Insulin resistance: targeting dyslipidemia beyond the LDL-cholesterol

Rocky Mountain Metabolic Syndrome Symposium
May 14th 2010

Mori Krantz MD FACC
Associate Professor, University of Colorado
Director of CV Prevention Programs, CPC
Staff Cardiologist, Denver Health

Disclosures:
• Speaking and grant support: GSK, Pfizer
• Major stock holder: none
• Acknowledgment: selected slides from AHA Spotlight series lipid group

Presentation outline
• Describe all components of the metabolic syndrome
  – How common is this syndrome?
  – Understand pathogenesis of insulin resistance & atherogenic dyslipidemia
• What is our principal focus to reduce CVD in DM?
  – Lipids vs. Glycemic control
• Treatment of LDL cholesterol
• Beyond LDL cholesterol
  – Are there better predictors of CVD risk than LDL-C?
  – Review the concept of "residual risk"
  – Atherogenic dyslipidemia defined: lipid particles made simple
    • Does size matter?
    • Are Triglycerides (TG) an independent CVD risk factor?
    • Non-HDL-C, ApoB, and the TC/HDL ratio
• What are the therapeutic strategies for atherogenic dyslipidemia?
  – Fibrates, Omega-3 fatty acids, Niacin, Diet, Exercise
• Treatment targets
• Q & A
Components of the metabolic syndrome (a precursor to diabetes)

<table>
<thead>
<tr>
<th>Risk Factor (Risk Factor Level)</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>&gt;40 &amp; &gt;35 inches (men/women)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dl</td>
</tr>
</tbody>
</table>
| HDL-C                          | >40 mg/dl men  
                           | >50 mg/dl women. |
| Blood pressure                 | >= 120/80 mm Hg |
| Fasting glucose                | >= 100 mg/dl |


The evolution of insulin resistance and the metabolic syndrome

The Economist, December 11, 2003

Obesity & diabetes track in US adults

Diabetes  
1997: 19.5%  
2004*: 24.3%  
30% increase

Obesity (BMI ≥ 30 kg/m²)  
1997: 5.3%  
2004*: 6.9%  
30% increase

*Jan–June
Incidence of CVD by the number of components of the Metabolic Syndrome

![Incidence graph]

Diabetes Care 25:1790, 2002

Over half of patients referred to cardiologists have insulin resistance

![Over half graph]


Insulin Resistance Etiology: Central Adiposity (not inert but metabolically active)

![Insulin resistance diagram]
Atherogenic Dyslipidemia: the hallmark of metabolic syndrome

- Elevated Triglycerides — (>150 mg/dL)
- Reduced HDL-C — (<40 mg/dL in men; <50 mg/dL in women)
- Elevated small dense LDL particles
- Highly likely in the setting of elevated TG, reduced HDL-c and borderline elevated LDL-c
- Elevated non-HDL-c and/or Apo B

NHANES: Room for improvement < 50% of Diabetics Achieve Risk-Factor Goals

- Good control indicates HbA1c, BP, and TC were at recommended levels.
- National Health and Nutrition Examination Study (NHANES): cross-sectional survey of a nationally representative sample of the noninstitutionalized civilian US population, aged 20 years and older, with previously diagnosed diabetes.


We’ve gotten worse in terms of glycemic control and better with regard to lipids.

Should I focus on lipids or blood sugar?
ACCORD: Study design

N = 10,251 with T2DM and existing CVD or additional CV risk factors

<table>
<thead>
<tr>
<th>BP trial (n)</th>
<th>Lipid trial* (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C &lt;6%</td>
<td>Group A</td>
</tr>
<tr>
<td>1178</td>
<td>1383</td>
</tr>
<tr>
<td>1184</td>
<td>1370</td>
</tr>
<tr>
<td>A1C 7.0%-7.9%</td>
<td>Group B</td>
</tr>
<tr>
<td>1193</td>
<td>1374</td>
</tr>
<tr>
<td>1178</td>
<td>1391</td>
</tr>
</tbody>
</table>

| 2362        | 5120            |
| 2371        | 5121            |

Glycemia trial

Primary outcome: CV death, MI, stroke

www.accordtrial.org

ACCORD: Treatment effects on glucose control

ACCORD: significant increase in death with intensive therapy
ADVANCE: Study design

N = 11,140 with T2DM and high risk for CV events

<table>
<thead>
<tr>
<th>Perindopril + Indapamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive glucose control</td>
<td>Intensive glucose + Placebo</td>
</tr>
<tr>
<td>Standard glucose control</td>
<td>Standard glucose + Placebo</td>
</tr>
</tbody>
</table>

n = 5569  n = 5571

Primary outcome: Macro (CV death, MI, stroke), micro (neuropathy, nephropathy)


ADVANCE: Treatment effect on glucose control

![Graph showing mean A1C (%) over follow-up (months) with standard and intensive control groups.

