Treating Lipids in Metabolic Syndrome

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Disclosures

• Speakers Bureau For: Abbott, Astra Zenica, Pfizer, Bristol Myers-Squibb, Novartis, Glaxo Smith-Kline, Takeda, Merck, MERCK Schering-Plough, Sanofi-Aventis, CV Therapeutics

Metabolic Syndrome Increases Risk for CHD and Type 2 Diabetes

ATP III: The Metabolic Syndrome*

*Diagnosis is established when ≥3 of these risk factors are present

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
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</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>(Waist circumference)</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Men</td>
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<tr>
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<tr>
<td>TG</td>
<td>&gt;150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/65 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

Definitions of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Original Level</th>
<th>Update</th>
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ATP III: The Metabolic Syndrome

AHA/NHLBI Scientific Statement. Circulation 2005;112
Prevalence of the NCEP Metabolic Syndrome: NHANES III by Age

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>30-39</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>40-49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>60-69</td>
<td>25%</td>
<td>16%</td>
</tr>
<tr>
<td>70+</td>
<td>28%</td>
<td>21%</td>
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Prevalence of the NCEP Metabolic Syndrome: NHANES III by Sex and Race/Ethnicity

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<tr>
<th>Race/Ethnicity</th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>White</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>African American</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Mexican American</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Other</td>
<td>21%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Cardiovascular Disease Mortality Increased in the Metabolic Syndrome: Kuopio Ischaemic Heart Disease Risk Factor Study

Cumulative Hazard, %

Follow-up, y

Cardiovascular Disease Mortality Among 1,000 Men (10 yr follow-up)

RR (95% CI) 3.55 (1.98-6.43)

Treatment Strategies for Diabetic Dyslipidemia

- Primary
  - Lower LDL-C
- Secondary
  - Raise HDL-C
  - Lower triglycerides
- Other Approaches
  - Non-HDL-C
  - Apo B, NMR Particle Concentration
  - Remnants

Effects of Insulin Resistance and Type 2 Diabetes on Lipoprotein Subclass Particle Size and Concentration Determined by Nuclear Magnetic Resonance


Diabetes 2003;52(2):453-462

Study Design

- 148 subjects (48 with untreated Type 2 DM) assessed for insulin sensitivity using hyperinsulinenic euglycemic clamp
- Glucose disposal rate (GDR) < 12.8 mg/kg/min used to define insulin resistant non-diabetic subjects
- Lipoprotein subclass concentrations measured by NMR spectroscopy and lipids by standard methods

When compared with IS, the IR and diabetes subgroups exhibited:

- A two- to threefold increase in large VLDL particle concentrations (no change in medium or small VLDL), which produced an increase in serum triglycerides;
- A decrease in LDL size as a result of an increase in small and a reduction in large LDL subclasses, plus an increase in overall LDL particle concentration, which together led to no difference (IS) or a minimal difference (IS versus diabetes) in LDL cholesterol;
- A decrease in the large cardioprotective HDL, combined with an increase in the small HDL subclass such that there was no net significant difference in HDL cholesterol.

**Conclusions**

Do We Have Evidence That Treating The Metabolic Syndrome and the Components of the Metabolic Syndrome Makes a Difference?

- Jupiter Trial
- Steno 2 Trial
- The SANDS Trial

**Primary Endpoint**

Time to first occurrence of a CV death, stroke, MI, hospitalization for unstable angina or arterial revascularization

- Mean Age 55.1 Years
- Mean F/U 7.8 Years
- Trial Used 1988 Danish Medical Association Guidelines Initially Which Were Upgraded in 2000
- Targeted Therapy: Hyperglycemia, Hypertension, Dyslipidemia, Microalbuminuria and Secondary Prevention of CVD with Aspirin

**JUPITER Study Design**

- Rationale for the Use of statins in primary prevention: an Intervention Trial Evaluating Rosuvastatin
- 4 Week Placebo Run-in
- No History of CVD
- Men ≥ 50 years; Women ≥ 60 years
- LDL-C < 130 mg/dL, hs-CRP levels ≥ 2.0 mg/L
- 4 Week Placebo Run-in
- JUPITER Study Design
- Rosuvastatin 20 mg (n=8901)
- Placebo (n=8901)
- Follow-up visits included: Laboratory evaluations, pill counts, structured interviews for outcomes and adverse events
- Included: LDL-C, hs-CRP and other laboratory evaluations

