/dl</th>
<th>Discordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 130 mg/dl</td>
<td>734</td>
<td>607</td>
<td>127</td>
</tr>
<tr>
<td>≥ 130 mg/dl</td>
<td>696</td>
<td>95</td>
<td>601</td>
</tr>
</tbody>
</table>


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Effect of Lowering Triglycerides (with Fibrates) in Reducing Residual Risk?

NHANES Circ 2011; 123: 2292-2333

TG > 200 mg/dl: ~35% Prevalence in Adults with Diabetes

NHANES, 1999-2002

Recommendation...Up to 50% reduction in TG levels by intensive lifestyle measures, including reduction in sucrose and fructose.


n=5518
Mean f/u: 4.7 yr
Adherence ~80%
No Rhabdo.
CR > 7.5: 0.8 vs 0.3%
ALT > 3x: 1.9 vs 1.5%

ACCORD: Lipid Results

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Algorithm for Dyslipidemia Assessment and Management

Order lipid profile:

LDL-C > 100 mg/dL
- Lifestyle = Statin Rx
- Goal: LDL-C < 100 mg/dL.
- CVD-yes
- CVD-no

LDL-C > 70 mg/dL, TG > 200 mg/dL/2
- Measure Apo B
- Non-HDL-C ≥ 100 mg/dL or Apo B > 80 mg/dL.
- Intensify LDL Rx; may need fibrate or niacin

LDL-C < 70 mg/dL, TG > 500 mg/dL
- Treatment: Lifestyle + Statin Rx
- Goal: LDL-C < 100 mg/dL.
- Treat TG ≥ 500 mg/dL.
- Fibrates and/or fish oil if > 1000 mg/dL

LDL-C < 70 mg/dL, TG < 500 mg/dL
- CVD-yes
- CVD-no

Lifestyle + Statin Rx
- LDL-C < 100 mg/dL


* 130 mg/dL if fasting.
Origin and Metabolic Fate of HDL

Putative Mechanisms Mediating the Anti-Atherogenic Effects of HDL-C

- Reverse cholesterol transport
- Antioxidant effects
- Inhibition of adhesion molecule expression
- Inhibition of platelet activation
- Prostacyclin stabilization
- Promotion of NO production
- Association with increased adiponectin

Audience Response Question 2

Is HDL-C an important determinant of CVD events in patients with LDL-C < 70 mg/dL

A. Yes
B. No
C. Maybe
Lipid Changes and Outcomes

<table>
<thead>
<tr>
<th>Placebo + Statin</th>
<th>Niacin + Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30 months</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>50</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>152</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>110.3 ± 26.0</td>
</tr>
</tbody>
</table>

Primary and composite end point: Death from CHD, non-fatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebrovascular recascularization

- Placebo + Statin: 16.2%
- Niacin + Statin: 16.4%

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

n=25,673

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

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

Occurrence of serious adverse events in HPS2-THRIVE

Note: RR = relative risk
Source: Dr. Armage, ACC, 2013

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Potential HDL Therapies Saga

- Cholesterol ester transfer protein (CETP) inhibitors (Torcetrapib, Dalcetrapib, Anacetrapib)
- APO A-1 mimetic agents
- PPAR-\(\gamma\)/\(\alpha\) - dual agonists (Muraglitazar, Tesaglitazar, Aleglitazar)
- MK-0524A: ER Niacin + DP-1 receptor antagonist (Laropiprant) - Tredaptive

Inflammatory Pathways underlying Plaque Rupture and Thrombosis

Libby, P. *NEJM* 2013; 368: 2004-2013

- LP-PLA-2 Inhibitor: Darapladib (SOLID-TIMI-52)
- IL-1-\(\beta\) antibody: Canakinumab Trial (CANTOS)
- Low dose Methotrexate (CIRT)
Thank You!