P < 0.001


ADVANCE: Effect on macrovascular outcomes

![Graph showing cumulative incidence (%) of CV death, MI, stroke over follow-up (months) with standard and intensive control groups.

HR 0.94 (0.84-1.06)  P = 0.32

NCEP: approach to lipids

Step one - No surprise - lower LDL-C

HPS and CARDS: Benefits of lowering LDL-C in diabetes

<table>
<thead>
<tr>
<th></th>
<th>Event rate (%)</th>
<th>Statin better</th>
<th>Placebo</th>
<th>P</th>
<th>LDL-C (mg/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPS</td>
<td>All diabetes</td>
<td>9.4</td>
<td>12.6</td>
<td>0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Diabetes, no CVD</td>
<td>9.3</td>
<td>13.5</td>
<td>0.67</td>
<td>0.0003</td>
</tr>
<tr>
<td>CARDS</td>
<td>5.8</td>
<td>9.0</td>
<td>0.63</td>
<td>0.001</td>
<td>46.4</td>
</tr>
</tbody>
</table>

*Statin vs placebo
HPS = Heart Protection Study
CARDS = Collaborative Atorvastatin Diabetes Study

ASCOT-LLA: Statin reduces CV events in DM & HTN

\[ N = 2532, \text{baseline LDL-C 128 mg/dL} \]

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Atorvastatin 10 mg</th>
<th>HR = 0.77 (0.61-0.98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1208</td>
<td>1237</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1231</td>
<td>1231</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1230</td>
<td>1237</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1171</td>
<td>1171</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1055</td>
<td>1055</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1055</td>
<td>1055</td>
<td></td>
</tr>
<tr>
<td></td>
<td>714</td>
<td>714</td>
<td></td>
</tr>
<tr>
<td></td>
<td>375</td>
<td>375</td>
<td></td>
</tr>
</tbody>
</table>

Nonfatal MI, CV mortality, UK, stable angina, arrhythmias, stroke, TIA, PAD, retinal vascular thromboses, revascularization
ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
NCEP approach: Step 2, beyond LDL

The concept of "residual dyslipidemia risk"

Residual Risk in Patients Treated With Intensive Statin Therapy

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>PROVE I D-22</th>
<th>HPAZ</th>
<th>IDEAL 104</th>
<th>PLAN 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>95</td>
<td>62</td>
<td>104</td>
<td>101</td>
</tr>
</tbody>
</table>

Statistically significant but clinically inadequate LDL reduction.
- Standard statin therapy
- Intensive high-dose statin therapy

Superko HR. Br J Cardiol. 2006;13:131-136

*Mean LDL-C after treatment

Heart Protection Study

© Among Simvastatin-treated patients who entered the trial with LDL-C levels < 116 mg/dL and who had mean LDL-C levels of ~ 70 mg/dL during the study:

The 5-year risk of a major vascular event was still 18%.
This would equate to a 10-year risk of 35%.

Heart Protection Study Collaborative Group. Lancet. 2002;360:7-22
**Shortcomings of LDL: both calculated and measured**

- Friedewald equation (LDL-C = TC – HDL-C - TG/5)
  - Cholesterol content in LDL varies between individuals
  - Influenced by metabolic factors (insulin resistance)
  - Changes with statin treatment
  - Less accurate at LDL < 100 mg/dL
  - Less accurate as triglycerides >150 mg/dL
  - Does not represent all atherogenic ApoB-lipoproteins
  - Does not accurately represent the number of LDL particles

- Direct LDL cholesterol measures
  - Poor standardization
  - Does not represent all atherogenic ApoB-containing lipoproteins...