**Steno-2 Trial**

- Mean Age 55.1 Years
- Mean F/U 7.8 Years
- Trial Used 1988 Danish Medical Association Guidelines Initially Which Were Upgraded in 2000
- Targeted Therapy: Hyperglycemia, Hypertension, Dyslipidemia, Microalbuminuria and Secondary Prevention of CVD with Aspirin
Steno-2: Effect of Therapies on Selected Risk Factors

The SANDS Trial

- 499 Patients with DM II
- Primary Endpoint-Change in CITM and LVH
- Two Arms:
  - Standard Care: LDL < 100 mg/dL, Non-HDL Chol < 130 mg/dL, BP < 130/80
  - Intensive Care: LDL < 70 mg/dL, Non-HDL Chol < 100 mg/dL, BP < 115/75
- Intensive Care had 2 Groups: Simvastatin alone (154) and Simvastatin + Ezetimibe (69)
- Simvastatin + Ezetimibe At Least as Effective, Statistically Better
- Average Hgb A1c – 8.1 mg/dL

Steno 2 Results at 13 Years

Number of Cardiovascular Events
Guidelines for the Management of Hyperlipidemia

• Review the Recent Guideline Recommendations
• Review the Data Upon Which the Guideline Updates Were Based
• Examine New Data That Raise Questions as to Whether Current LDL-C Guidelines Adequately Explain Residual Risk
• Review Data From Fibrate, Niacin and Omega-3 Fish Oil Trials

Fibrate Clinical Trials

• BIP Trial
• Helsinki Heart Study
• VA-HIT Trial
• DAIS Trial
• FIELD Trial
• ACCORD Trial

Summary of Fibrate Clinical Trial Data

• Positive Trial Data in Primary and Secondary Prevention Trials With Gemfibrozil
• Most of Clinical Benefit Seen in Patients High TG, Low HDL-C, Obesity, and Insulin Resistance in Both Trials

Summary of Fibrate Clinical Trial Data

• Summary of Fibrate Trials (BIP, FIELD, ACCORD)
  – Primary Endpoint Negative
  – Subpopulation Positive
    • High TG, Low HDL, Metabolic Syndrome

Niacin Based Trials

• Coronary Drug Project
• FATS Trial
• HATS Trial
• Armed Forces Regression Trial
• ARBITER 2
• ARBITER 3
• ARBITER 6 (HALTS)

Simvastatin and Niacin, Antioxidant Vitamins, or the Combination For the Prevention of Coronary Disease

### ARBITER 2: A Double-blind, Placebo-controlled Study of Extended-release Niacin on Atherosclerosis Progression in Secondary Prevention Patients Treated with Statins

**Clinical Events**

- Composite clinical event endpoint
  - Unstable angina/MI hospitalization
  - Stroke
  - Sudden cardiac death
  - Percutaneous coronary revascularization, CAGB, or peripheral revascularization

**Lipid Values**

- Patients were well-controlled on statin therapy at baseline
  - LDL-C “at goal” – < 90 mg/dL
  - HDL-C “moderately low” – 40 mg/dL

- After 12 months, HDL-C and triglycerides were significantly improved with Niaspan® vs.. baseline

**Progression in Secondary Prevention Patients Treated with Statins**


**CIMT at 12 Months vs.. Baseline**

- Within-Group Comparison
  - Significant progression in placebo group – 1st endpoint met
  - Progression rate 68% lower in Niaspan® group

**Armed Forces Regression Study (AFREGS)**

- Double-Blind Trial
- 143 Retired Military Personnel
- Low HDL and Stable CAD
- <76 YOA
- LDL<160 mg/dL
- HDL<40 mg/dL
- Had to have Coronary Stenosis of 30-80% of Luminal Diameter

**ARBITER 2: Key Points Regarding Lipid Values**

- Patients were well-controlled on statin therapy at baseline
  - LDL-C “at goal” – < 90 mg/dL
  - HDL-C “moderately low” – 40 mg/dL

- After 12 months, HDL-C and triglycerides were significantly improved with Niaspan® vs.. baseline


**Armed Forces Regression Study (AFREGS)**

- 30 Month Study
- Cardiac Catheterization at Baseline and 30 Months
- Double-Blind Placebo Controlled Trial
- Drug Regimen
  - Gemfibrozil 600 mg BID
  - Niacin 250 mg/day Titrated to 3 g/day
  - Cholestyramine 2 g/day titrated to 16 g/day


