Treating Dyslipidemia: An Evolving Paradigm

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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

Multivariate adjusted

Inflammation in Coronary Artery in Patients With Sudden Coronary Death

Type 1=16, Type 2=50, NDM = 66 matched for age, gender, race

Hyperlipidemia = Total-C >200 mg/dL or TC/HDL-C ratio >5

Supremacy of Statins in CVD Risk Reduction

HPS: Major Vascular Events by LDL Cholesterol

Risk ratio and 95% CI

Major Vascular Events with or without Diabetes: Effect per 40-mg/dL Reduction in LDL-C

14 RCTs
15,586 with DM
71,570 without DM

No differences by presence or absence of vascular disease, other risk factors, or baseline lipid levels

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Joslin Diabetes Center  
Primary Care Congress for Cardiometabolic Health 2013  
Treating Dyslipidemia: An Evolving Paradigm

**LDL-C: Less is More**

- Grundy, S. et al., Circulation 2004;110:197-198

**CTT: Meta-analysis of 26 Statin Trials**

Grundy, S. et al., Circulation 2004;110:227-239

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**Is there a point of No-Return?**

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

  **Underlying Mechanism(s)?**

- FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for simvastatin to reduce the risk of muscle injury

  **FDA Drug Safety Communication:** New restrictions, contraindications, and dose limitations for simvastatin to reduce the risk of muscle injury

  **Intending Drug** | **Updated Label**
  --- | ---
  Strong CYP3A4 inhibitors | Use with simvastatin is contraindicated
  Erythromycin, troleandomycin, ketoconazole, clarithromycin, nefazodone, HMG-CoA reductase inhibitors | Use with simvastatin is contraindicated
  Lovastatin, simvastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, fenofibrate | Use with simvastatin is contraindicated
  Amiodarone, verapamil, diltiazem | Do not exceed 10mg of simvastatin daily
  Antihypertensives, ranolazine | Do not exceed 10mg of simvastatin daily

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Audience 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

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

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

JUPITER: Diabetes and CVD Incidence

Risk Factors for DM: Met Synd, BMI ≥ 30, IFG or A1c > 6.0%

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: REGN 727
  Prevent degradation of LDL receptors
From Dobbs, H, 2006
Effect of PCSK9 antibody (AMG-145),
add-on to statin +/- Eze on LDL-C
Baseline LDL-C = 125 mg/dl

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>Study</th>
<th>Event Rate (Diabetes)</th>
<th>Event Rate (No Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Statin</td>
<td>On Placebo</td>
</tr>
<tr>
<td>HPS*</td>
<td>19.8%</td>
<td>25.7%</td>
</tr>
<tr>
<td>CARE†</td>
<td>19.4%</td>
<td>24.6%</td>
</tr>
<tr>
<td>LIPID‡</td>
<td>11.7%</td>
<td>15.2%</td>
</tr>
<tr>
<td>PROSPER§</td>
<td>13.1%</td>
<td>16.0%</td>
</tr>
<tr>
<td>ASCOT-LLA‡</td>
<td>4.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>TNT</td>
<td>7.8%</td>
<td>9.7%</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, stroke


Mechanisms Relating Insulin Resistance and Dyslipidemia

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>Apo-B (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>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</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>&lt; 100</td>
<td>&lt; 130</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

*Smoking, HBP, 5th premature CHD

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

<table>
<thead>
<tr>
<th>non-HDL-C &lt; 130 mg/dL</th>
<th>Apo-B &lt; 90 mg/dL</th>
<th>Apo-B ≥ 90 mg/dL</th>
<th>Discordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=734</td>
<td>607</td>
<td>127</td>
<td>+ 17.3 %</td>
</tr>
<tr>
<td>n=696</td>
<td>95</td>
<td>601</td>
<td>- 13.6 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>non-HDL-C ≥ 130 mg/dL</th>
<th>Apo-B &lt; 80 mg/dL</th>
<th>Apo-B ≥ 80 mg/dL</th>
<th>Discordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=131</td>
<td>123</td>
<td>8</td>
<td>+ 6.1 %</td>
</tr>
<tr>
<td>n=1299</td>
<td>232</td>
<td>1067</td>
<td>- 17.8 %</td>
</tr>
</tbody>
</table>

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

ACCORD: Lipid Results


ACCORD Lipid: Primary Outcome in Pre-specified Subgroups


Triglycerides and Cardiovascular Disease

A Scientific Statement From the American Heart Association

NHANES

Recommendation...Up to 50% reduction in TG levels by intensive lifestyle measures, including reduction in sucrose and fructose.
Effect of Raising HDL-C in Reducing Residual Risk?

**AIM-HIGH: Baseline Data**
- n= 3,414, 85% men, 92% White
- Mean age, 64.9
- Diabetes, 34%; Metabolic Syndrome, 81%
- CHD 92%, PAD, 11%, Cerebro-vascular 12%
- Prior MI 54%
- Prior statin Rx: 94%
  - Mean LDL-C : 71 mg/dl (Non-HDL: 107 mg/dl)
  - Mean TG : 161 mg/dl
  - Mean HDL-C: 34.9 mg/dl
- Simvastatin 40 mg + Niaspan 1500-2000 mg, vs Simva 40 + Placebo
- LDL-C Goal 40-80 mg/dl

AIM-HIGH: Primary Endpoints

25,673 high-risk patients with occlusive arterial disease from China, Scandinavia and UK

**Randomized comparison:**
- ER niacin/laropiprant (ERN/LRPT) 2g daily versus placebo

**Primary end point:** Major vascular events after median follow-up of 4 years

**Pre-specified safety analyses:** Median follow-up of 3.4 years (to January 2012)

**Background LDL-lowering therapy with:**
- Simvastatin 40mg (+/- ezetimibe 10mg) daily

**Occurrence of serious adverse events in HPS2-THRIVE**

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Potential HDL Therapies Saga

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