Severe Hypertriglyceridemia
Confronting the Complex Issues in Etiology and Treatment

Course Chair
Peter P Toth, MD, PhD
Hypertriglyceridemia: A Clinical, Pathophysiological, and Personal Perspective

Allan D Sniderman
Edwards Professor of Cardiology
McGill University
Montreal, QC
Objectives

• Demonstrate that HTG is not a unitary entity
• Define HTG based on lipoprotein particles
• Evaluate cardiovascular risk and outline treatment of the different phenotypes

HTG: Hypertriglyceridemia
### Hypertriglyceridemia is Not a Diagnosis but a Group of Disorders with Differing Causes, Risks, and Treatment

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Vascular Risk</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td></td>
<td>F/FO</td>
</tr>
<tr>
<td>Chylo + VLDL</td>
<td></td>
<td>F/FO</td>
</tr>
<tr>
<td>Chylo + VLDL remnants</td>
<td>↑↑↑↑</td>
<td>S/?F</td>
</tr>
<tr>
<td>VLDL NormoapoB</td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>VLDL HyperapoB</td>
<td>↑↑↑↑</td>
<td>S</td>
</tr>
</tbody>
</table>
What is ApoB?
The More ApoB Particles in Plasma, the More Enter and Are Trapped in the Arterial Wall
What Is Wrong With This Patient?

- TC: 345 mg/dL
- Non-HDL C: 271 mg/dL
- HDL C: 36 mg/dL
- TG: 539 mg/dL
## What Is Wrong With This Patient?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>345 mg/dL</td>
</tr>
<tr>
<td>Non-HDL C</td>
<td>271 mg/dL</td>
</tr>
<tr>
<td>HDL C</td>
<td>36 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>539 mg/dL</td>
</tr>
<tr>
<td>ApoB</td>
<td>104 mg/dL</td>
</tr>
</tbody>
</table>
Based on only apoB, TC, and TG, all the apoB dyslipoproteinemias can be accurately diagnosed and separately treated.

apoB

NormoapoB < 120 mg/dL

NormoTG < 130 mg/dL

TG/apoB ≥ 8.8

apoB ≥ 75

Normal

apoB < 75

Chylo + VLDL

Chylo

Chylo + VLDL Remnants

HyperapoB ≥ 120 mg/dL

HyperTG ≥ 130 mg/dL

TG/apoB < 8.8

TC/apoB ≥ 2.4

VLDL

TC/apoB < 2.4

VLDL

HyperTG < 130 mg/dL

NormoTG < 130 mg/dL

LDL

HyperTG ≥ 130 mg/dL

VLDL + LDL
Mobile Application for Calculating ApoB
Mobile Application for Calculating ApoB

Advanced Lipid Diagnosis
The ApoB Diagnostic Algorithm

ApoB diagnostic algorithm for lipoprotein disorders: As easy as 1, 2, 3

Jacqueline de Graaf, MD PhD, internist
Allan Sniderman, MD PhD, cardiologist
Patrick Couture, MD PhD, internist
Mobile Application for Calculating ApoB

Step 1

Advanced Lipid Diagnosis
A simple diagnostic algorithm to determine which lipoproteins are elevated to help you diagnose lipid disorders.

Step-by-step Diagnosis
Use the algorithm step-by-step

Quick Diagnosis
Enter values and show elevated lipoproteins

Diagnostic Algorithm
View the chart of the algorithm

Information
About this app, contact & disclaimer

ApoB Lipoproteins App.
Mobile Application for Calculating ApoB

Step 2

ApoB
TC
TG

Quick Diagnosis

Enter the apoB value: 104
Enter the TC value: 345
Enter the TG value: 539

Apply Algorithm

ApoB Lipoproteins App.
Mobile Application for Calculating ApoB

Step 3: The Answer
Hyper Remnant Disorder (Type III)
Hyperchylomicronemia (Type I)
Hyper Chylomicrons and VLDL (Type V)
HTG HyperapoB (Type IV)
HTG NormoapoB (Type IV)
Hyper Remnant Disorder (Type III)
Frequency of Hyper Remnant Disorder

- LRC Prevalence Study - 0.4% of men >20 and 0.2 in women not on hormones
- Hopkins et al - 0.68% in a general population of 1700
- Most cases have triglycerides 150 to 300 mg/dL
- Prevalence amongst CAD is 2.7%
- Prevalence by apoB mobile application: 10.6% of 3,272 consecutive patients in lipid clinic
- By contrast, prevalence of FH is perhaps 0.2%

