Treatment of Insulin Resistance and Pre-diabetes to Reduce CVD Risk

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- **Honoraria as Speaker:** Amarin, Amgen, AstraZeneca, Janssen, Kowa, Merck, Regeneron, Sanofi-Aventis, Takeda

Dr. Brinton will reference unlabeled/unapproved uses of drugs in his presentation.

Learning Objectives

- Explain how **visceral adiposity** leads to low-grade systemic inflammation, fatty liver, and insulin resistance.
- Discuss how **fatty liver** and **insulin resistance** lead to dyslipidemia, atherosclerosis and **increased risk of cardiovascular disease (CVD)** events.
- Implement evidenced-based best-practice strategies for diagnosis and **treatment of insulin resistance** for **CVD risk reduction**.
Insulin Resistance (Ins. Levels) Predicts ↑CHD Mortality

Number of CHD Deaths Out of Total Population (N = 970)

AUC Fasting Plasma Insulin Quintiles, pmol/L.h

- ≤237
- 238-337
- 338-427
- 438-669
- >669

Insulin Sensitive
Insulin Resistant


Insulin Resistance + ↓HDL-C or ↑TG Predict CHD: Framingham Heart Study

CHD % Incidence

IR + or - and HDL-C ↓ or ↑

IR + or - and TG ↑ or ↓

Insulin Resistance Parameters

- Serum glucose
  - Fasting > 110 vs > 100 mg/dL
  - OGTT (75g, 2h) > 140 mg/dL
- Fasting insulin
  - how high? (95th vs 50th %ile)
- HOMA-IR
- Lipids
  - ↑TG and/or ↓HDL-C (ratio > ~3?)
- Central Adiposity
  - BMI,
  - Waist, waist/hip ratio
  - MRI for visceral adiposity
- Inflammatory Markers (hsCRP, LpPLA2…)

N=2910

Adiposity as a Key Factor in Inflammation, Fatty Liver and Insulin Resistance

Increases in Obesity Among U.S. Adults 1990 Through 2006

Adipocytes and Macrophages are 1° Sources of Inflammatory Cytokines

Visceral vs Peripheral Adipocytes

- Androgens & polygenic factors predispose
- Unique access to liver via Portal Vein
- ↑ FFA/TG turnover (↑insulin resistance?)
- ↑ Pro-inflammatory tendencies?
  - Adipocyte hypertrophy vs. hyperplasia
  - Increased ER stress due to cytoplasmic stretch?
  - Greater adipocytokine secretion?
  - Greater inflammatory cell recruitment?

Lp-PLA₂ and CRP Additively Predict Stroke Risk (ARIC Study)

Fatty Liver and Insulin Resistance as Causes of Dyslipidemia, Atherosclerosis and CVD

Causes and Effects of Fatty Liver

**Causes of Hepatic FFA/TG Excess**
- Excess portal FFA & TG from visceral adipocytes → hepatic storage
- Excess systemic FFA & TG (excess intake vs utilization) → hepatic storage
- Excess fructose (portal & systemic) → hepatic FFA synthesis

**Effects of Hepatic FFA/TG Excess**
- ↑ VLDL synthesis → ↑TG & apo B, ↓LDL size
- ↑ Hepatic Insulin resistance → ↑Glycemia
- ↑ NASH/hepatic inflammation
- ↑ Cirrhosis and hepatic failure??

CHD Risk Is Increased With TG Levels ≥200 mg/dL

TGs are independently associated with premature familial CHD*  

![Graph](image)

*Triglyceride odds ratio adjusted for HDL-C; n=1029 (control)


TG >150 mg/dL Increases CHD Risk Even w/ LDL-C < 70 mg/dL on a Statin*

PROVE IT-TIMI 22 Subanalysis

![Graph](image)

*N=3718

*Death, MI, and recurrent ACS

*ACB patients on atorvastatin 80 mg or pravastatin 40 mg

*Adjusted for age, gender, sex HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment

Lipid values are in mg/dL

Three Atherogenic Consequences of Hypertriglyceridemia

1. ↑ TG/VLDL-C
2. ↑ LDL size
3. ↑ Apo A-I/HDL-C

Also, ↑ VLDL synthesis is assoc. w/ ↑ apo B & ↑ LDL-P

LDL-C Doubly Underestimates CVD Risk in Cases of Small, Dense LDL

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

↑ SD LDL < TG 100 mg/dL w/ Normal CETP Action

and SD LDL → ↑ ASCVD
Independent of ↑ LDL-C
SD LDL Predicts CHD Better than LDL-C (ARIC)