**Armed Forces Regression Study (AFREGS)-Lipid Results**

- Change in Lipids Relative to Placebo
  - TC 19.6% Lower
  - LDL 26.4% Lower
  - TG 49.8% Lower
  - HDL 35.9% Higher


**Armed Forces Regression Study (AFREGS)-Angiographic Results**

- Placebo
  - Focal Coronary Stenosis Increased 1.4%
- Treatment Regimen
  - Focal Coronary Stenosis Decreased 0.8%


**Armed Forces Regression Study (AFREGS)-Clinical Outcomes**

- Drug Regimen
  - Death 1.4%
  - UAP 9.9%
  - PCI 2.8%
  - CABG 2.8%
  - Composite 12.7%

- Placebo
  - Death 2.8%
  - UAP 20.8%
  - PCI 2.8%
  - CABG 11.1%
  - Composite 26.4%


**Predictors of Risk Reduction in Lipid Trials**

- Objective
  - Determine relative importance of changes in specific lipid parameters in predicting risk reduction observed in lipid-altering trials
- Meta-analysis of 17 studies, including:
  - HHS, FATS, 4S, WOSCOPS, CARE, LIPID, AFCAPS, VA-HIT, BIP, DAIS, HATS, PROSPER, HPS, ALLHAT, ASCOT
- 44,170 patients; 3869 CHD events


**Composite Outcomes Benefit**

- Combine FATS, HATS, ARBITER 2,3,6, AFREGS
- Total Patients~1500
- Expected Change in Outcomes Based on:
  - For Every 1% Decrease in LDL, There is a 1% Decrease in Events
  - For Every 1% Rise in HDL, There is a 1 1/2-2% Decrease in Events
- Expected Change in Events for Combined Trials 70-80%
- Actual Change in Events for Combined Trials 70-80%
AIM-HIGH
3300 Patients
Men and Women With Known CAD
Statin Therapy to LDL<80 mg/dL
Randomized to Niaspan Versus Placebo
Expected Completion 2012

HPS-2 THRIVE
20,000 Patients
Men and Women with Known CVD
Statin, Ezetamibe ER Niacin/Laropiprant
Expected Completion 2013

Omega 3 Fish Oil: Clinical Benefit for Patients Undergoing Carotid Endarterectomy
- Randomized Trial of Omega-3 Fish Oil, Sunflower Oil (Omega-6), Controls (80:20 Palm and Soybean)
- 188 Patients Randomized to 3 Groups
- Supplemental Oil Started an Average of 42 Days Prior to Surgery
- Primary Outcome was Plaque Stability at the Time of Surgery and Concentrations of Various Oils in the Plaque

Lancet 2003; 361:477 - 485

Omega-3 Fish Oil: Clinical Benefits
- Levels of EPA and DHA Increased in Phospholipids, Cholesterol Esters and Tracyglycerols
- Proportion of EPA and DHA in Plaque Removed was Significantly Higher
- More Well-Formed Fibrous Caps and Fewer Thin Wall Caps
- Lower Distribution of Macrophages Within the Plaque

Lancet 2003; 361:477 - 485

Japan EPA Lipid Intervention Study (JELIS Trial)
- 18645 Patients Randomized
- Average Age 61
- Male 31%, Female 69%
- Eligibility Criteria
  - Total Cholesterol ≥ 6.5 mmol/L (254 mg/dL)
  - LDL Cholesterol ≥ 4.4 mmol/L (172 mg/dL)
  - With or Without CAD
- Randomized to Statin plus 1.8 Grams of EPA vs. Statin Alone (Control Group)
- Primary Outcome: Any Major Coronary Event

Lancet 2007; 369:1090-1098

JELIS Trial: Effect of EPA
- 19% Relative Reduction in Major Coronary Events (p=0.011)
- UAP and Non-Fatal MI Were Also Significantly Reduced
- Sudden Death and Coronary Death Were Not Significantly Affected
- Secondary Prevention 19% Relative Reduction in Major Coronary Events (p=0.048)
- Primary Prevention 18% Relative Reduction Which Was Not Significant
- Baseline EPA Levels in the Study Patients 2.9 mol% vs. US Population 0.3 mol%

Lancet 2007; 369:1090-1098

Effects of EPA on Coronary Artery Disease in Hypercholesterolemic Patients with Multiple Risk Factors: Sub-Analysis of JELIS
Atherosclerosis 2008;200:135-140
Questions ?