Lipids vs Lipoproteins in Type 2 Diabetes Mellitus

Patients with diabetes have high TG, low HDL-C; LDL-C tends to be normal

<table>
<thead>
<tr>
<th>Phenotype Frequencies based on TG and apoB</th>
<th>Phenotype Frequencies based on TG and LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.1% NormoTG, NormoapoB</td>
<td>35.7% Normal</td>
</tr>
<tr>
<td>30.1% HyperTG, HyperapoB</td>
<td>12.8% HyperTG, HyperLDL-C</td>
</tr>
<tr>
<td>26.5% HyperTG, NormoapoB</td>
<td>41.3 % HyperTG, NormoLDL-C</td>
</tr>
<tr>
<td>9.2% NormoTG, HyperapoB</td>
<td>10.2% NormoTG, HyperLDL-C</td>
</tr>
</tbody>
</table>

Which of These Patients Is at Higher Risk of CVD?

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>227</td>
<td>143</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>169</td>
<td>150</td>
</tr>
<tr>
<td>LDL-C</td>
<td>129</td>
<td>123</td>
</tr>
<tr>
<td>apoB</td>
<td>87</td>
<td>98</td>
</tr>
</tbody>
</table>

HTG NormoapoB (Type IV)
HTG HyperapoB (Type IV)
TG vs ApoB as Risk Factors: The Quebec Cardiovascular Study

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio of Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Risk</td>
<td>1.0</td>
</tr>
<tr>
<td>HyperTG, NormoapoB</td>
<td>1.0</td>
</tr>
<tr>
<td>HyperTG, HyperapoB</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Evidence CV Risk:
HTG HyperapoB > HTG NormoapoB

- 5/5 cross-sectional studies
- 3/3 prospective studies
  - Quebec Cardiovascular Study¹ *AJC* 1995
  - AMORIS² *Lancet* 2001
  - Northwick Park Heart Study³ *ATVB* 2002

Total ApoB = VLDL ApoB + LDL ApoB

- As apoB increases in hypertriglyceridemic patients, the same proportion of VLDL and LDL particles are retained
  - Exceptions: Type III, very high triglycerides
  - TG have been thought of as a VLDL disease, but they are an LDL catastrophe

That is why statins are so effective in these patients and fibrates are not.
Linked markers must be compared when they differ, not when they agree.
Discordance Analysis:
Compare Them When They Disagree, Not When They Agree

- **LDL I**
  - disagree
  - LDL C > apoB
  - Discordant

- **LDL II**
  - agree
  - LDL C = apoB
  - Concordant

- **LDL III**
  - disagree
  - LDL C < apoB
  - Discordant
# INTERHEART: ApoB vs Non-HDL-C Discordance Study

<table>
<thead>
<tr>
<th>Discordance (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB&lt; Non-HDL</td>
<td>0.76</td>
<td>0.7</td>
</tr>
<tr>
<td>ApoB~Non-HDL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ApoB&gt;Non-HDL</td>
<td>1.35</td>
<td>1.25</td>
</tr>
<tr>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB&lt; Non-HDL</td>
<td>0.75</td>
<td>0.7</td>
</tr>
<tr>
<td>ApoB~Non-HDL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ApoB&gt;Non-HDL</td>
<td>1.4</td>
<td>1.31</td>
</tr>
<tr>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB&lt; Non-HDL</td>
<td>0.73</td>
<td>0.68</td>
</tr>
<tr>
<td>ApoB~Non-HDL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ApoB&gt;Non-HDL</td>
<td>1.38</td>
<td>1.29</td>
</tr>
<tr>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB&lt; Non-HDL</td>
<td>0.73</td>
<td>0.68</td>
</tr>
<tr>
<td>ApoB~Non-HDL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ApoB&gt;Non-HDL</td>
<td>1.44</td>
<td>1.35</td>
</tr>
<tr>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB&lt; Non-HDL</td>
<td>0.72</td>
<td>0.67</td>
</tr>
<tr>
<td>ApoB~Non-HDL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ApoB&gt;Non-HDL</td>
<td>1.48</td>
<td>1.38</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB&lt; Non-HDL</td>
<td>0.67</td>
<td>0.61</td>
</tr>
<tr>
<td>ApoB~Non-HDL</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ApoB&gt;Non-HDL</td>
<td>1.61</td>
<td>1.48</td>
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According to INTERHEART: ApoB > Non-HDL-C as a marker of CV risk