Mechanisms of ↑Atherogenicity with SD LDL

- Passes endothelium easier into wall (sub-endothelial space)
- Stickier/longer retention in SE space
- More readily oxidized (in SE space)
- Less clearance (↓LDL-R binding)

*But remember: ALL LDL is atherogenic!*

Insulin Resistance May Increase CVD More in *Women*

Greater *relative* ↑CVD risk in *women*
- ↑TG
- ↓HDL-C
- IFG
- Central Adiposity
- HBP
- DM-2

*Narrows gender-gap (CVD risk ≈ men)*
Insulin Resistance as a Mechanism of CVD Risk

INSULIN SIGNAL TRANSDUCTION SYSTEM IN HUMANS

Insulin Resistance Blocks IRS-1 Induction of Favorable Arterial Effects of Insulin
Insulin Resistance/Insulin-Providing Rx Causes Allows Increased Harmful MAP Kinase Effects


Practical Treatment of the Atherometabolic Syndrome

NCEP ATP III Definition of Insulin Resistance Syndrome ("Metabolic Syndrome")

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, inches</td>
<td>&gt;40</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>≥150</td>
<td>≥150</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>≥130/≥85</td>
<td>≥130/≥85</td>
</tr>
<tr>
<td>FPG, mg/dL*</td>
<td>100-125</td>
<td>100-125</td>
</tr>
</tbody>
</table>

Presence of 3 or more = Metabolic syndrome ICD-9-CM code: 277.7

*ADA cutpoint for FPG is ≥100 mg/dL.
Rx of Small, Dense LDL

LDL-C/Non-HDL-C/apo B
- Statins, Niacin, Rx om-3 EPA
- Insulin Resistance
  - Diet, exercise, weight loss
  - Pioglitazone, metformin
  - ACEI's? Fibrates? GLP1? SGLT2?
- ↑LDL Size (w/o ↑LDL concentr.)
  - Niacin
  - Pioglitazone
  - Fibrates?
  - Rx Omega-3? (EPA only?)

Insulin Resistance as a Therapeutic Target in CVD Prevention

Lifestyle and Diet Can Improve Dyslipidemia

<table>
<thead>
<tr>
<th>Diet/Lifestyle Change</th>
<th>Lipid Profile Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>↑ HDL-C 4 mg/dL¹</td>
</tr>
<tr>
<td>Weight loss (5-10%)</td>
<td>↓ TG 20%, ↑ LDL-C 15%, ↑ HDL-C 10%²</td>
</tr>
<tr>
<td>Diet</td>
<td>↑ LDL-C, ↑ HDL-C¹</td>
</tr>
<tr>
<td>Total carb &amp; ↑ fat (to 33-50% of calories)</td>
<td>↓ TG 9.4 mg/dL²</td>
</tr>
<tr>
<td>Brisk 30-min walk, 3x/wk</td>
<td>↑ LDL-C, ↑ HDL-C 5-10%¹</td>
</tr>
</tbody>
</table>

Fibrates: Well-Established Treatment for Metabolic Syndrome

VA-HIT: Gemfibrozil Prevents CVD With Average to Elevated Insulin Levels


Fibrates reduce CVD best in Insulin Resistant Pts.

Lower-Extremity Amputations w/ Fenofibrate (Esp. "Minor" = Below Ankle; w/o Large-Vessel Disease)

FIELD 2007 Ophthalmology Substudy
(1st Outcome: Retinopathy Progression - 22%, p=0.2)


Placebo (n = 500)
Fenofibrate (n = 512)
P=0.004

Pioglitazone:
A Logical (but novel)
Treatment for Metabolic Syndrome

TZD Activates Favorable IRS-1 Effects and Blocks MAP Kinase (via ↓Insulin)
Pioglitazone for Diabetes and Pre-Diabetes?

**Pros**
- Strongest available insulin sensitizer
- ↓ Fatty liver (~50%) & visceral fat
- ↑ Beta-cell survival/function
- Prevents DM-2 ~3/4 ↓
- ↓ TG, ↑ HDL-C
- Direct anti-inflammatory/anti athero effect
- Decreases CVD (std. MACE—2° endpt.)

