“Lipids, Lipoproteins and Residual CVD Risk: Where are We in 2015?”

Metabolic Syndrome Symposium
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Duality of Interests

– Consultant/Advisory Boards
  • Amgen
  • Amarin
  • Esperion
  • Genentech
  • ISIS Pharmaceuticals
  • Janssen
  • Novo Nordisk
  • Pfizer
  • Regeneron/sanofi aventis

– Grants/Research Fellowships
  • Esperion
  • Janssen
  • ISIS Pharmaceuticals

– Medical Education
  • Cardiometabolic Health Congress
  • HealthTeamWorks
  • Medscape
  • Medical Education Resources
  • VOX Media

Residual Risk

• 55 hear old man
  – Known CHD
  • Lifestyle is moderately healthy
  • On atorvastatin 80 mg daily
  – LDL-C 67, TG 300, HDL-C 32 mg/dL
  – ETT – normal

• Two months later
  – AMI at work
  • Resuscitation failed

• Could this have been avoided?
Which is True?

- We needed to know his level of small dense LDL.
- Therapy should have been directed at increasing HDL-C.
- According to the 2013 ACC/AHA Cholesterol Guideline he was inadequately treated.
- According to the 2013 ACC/AHA Cholesterol Guideline he was adequately treated.

An Opposite HDL-C Scenario

- 51 year old woman is referred with a coronary artery calcium score of 949
  - Strong F Hx of CHD
  - Lifestyle
    - and vegetables but limited in whole grains
    - Daily exercise
  - BP 128/80
  - BMI 25 kg/m²
- Lipids
  - Total C: 353 mg/dL
  - TG: 103 mg/dL
  - HDL-C: 85 mg/dL
  - LDL-C: 247 mg/dL
  - Lipoprotein (a): 92 mg/dL
- After rosuvastatin 5 mg, ezetimibe, cholestyramine
  - Total C: 223 mg/dL
  - TG: 117 mg/dL
  - HDL-C: 87 mg/dL
  - LDL-C: 113 mg/dL
  - Lipoprotein (a): 99 mg/dL

Which is True?

- Higher levels of HDL-C always reduce CVD risk.
- Niacin should be used to further lower LDL-C and lipoprotein (a).
- According to the 2013 ACC/AHA Cholesterol Guideline he was inadequately treated.
- According to the 2013 ACC/AHA Cholesterol Guideline he was adequately treated.
Lipids, Lipoproteins and Residual CVD Risk

• HDL
• Hypertriglyceridemia
  – Apolipoprotein B
• Lipoprotein (a)

4 Statin Benefit Groups

1. Secondary Prevention 2. Diabetes 3. LDL-C ≥ 190 mg/dL
40 to 75 yrs LDL-C 70-189 mg/dl
Rx: Optimal benefit with high intensity fixed dose statin → lower LDL-C ≥ 50% Use moderate intensity if age >75 or can’t tolerate high intensity

4. Primary Prevention 40 to 75 yrs
LDL-C 70-189 mg/dl
ASCVD Risk ≥ 7.5 %
Rx: Moderate intensity or high intensity fixed dose statin

Statin Rx not automatic, requires clinician-patient discussion

HDL:
So what do we really know?
**HDL-C Predictive Value**

HDL-C is a strong predictor of CHD in subjects with desirable Total-Cholesterol.

**Statin Trials:**

Effects on CVD Risk by Baseline HDL-C

The HDL Proteome

HDL and Atherosclerosis

- Anti-oxidant
- Anti-inflammatory
- Anti-thrombotic
  - ↑ prostacyclin
- Promotes vascular reactivity
  - ↑ NOS
- Decreases myeloproliferative cell development
- Reverse cholesterol transport

HDL Metabolism and Reverse Cholesterol Transport

Cholesterol Efflux Capacity Beyond HDL Cholesterol Levels in Coronary Artery Disease (CAD)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.82 (1.26-2.63)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.30 (1.13-1.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.30 (0.95-1.78)</td>
<td>0.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.61 (0.86-3.08)</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.95 (0.70-1.31)</td>
<td>0.69</td>
</tr>
<tr>
<td>Efflux capacity</td>
<td>0.75 (0.43-1.30)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors. The logistic regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

What are the genetics of HDL and CVD?

Common SNPs Act in Concert to Affect Levels of HDL Cholesterol


Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study


Common SNPs Act in Concert to Affect Levels of HDL Cholesterol


Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

Heart Healthy HDL-C Raising Therapies

- Exercise: ≤10%
- Sustained Weight Loss: ~5%
- Alcohol: 5-15%
  - Gaziano JM et al, NEJM 329:1829, 1994
- Smoking cessation: 5-10%

For HDL, where’s the evidence?