<table>
<thead>
<tr>
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<th>Non-HDL-C &gt; ApoB</th>
<th>ApoB &gt; Non-HDL-C</th>
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Sniderman A et al Atherosclerosis 2012; 225: 444-49
Published Discordance Analyses

Risk: ApoB > non-HDL-C > LDL-C
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>ApoB</th>
<th>LDL-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>100</td>
<td>130</td>
<td>80</td>
<td>1000</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>70</td>
<td>100</td>
<td>70</td>
<td>800</td>
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Hypertriglyceridemia Is Not a Diagnosis but a Group of Disorders With Differing Causes, Risks, and Treatment

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</tr>
<tr>
<td>VLDL HyperapoB</td>
<td>↑↑↑↑</td>
<td>S</td>
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</table>
My Three Golden Rules for Treatment

1. When LDL apoB particles are elevated a lot, lower them a lot
2. When remnants are elevated a lot, lower them a lot
3. When risk is high, but neither remnants nor LDL are markedly elevated, lower LDL particles by lowering apoB
Confronting Issues of Concern in Hypertriglyceridemia

Sergio Fazio, MD, PhD
William and Sonja Connor Professor of Preventive Cardiology
Professor of Medicine
Director, Center of Preventive Cardiology
Oregon Health & Science University
Portland, Oregon
Secondary Hypertriglyceridemia
Secondary Causes of HTG

- Calorie excess
- Alcohol
- Physical inactivity
- Central adiposity
- Insulin resistance/metabolic syndrome/prediabetes
- Diabetes mellitus (poor glycemic control)
- Hypothyroidism
- Nephrotic syndrome
- Medications:
  - Oral estrogen, tamoxifen
  - Glucocorticoids
  - Antiretrovirals
  - Isotretinoin
  - Phenothiazines and some second-generation antipsychotics
  - Nonselective beta blockers, thiazide diuretics

Secondary Causes of HTG

- Practical Hints
  - Do not blame it on the genes too quickly
  - Consider every form of severe HTG as secondary and search for the cause
  - Think of alcohol as contributing cause if HDL is up with TG
  - Always get a direct LDL (low LDL is expected in exclusive HTG)
  - If LDL is high, combined dyslipidemia is likely to be genetically determined
  - Do not be too stern on fasting requirement
  - Consider a lipid panel 2 hours after a test meal (ie, McDonald’s EVM1, QPC)
  - Consider transient discontinuation of TG-lowering meds if you do not know the patient’s lipid baseline or if you are curious whether panel adjustment is due to recent lifestyle adjustments
Pancreatitis and More
Complications of Hypertriglycerideridemia

- Pancreatitis
- Eruptive xanthomatosis
- Perception of health status
- Reduced HDL, inappropriate LDL calculation
- Interference with lab tests
- Aggravation of the insulin resistance cycle
- Contribution to fatty liver and NASH
- Memory loss, lethargy, paresthesia
- Atherosclerosis

Hypertriglyceridermia and Pancreatitis

- TG-induced pancreatitis 10% of all cases
- Third most common cause after alcohol and gallstone disease
- 15% prevalence in Canadian lipid clinic cohort with TG>1700 mg/dL
- 20% prevalence in French lipid clinic cohort with TG>1000 mg/dL
- 19% prevalence in German lipid clinic cohort with TG>1000 mg/dL
- 10% prevalence among Spanish registry patients with TG>1000 mg/dL
- Average TG at admission: 4336 mg/dL

Pathophysiology of Pancreatitis

- Chylomicrons may obstruct capillaries, causing initial acinar damage and exposing TG to pancreatic lipase
- Release of free fatty acids leads to more sustained acinar damage
- Conversion of trypsinogen to trypsin leads to the release of inflammatory cytokines

An Illustrative Case, Although Atypical

• A 68 y/o previously healthy man without significant medical/surgical history
• Three hospitalizations for pancreatitis in the last year, with admission TG ranging from 4000 to 6500 mg/dL
• Underweight (BMI: 19 kg/m²), exercises, eats only organic foods, and grows most of it (no chemical fertilizers)
• Retired 2 years ago from running a construction company, and now spends hours every day in his studio painting
• Drinks alcohol daily but moderately (1 glass of wine)
• Used to be on no meds except for multivitamins and ASA 81 mg until last year
• Now on fibrate and supplemental high-dose fish oil
An Illustrative Case, Although Atypical