**Cons**
- ↑ Bladder cancer (not causal? & 1:23 vs CVD)
- ↑ CHF (water retention only)
- ↑ Adiposity (peripheral only—good?)
- ↑ Osteoporosis (women only)

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Niacin: A Paradoxical Treatment for Metabolic Syndrome

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CDP at 6 yr: Nonfatal MI by Baseline FBG*
Niacin May Reduce CVD Better in Patients with Metabolic Syndrome


Preliminary Hazard
- Placebo: 0.78
- Niacin: 0.30

**Z(int) = –1.78**

- Placebo: n=243, n=99
- Niacin: n=111, n=39

**Placebo**
- MS (0–2 RF’s): n=354
- MS+ (3–5 RF’s): n=138

**Niacin**
- MS (0–2 RF’s): n=354
- MS+ (3–5 RF’s): n=138

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto-OR 95% CI</th>
<th>Peto-OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER-HIHTS</td>
<td>8/189</td>
<td>9/176</td>
<td>0.88 (0.68, 1.15)</td>
<td>0.88 (0.68, 1.15)</td>
</tr>
<tr>
<td>Quemener et al</td>
<td>1/274</td>
<td>1/272</td>
<td>0.86 (0.64, 1.16)</td>
<td>0.86 (0.64, 1.16)</td>
</tr>
<tr>
<td>APPROS</td>
<td>2/191</td>
<td>2/191</td>
<td>0.82 (0.61, 1.12)</td>
<td>0.82 (0.61, 1.12)</td>
</tr>
<tr>
<td>APIVOR-2</td>
<td>3/197</td>
<td>3/197</td>
<td>0.87 (0.65, 1.16)</td>
<td>0.87 (0.65, 1.16)</td>
</tr>
<tr>
<td>HATS</td>
<td>1/288</td>
<td>1/288</td>
<td>0.88 (0.64, 1.22)</td>
<td>0.88 (0.64, 1.22)</td>
</tr>
<tr>
<td>Lp(a) Scoring</td>
<td>1/165</td>
<td>1/165</td>
<td>0.89 (0.62, 1.25)</td>
<td>0.89 (0.62, 1.25)</td>
</tr>
<tr>
<td>STROKELONG</td>
<td>7/373</td>
<td>7/373</td>
<td>0.89 (0.62, 1.25)</td>
<td>0.89 (0.62, 1.25)</td>
</tr>
<tr>
<td>CLAS</td>
<td>10/126</td>
<td>11/126</td>
<td>0.86 (0.60, 1.23)</td>
<td>0.86 (0.60, 1.23)</td>
</tr>
<tr>
<td>CDP</td>
<td>9/112</td>
<td>9/112</td>
<td>0.87 (0.60, 1.23)</td>
<td>0.87 (0.60, 1.23)</td>
</tr>
</tbody>
</table>

**AIM-HIGH: ERNA beats Control in HTG/low HDL-C pts**

**# Pts. with Events (% of Category)**
- Placebo
  - TG ≥ 190 and HDL < 35
    - Yes: 54 (22.4) vs 48 (17.0)
    - No: 220 (15.1) vs 234 (16.3)
  - TG ≥ 200 and HDL < 32
    - Yes: 50 (25.0) vs 40 (16.7)
    - No: 224 (15.0) vs 242 (16.2)
- ERN
  - Better: Hazard Ratio (95% CI)
  - Worse: Hazard Ratio (95% CI)
  - P-val. ** Int.

**Stat sig 27%**

- AIM-LOW: ERNA beats Control in HTG/low HDL-C pts
- Bruckert, E. Atherosclerosis 2010; 210:353-361

Guyton JR JACC 2013 62(17)1580–1584
AIM-HIGH: ERNA beats Control in HTG/low HDL-C pts

<table>
<thead>
<tr>
<th>Category</th>
<th>ERN Better</th>
<th>ERN Worse</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-val.**</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG &gt; 190 &amp; HDL &lt; 55</td>
<td>Yes</td>
<td>54 (22.4)</td>
<td>48 (17.0)</td>
<td>0.74 (0.50, 1.10)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>220 (15.1)</td>
<td>234 (16.3)</td>
<td>1.00 (0.91, 1.13)</td>
</tr>
<tr>
<td>TG &gt; 400 &amp; HDL &lt; 32</td>
<td>Yes</td>
<td>50 (25.0)</td>
<td>40 (16.7)</td>
<td>0.63 (0.40, 0.98)</td>
</tr>
</tbody>
</table>

Niacin →↓CVD in patients with HTG/low HDL-C

*Highest tertile of TG and lowest tertile of HDL-C  **Heterogeneity by treatment

Guyton JR JACC 2013 62(17)1580–1584

Niacin →↓CVD in
patients with
HTG/low HDL-C

HPS2-THRIVE: No Overall ↓CVD w/ ERN + LRPT

N=25,673 with Pre-existing CVD
Baseline Lipids on Statin Rx

<table>
<thead>
<tr>
<th>Lpid</th>
<th>Mean (SDM) at baseline, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>128 (22)</td>
</tr>
<tr>
<td>Direct LDL</td>
<td>63 (17)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (11)</td>
</tr>
<tr>
<td>TG</td>
<td>125 (14)</td>
</tr>
</tbody>
</table>

HPS2 studied niacin in patients without lipid indication

HPS2 stopped when curves started to diverge!