Definitive HDL Cholesterol Outcome Studies

- AIM-HIGH
  - Purpose: This study intended to examine the CVD risk reduction of participants with CHD and low HDL-C and high TGs who were taking extended release niacin plus statins or statins alone.
    - N = 3414 enrolled
    - LDL-C was targeted to low levels in both groups
  - On May 26, 2011 AIM-HIGH was stopped 18 months early!
The Premature Termination of AIM-HIGH

- Study lasted 32 months
  - No benefit on primary outcome
- LDL cholesterol lowered to 71 mg/dl
- HDL cholesterol was increased by 15% in the niacin group
- Triglycerides were also reduced
- Strokes
  - 28 in niacin group
  - 12 in placebo group

AIM HIGH:
Niacin + Statin Fails to Reduce CVD Events

Definitive HDL Cholesterol Outcome Studies

- HPS2-Thrive
  - Purpose: The primary aim is to assess the effects of raising HDL-C with extended release niacin/laropiprant vs. matching placebo on the risk of MI or coronary death, stroke, or the need for revascularization in people with a history of circulatory problems.
  - Trial stopped on Dec 20, 2012 because of futility
HPS2 Thrive and CVD Risk: Another Niacin Failure

The HPS2-THRIVE Collaborative Group, NEJM 371:203, 2014

HPS2 Thrive and CVD Risk: Niacin/Laropiprant Adverse Effects

- Gastrointestinal
- Musculoskeletal
- Skin-related
- Infection
- Bleeding
- New-onset T2DM
- In T2DM – ↑ glycemia

All p<0.001 vs. placebo

The HPS2-THRIVE Collaborative Group, NEJM 371:203, 2014

CETP Inhibitors Markedly Increase HDL-C Levels

The HPS2-THRIVE Collaborative Group, NEJM 371:203, 2014
Dal-OUTCOMES: Lipid Effects

Schwartz GG et al. NEJM 367:208, 2012

Dal-OUTCOMES: Incidence of the Primary Efficacy End Point

Schwartz GG et al. NEJM 367:208, 2012

But if reverse cholesterol transport is the mechanism by which HDL reduces CVD risk, don't CETP inhibitors effectively allow the 'garbage truck to remain on the street longer'?
Drugs that Increase HDL-C

• Niacin ↑ 15-35%
• Fibrates ↑ 5-15%
• Statins ↑ 5-10%
• Resins ↑ 5-10%
• Estrogens – p.o. ↑ 10-15%
• CETP inhibitors ↑ 25–100%
  – Torcetrapib - abandoned
  – Dalcetrapib (JTT-705): Dal-OOUTCOMES stopped
  – Anacetrapib (MK-0859): REVEAL, EDC January, 2017

Hypertriglyceridemia and Apolipoprotein B

Plasma Triglycerides and CHD: Meta-Analysis of 29 Studies

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
<th>N = 262,525</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 years</td>
<td>5992</td>
<td>4256</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>7728</td>
<td>1994</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7484</td>
<td>2674</td>
</tr>
<tr>
<td>Female</td>
<td>4469</td>
<td>5689</td>
</tr>
<tr>
<td>Fasting status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>7484</td>
<td>2674</td>
</tr>
<tr>
<td>Non-fasting</td>
<td>4469</td>
<td>5689</td>
</tr>
<tr>
<td>Adjusted for HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.72 (1.56-1.90)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Individuals in top or bottom third of usual log-TG values; adjusted for at least age, sex, smoking status, and lipid concentrations; also adjusted for BP (in most studies).


TG = triglyceride.
Hypertriglyceridemia - the Most Difficult Lipid Disorder to Evaluate and Treat

- The genetic disorders are not monogenic.
  - Exceptions - LPL, apo CII, GPIHBP1 deficiency
- The acquired disorders are almost infinite.
- Is it the TG-rich particles that confer risk for ASCVD and/or the company they keep?

Atherogenicity of TG-Rich Lipoproteins

The Harmonized Definition of The Metabolic Syndrome (3 or more)
Approved by NHLBI, AHA, IDF, IAS, World Heart Federation

- Abdominal circumference (1 of 5)
  - men > 94 cm
  - women > 84 cm
  - adjusted locally around the world
- Triglycerides > 150 mg/dl
- HDL cholesterol
  - men < 40 mg/dl
  - women < 50 mg/dl
- Blood pressure > 130/85
- Glucose > 100 mg/dl


Hypertriglyceridemia - the Most Difficult Lipid Disorder to Evaluate and Treat

- The genetic disorders are not monogenic.
  - Exceptions: LPL, apo CII, GPIHDLBP1 deficiency
- The acquired disorders are almost infinite.
- Is it the TG-rich particles that confer risk for ASCVD and/or the company they keep?
- The clinical trials with fibrates to ↓ TG have suffered:
  - design
  - number of trials
  - results are hypothesis-generating at best

So Let’s See What We Can Conclude Here

- Fibrates do not reduce CHD events in high risk patient groups.
- The impact of hypertriglyceridemia on CHD outcomes remains unclear.
  - Post-hoc analysis indicates that high risk patients with TGs > 200 mg/dl (and ↓ HDL-C) may be more likely to benefit.
  - The amount of TG lowering may not predict benefit.
- Do you treat patients with fibrates who are not hypertriglyceridemic?
- The optimal trial awaits us!
  - VAFIT is approved and ready for recruitment.