- Patient educated and compliant; shared all details about paints and natural fertilizers; no connections with TG problems found in the literature
- TG swinging from 350 to 2500 mg/dL, without apparent reason
- TG meter approved by medical insurance
- Stopped alcohol for 4 weeks; did not help with TG swings
- Increased the amount of exercise to 2 hours a day and reports: “I think exercise increases my triglycerides”
- No antibody against LpL identified
1. Is genetic testing warranted?
2. Is a post-heparin LpL activity test useful?
3. Would testing for apoB48 be informative?
4. EPA vs EPA/DHA?
5. Is ex-adjuvant anti-immune therapy advisable?
Hypertriglyceridemia and Atherosclerosis

- TG-rich lipoproteins carry as much cholesterol as LDL
- Fatty acids released by LPL are pro-inflammatory
- HyperTG causes atherogenic changes in LDL (increased particle number) and HDL (reduced particle number)
- ApoB levels are elevated in most forms of HyperTG
- TG-lowering drugs reduce CVD rates only in patients with HTG and low HDL-C

FFA = free fatty acid; LPL = lipoprotein lipase
**Meta-analysis of 29 Studies Shows TG Level Is a Significant CVD Risk Factor**

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

Triglycerides and CAD Risk: Evidence from Genetic Epidemiology Studies

A. 185 common variants for plasma lipids. For loci associated with both LDL-C and TG levels, direction and magnitude of both traits influence CAD risk. For loci with only a strong association with TG levels, association with CAD is also reported.

B. Four rare mutations in APOC3 associated with lower TG levels. Approximately 1 in 150 persons in the study was a heterozygous carrier of at least one of these mutations. Carriers had 39% lower TG levels than noncarriers. The risk of coronary heart disease among 498 carriers was 40% lower than the risk among 110,472 noncarriers.

CAD Risk is Increased with TG Levels ≥ 200 mg/dL

↑TG is independently associated with premature familial CAD*

*OR adjustments included HDL-C; n=653 (FHx early CAD), n=1029 (control).

FHx = family history.
TG ≥ 150 mg/dL Predicts Higher CHD\textsuperscript{a} Risk in Statin Patients Despite LDL-C < 70 mg/dL

**PROVE IT-TIMI 22 Trial\textsuperscript{b}**

(N=4162)

<table>
<thead>
<tr>
<th>LDL-C &lt; 70 mg/dL</th>
<th>CHD Event Rate After 30 Days\textsuperscript{c}</th>
<th>HR</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG &lt; 150 mg/dL</td>
<td>11.7%</td>
<td>0.72</td>
<td>0.017</td>
</tr>
<tr>
<td>TG ≥ 150 mg/dL</td>
<td>16.5%</td>
<td>0.84</td>
<td>0.192</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Death, MI, and recurrent ACS. \textsuperscript{b}ACS patients on atorvastatin 80 mg or pravastatin 40 mg. \textsuperscript{c}Adjusted for age, gender, low HDL-C, smoking, hypertension (HTN), obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment. CHD=coronary heart disease; HR=hazard ratio; PROVE IT-TIMI=Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis In Myocardial Infarction.

In HTG Patients, LDL-C Level Is Underestimated

Fasting Lipid Panel:
- TC: 198 mg/dL
- LDL: 130 mg/dL
- TG: 90 mg/dL
- HDL-C: 50 mg/dL
- Non-HDL-C: 148 mg/dL
- ApoB: 105 mg/dL

Fasting Lipid Panel:
- TC: 210 mg/dL
- LDL: 130 mg/dL
- TG: 250 mg/dL
- HDL-C: 30 mg/dL
- Non-HDL-C: 180 mg/dL
- ApoB: 130 mg/dL

The Friedewald calculation is affected by TG level
  – Additional technical consideration during diagnosis and treatment

The accuracy of LDL-C measurement decreases as TG level increases

Non-HDL Predicts ASCVD Risk Independently of LDL-C

Meta-analysis data at baseline and at 1-year follow-up from 62,154 patients enrolled in 8 randomized controlled statin trials published from 1994–2008.