**Atherogenic lipoproteins: “non-HDL-C”**

- **Very low-density lipoprotein (VLDL)**
  - Made in the liver
  - TG-rich
  - Atherogenic

- **Low-density lipoprotein (LDL)**
  - Formed from IDL due to further TG lipolysis
  - Also known as a VLDL remnant particle
  - Major atherogenic particle

- **Intermediate-density lipoprotein (IDL)**
  - Formed from VLDL by TG lipolysis
  - Also known as a VLDL remnant particle
  - Atherogenic

- **High-density lipoprotein (HDL)**
  - Anti-atherogenic: carries cholesterol away from artery wall for metabolism or excretion
  - Other possible antiatherogenic effects include anti-inflammatory and antioxidant actions, and improvement in endothelial function

---

**Are there stronger CVD risk predictors beyond LDL-C?**
LDL-C a weaker predictor of CVD vs. non-HDL or ApoB
Combined Analysis of >18,000 patients in TNT & IDEAL trials

<table>
<thead>
<tr>
<th>Measure</th>
<th>Hazard Ratio Model 1*</th>
<th>Hazard Ratio Model 1 + LDL-C</th>
<th>Hazard Ratio Model 1 + Non-HDL</th>
<th>Hazard Ratio Model 1 + ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>1.15 (1.10-1.20)</td>
<td>0.09 (0.82-0.99) §</td>
<td>1.09 (0.97-1.20)</td>
<td>1.09 (0.97-1.20) §</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.38 (1.36-1.40)</td>
<td>1.31 (1.19-1.44) §</td>
<td>1.30 (1.30-1.30) §</td>
<td>1.24 (1.33-1.36) §</td>
</tr>
<tr>
<td>ApoB</td>
<td>1.38 (1.36-1.40)</td>
<td>1.34 (1.33-1.36) §</td>
<td>1.28 (1.13-1.30) §</td>
<td>1.19 (1.08-1.30) §</td>
</tr>
</tbody>
</table>

* Model 1: age, sex and study (TNT/IDEAL)

ApoB better agreement vs. TG and decreased variability

What is perhaps the most common metabolic manifestation of obesity?

Do I need to measure ApoB/Apo A ratio or is TC/HDL adequate?

Answer:

Minimal incremental predictive value in measuring Apolipoproteins
ApoB better statistical agreement vs. TG and decreased variability
Large economic cost
Hypertriglyceridemia Prevalence

US Adult Population
Total = 217 million

Clinical Relevance

• Risk for CVD

*This census is outdated as there are roughly 305 million in the US
*Numbers exceeding metabolic syndrome cut-point (>150 mg/dl) are much greater

Does high TG matter or just LDL-C?

Incidence of CHD Events According to Serum LDL-C and TG Concentration*

* Lipids from 4849 middle-aged men who were followed up for 8 years to record incidence of CHD. Study demonstrated that fasting levels of TGs were an independent risk factor for CHD events, irrespective of serum levels of LDL-C.

Hypertriglyceridemia Increases CHD Risk
In Patients with good versus bad “Ratios”
Do high triglycerides matter?
Independent predictor in post-ACS patients

Triglycerides summary
Independent Risk Factor for CHD

- Meta-analysis of 17 prospective studies that evaluated fasting
  TG levels and CVD endpoints
- 8 studies adjusted for HDL-C
- Results when adjusting for HDL-C
  - Relative risk (RR) = 1.14 for men, RR = 1.37 for women
  - Higher CVD risk for women
- Conclusion: elevated TG is a risk factor for CVD independent
  of HDL-C and the risk is greater for women
- Note: Triglyceride goals (< 150 mg/dl) are rarely achieved

Impact of LDL Size Differences
At the Same LDL Cholesterol Concentration

- Up to 70% More Particles
High TG lead to a decrease in Particle Size & an increase in Particle Number

- Fewer Particles
- More Particles

- Correlates with:
  - TC: 198 mg/dL
  - LDL-C: 130 mg/dL
  - TG: 90 mg/dL
  - HDL-C: 50 mg/dL
  - Non-HDL-C: 148 mg/dL

- More Apo B

High Triglycerides Are Associated With LDL Subclass Pattern B = BAD

- Pattern A (large, fluffy)
- Pattern B (small, dense)

Small, Dense LDL

- ↑ susceptibility to oxidation
- ↑ vascular permeability
- Conformational change in ApoB component
- ↓ affinity for LDL receptor for hepatic clearance
- Association with insulin resistance = high TG and low HDL-C (atherogenic dyslipidemia phenotype)
Outcomes: Technically, Size doesn’t matter particle number does

- The relationship between small LDL particle size and CHD is intertwined with a complex physiologic syndrome “atherogenic dyslipidemia” which includes high TG, low HDL-C, and increased LDL particle number.

- Following multivariate analysis that includes TGs, HDL-C, and LDL-particle number among 17 cross-sectional, 8 prospective and 6 interventional trials:
  - LDL particle size is rarely a significant, independent predictor of CHD events.