HPS2: MVE by age, sex, region & statin therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Randomized allocation</th>
<th>Risk ratio &amp; 95% CI</th>
<th>Het or trend p (uncorrected p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>ERN/LRPT</td>
<td>Placibo</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>(12,813)</td>
<td>(12,805)</td>
<td></td>
</tr>
<tr>
<td>65-70</td>
<td>740 (11.4%)</td>
<td>786 (12.2%)</td>
<td>0.90 (0.50)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>302 (25.9%)</td>
<td>367 (23.1%)</td>
<td>1.28 (p=0.26)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1397 (13.2%)</td>
<td>1485 (14.0%)</td>
<td>1.05 (p=0.07)</td>
</tr>
<tr>
<td>Female</td>
<td>293 (13.4%)</td>
<td>273 (12.3%)</td>
<td>0.96 (p=0.07)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>832 (11.3%)</td>
<td>913 (12.4%)</td>
<td>1.28 (p=0.26)</td>
</tr>
<tr>
<td>China</td>
<td>864 (15.0%)</td>
<td>845 (15.5%)</td>
<td>0.83 (p=0.06)</td>
</tr>
<tr>
<td>Statin-based therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin/40mg</td>
<td>543 (14.0%)</td>
<td>549 (14.0%)</td>
<td>1.28 (p=0.26)</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin</td>
<td></td>
<td>754 (12.4%)</td>
<td>0.83 (p=0.06)</td>
</tr>
<tr>
<td>All</td>
<td>1606 (13.2%)</td>
<td>1758 (13.7%)</td>
<td>3.5% SE 3.3 reduction</td>
</tr>
</tbody>
</table>
HPS2: MVE by age, sex, region & statin therapy

**Randomized allocation**
- ERN/LRPT: (12,835)
- Placebo: (12,838)

**Risk ratio & 95% CI**
- Regional difference is Biologically Plausible, but Gender Difference is Not

**Het or trend χ²**
- (uncorrected p value)
- ERN/LRPT better
- Placebo better

**Age [years]**
- < 65
- ≥ 65
- <70
- ≥ 70

**Sex**
- Male
- Female

**Region**
- Europe
- China

**Statin-based therapy**
- Simvastatin 40mg
- Ezetimibe/simvastatin
- All

**Placebo better**

**ERN/LRPT better**

**HPS-2/THRIVE: Good & Bad**

**Appeared to avoid most AIM-HIGH problems**
- True placebo-control: good test of niacin?
- Longer duration (~4 yrs)
- Large N (~23,000 subjects)
- Little pre-study Rx "contamination"

**But had new problems**
- No selection for either low HDL-C or high TG pts (base HDL-C 44, TG 125—no niacin indication!); need AIM-HIGH-style subanalysis
- No need for further LDL-C lowering (base 63)
- Not a test of niacin alone (ERNA given w/ laropiprant (↑novel SAEs in Rx arm)
- Chinese had ↑myopathy and no CVD benefit

**Niacin and CVD: Summary**
- Monotherapy benefit well documented: useful for statin-intolerant pt
- Benefit as statin adjunct not shown clearly in recent trials; however
- AIM-HIGH appeared to show i CVD in HTG/low HDL-C pts, like fibrates (must confirm)
- HPS2-THRIVE
  - Benefit begins after 2 years? (results suggestive)
  - Benefit in Caucasians? (results suggestive)
  - Benefit if LDL-C ≥58? (results suggestive)
  - Benefit in HTG/low HDL-C? (not tested beyond >150/<40)
  - Lack of overall benefit from concurrent laropiprant?
Summary: Dx and Management of Insulin Resistance/Metabolic Syndrome

- **Make the Diagnosis:**
  - ≥3 of 5 Met/Synd factors + BMI, insulin, inflam.

- **TLC (diet and exercise)**
  - 1st-line Rx
  - Addresses underlying cause, but
  - Difficult, and
  - Usually not enough

- **Drug Rx (anti-obesity vs specific)**
  - 2nd-line Rx after TLC
  - Generally easier & more effective, but
  - No clinical trial evid. for ↓CVD w/ TLC or antiobesity Rx
  - Fibrates, om-3 & niacin (statin adj) may ↓CVD, but
  - This evidence is mainly subgroup/post-hoc

- Combination meds may be needed

Adapted from Grundy, S. et al., Circulation 2005;112:1-18.