Apolipoprotein B

- One apo B molecule/particle
- Assesses potentially atherogenic particle number
- Highly correlated with non-HDL cholesterol
  - 0.95 when TG < 300 mg/dl
  - 0.80 when TG higher
Is apo B useful in predicting risk in patients with hypertriglyceridemia?

Odds Ratios for the Development of CHD: Lipid and Lipoprotein Phenotypes

Odds are adjusted for age, smoking, alcohol, blood pressure, gender, and medications

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>1.8</td>
<td>(0.001)</td>
</tr>
<tr>
<td>IIIA</td>
<td>1.7</td>
<td>(0.005)</td>
</tr>
<tr>
<td>III</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>NITG ↑ TG</td>
<td>1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

Lamarche B et al., Am J Card 75:1189, 1995

Epidemiological, Non-Invasive Studies and Clinical Trials which Show that Apo B is a Better Marker of CVD Risk than LDL Cholesterol

**Two Major Unanswered Questions**

- Can apo B help distinguish CVD risk in hypertriglyceridemic patients with ‘acceptably low’ levels of LDL-C (with or without statins)?
- Should apo B lowering be a target for reducing CVD in hypertriglyceridemic patients with ‘acceptably low’ levels of LDL-C (with or without statins)?

**Lipids, Lipoproteins and Residual CVD Risk**

- HDL
- Hypertriglyceridemia
  - Apolipoprotein B
- Lipoprotein (a)
Lipoprotein (a) - a potential link between atherothrombosis and atherosclerosis?

- Present at very low to very high levels – (<0.1 → >250 mg/dL)
- Concentration is strongly influenced by hereditary

**Lipoprotein (a) et al and Atherosclerosis**

Tsimikas S and Hall JL, JACC 60:716, 2012
Lipoprotein (a) Genotype, Level and CHD Risk

Clarke R et al, NEJM 361:2518, 2009

Probability of CVD Events According to Increasing Quintiles of Lipoprotein(a) Levels

Suk Danik, J. et al. JAMA;296:1363, 2006

Lipoprotein (a) and CHD: The Reykjavik Study

Lipoprotein (a) and CVD Risk in Healthy Women

Table 3. Future Cardiovascular Events Among Initially Healthy Women According to Prespecified Thresholds of Lipoprotein (a).

<table>
<thead>
<tr>
<th>Coeff</th>
<th>Lipoprotein (a) Level, mg/dL</th>
<th>No. of Women</th>
<th>Cardiovascular Events, No. (%)</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>Fully Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h</td>
<td>110.3</td>
<td>910</td>
<td>72/160 (27%)</td>
<td>1.91 (1.24-2.94)</td>
<td>&lt;0.05</td>
<td>1.91 (1.24-2.94)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2h</td>
<td>165.0</td>
<td>910</td>
<td>72/160 (27%)</td>
<td>1.91 (1.24-2.94)</td>
<td>&lt;0.05</td>
<td>1.91 (1.24-2.94)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2h</td>
<td>&gt;150.0</td>
<td>910</td>
<td>72/160 (27%)</td>
<td>1.91 (1.24-2.94)</td>
<td>&lt;0.05</td>
<td>1.91 (1.24-2.94)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>


Aim-High, Lipoprotein (a) and CVD Events

Statin + Placebo (6% ↓ at Year 1)

Statin + Niacin (21% ↓ at Year 1)

Lipoprotein (a) is a critically important lipoprotein related to CVD Risk!

Now, what do we do about it?

Using the 2013 ACC/AHA Cholesterol Guidelines, there’s no evidence for measuring lipoprotein (a).

But no evidence doesn’t indicate that the evidence is no!
Lowering Lipoprotein (a)

- Niacin
- Mipomersen
- LDL apheresis
- CETP inhibitors
- Estrogens

Effect of HRT on Quintiles of Lipoprotein (a) and CVD Events in 27,736 Initially Healthy Women


Lowering Lipoprotein (a)

- Niacin
- Mipomersen
- LDL apheresis
- CETP inhibitors
- Estrogens
- Antisense oligonucleotide
Summary and Conclusions

- The epidemiology of HDL-C and CVD cannot be denied; however, at present HDL-C is not a target for drug therapy.
  - A heart healthy lifestyle is recommend.
- TG-lowering trials have failed but have suffered from design.
  - After ACC/AHA evidence-based statin, a fibrate should be considered for hypertriglyceridemic patients.
  - Apo B may be a better target.
- Lipoprotein (a) is pro-atherogenic but recommendations are absent at present.

Thank You!