Women’s Health Study
CVD Relative Risk* and Lipid Quartiles

<table>
<thead>
<tr>
<th>Lipid Quartile</th>
<th>Quartile of Lipid</th>
<th>LDL Particle Number</th>
<th>Triglycerides</th>
<th>Total-C</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDL</td>
<td>LDL</td>
<td>Total-C</td>
<td>HDL-C</td>
<td>Non-HDL-C</td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>35</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for aspirin or vitamin E use.


Why use Non-HDL-C Goals?
Treatment approach case 1 vs. case 2

<table>
<thead>
<tr>
<th>Cholesterol (mg/dL)</th>
<th>Case 1</th>
<th>Case 2</th>
<th>TC= 209 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>120 mg/dL</td>
<td>400 mg/dL</td>
<td></td>
</tr>
<tr>
<td>VLDL-C</td>
<td>24 mg/dL</td>
<td>88 mg/dL</td>
<td>Non-HDL = 177 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>145 mg/dL</td>
<td>89 mg/dL</td>
<td>(may not trigger Rx)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 mg/dL</td>
<td>32 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>169 mg/dL</td>
<td>177 mg/dL</td>
<td>(should trigger Rx)</td>
</tr>
<tr>
<td>TG/HDL-C ratio</td>
<td>3.0</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>6.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HDL=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglyceride; VLDL=very low-density lipoprotein.
Because Non-HDL contains Apo-B, all of these particles are involved in Atherogenesis

All ApoB lipoproteins: LDL, IDL, VLDL, RLP

An Unmet Clinical Need for TG Reduction in Insulin resistant patients: Rx options

Niacin
Omega 3’s
Fibrates
Sbtrns

Fibrates
Primary and Secondary Prevention: limited older data: more recent trials no benefit in FIELD and ACCORD
Niacin vs. Placebo among Insulin Resistance Patients: older data 6-yr AMI rate by baseline FPG

**Hazard Ratio**

- Placebo: 0.70
- Niacin: 0.76

**FBG, mg/dL**

- 95: 0.70
- 95–104: 0.76
- 105–125: 0.75
- ≥126: 0.43

**n=1119 for niacin; n=2787 for placebo.**

* z for interaction = -0.44 (p=0.66); indicates homogeneity.


Addition of Omega-3 FA esters 4 g/day in Patients Taking Simvastatin with Triglycerides 200-499 mg/dL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simvastatin + Omega-3 (n=132)</th>
<th>Simvastatin + Placebo (n=122)</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>206</td>
<td>102</td>
<td>-104</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TC</td>
<td>184</td>
<td>172</td>
<td>-12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>52</td>
<td>46</td>
<td>-6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-C</td>
<td>46</td>
<td>46</td>
<td>0</td>
<td>=0.05</td>
</tr>
<tr>
<td>LDL-C</td>
<td>91</td>
<td>88</td>
<td>+3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Response to the addition of Omega-3 fatty acids, 4 g/day after 8 weeks of simvastatin 40 mg therapy during lead-in.

Suggested Treatment Goals

**In Dyslipidemia Patients at High Risk**

<table>
<thead>
<tr>
<th>Category</th>
<th>LDL-C goal (mg/dL)</th>
<th>Non-HDL-C goal (mg/dL)</th>
<th>ApoB goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-risk patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known CVD;</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;60 (or 70 per Dr. tick)</td>
</tr>
<tr>
<td>Diabetes + ≥ 2 major CVD risk factor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes/know CVD AND</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;99</td>
</tr>
<tr>
<td>≥ 2 major CVD risk factor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes without major CVD risk factor*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Lipidprotein Management in Patients with Cardiovascular Risk (Diabetes Care 2008; 31:811-822.

* Major CVD risk factors: smoking, HTN, history of premature coronary artery disease
Don’t forget Lifestyle…Lyon Heart Study

Numbers in bars are # of events

Conclusions

• Insulin resistance (metabolic syndrome) is a growing epidemic
• BP & lipid control more important than glycemic control or aspirin to lower CVD risk in this primary prevention population
• Atherogenic dyslipidemia mediates the increased risk for CVD
• The strongest predictors of CVD include:
  — TC/HDL ratio (or ApoB/Apo A ratio)
  — Non-HDL cholesterol (VLDL, LDL, IDL)
  — LDL is actually a weaker CVD risk predictor
• Nonetheless, achieving LDL goals is the first step and we have the best prospective data for this paradigm
Next, manage high TG and low HDL
  — Exercise
  — Dietary modification
  — Omega-3s, Niacin, Fibrates
• Though further outcome studies are warranted