<table>
<thead>
<tr>
<th>Target Level</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>Major CV Events (n)</th>
<th>Subjects (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥100</td>
<td>≥130</td>
<td>1877</td>
<td>10,419</td>
<td>1.21 (1.13–1.29)</td>
</tr>
<tr>
<td></td>
<td>≥100</td>
<td>&lt;130</td>
<td>467</td>
<td>2873</td>
<td>1.02 (0.92–1.12)</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>≥130</td>
<td>283</td>
<td>1435</td>
<td>1.32 (1.17–1.50)</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>2760</td>
<td>23,426</td>
<td>1.00 [ref.]</td>
</tr>
</tbody>
</table>

Most HTG Patients* Do Not Achieve LDL-C and Non-HDL-C Goals

NEPTUNE II: Patients With CHD and CHD Risk Equivalents

*TG ≥2.25 mmol/L (200 mg/dL).

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt; 100; &lt; 70 (all very high-risk patients)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>As high as possible, but at least &gt; 40 in both men and in women</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>30 above LDL-C goal</td>
</tr>
<tr>
<td>TG</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Apo B</td>
<td>&lt; 90 (patients at risk of CAD, including those with diabetes)</td>
</tr>
<tr>
<td></td>
<td>&lt; 80 (patients with established CAD or diabetes plus ≥ 1 additional risk factor)</td>
</tr>
</tbody>
</table>

Summary

- Large scale genetic studies support a causal relationship between TG and CAD
- High TG levels (≥ 150 mg/dL) predict higher CHD risk in patients on statin therapy despite LDL-C levels < 70 mg/dL
- HTG causes inaccurate LDL-C measurement
- Pancreatitis is the most dramatic consequence of severe TG elevations (TG > 1700 mg/dL)
Hypertriglyceridemia: Approaches to Management

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Director of Preventative Cardiology
CGH Medical Center, Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois School of Medicine
Peoria, Illinois
Professor of Clinical Medicine
Michigan State University College of Osteopathic Medicine
East Lansing, Michigan
Adjunct Associate Professor
Johns Hopkins University School of Medicine
Baltimore, Maryland
# Effects of Nutrition Practices on Triglyceride Lowering

<table>
<thead>
<tr>
<th>Nutrition Practice</th>
<th>TG Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (5% to 10% of body weight)</td>
<td>20%</td>
</tr>
<tr>
<td>Implement a Mediterranean-style diet vs. low-fat diet</td>
<td>10% - 15%</td>
</tr>
<tr>
<td>Add marine-derived PUFA (EPA/DHA) (per gram)</td>
<td>5% - 10%</td>
</tr>
<tr>
<td>Decrease carbohydrates (1% energy replacement with MUFA/PUFA)</td>
<td>1% - 2%</td>
</tr>
<tr>
<td>Eliminate trans fats (1% energy replacement with MUFA/PUFA)</td>
<td>1%</td>
</tr>
</tbody>
</table>

# Effect of Lipid-Lowering Therapies on TG Reduction (%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>30% - 50%</td>
</tr>
<tr>
<td>Niacin</td>
<td>20% - 50%</td>
</tr>
<tr>
<td>Omega-3</td>
<td>10% - 40%</td>
</tr>
<tr>
<td>Statins</td>
<td>10% - 30%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5% - 10%</td>
</tr>
</tbody>
</table>
Treating Hypertriglyceridemia: Niacin Therapy
• TG do not float freely in serum
  – Must be packaged into either chylomicrons or VLDLs in the liver
• Many patients with HTG experience large remnant particle elevations
• LDL can be reduced due to reduced conversion of large triglyceride-enriched lipoproteins
• Nicotinic acid can lower TGs in a dose dependent fashion
  – 2 g daily:
    ▪ 16% ↓ in serum LDL-C
    ▪ 25% ↓ in serum Lp(a)
    ▪ 32% ↓ in serum TG levels

## AIM HIGH: Baseline Lipids (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>On Statin (n = 3,196)</th>
<th>Off Statin (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mean)</td>
<td>71</td>
<td>119</td>
</tr>
<tr>
<td>HDL-C (mean)</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Triglycerides (median)</td>
<td>161</td>
<td>215</td>
</tr>
<tr>
<td>Non-HDL (mean)</td>
<td>107</td>
<td>165</td>
</tr>
<tr>
<td>ApoB (mean)</td>
<td>81</td>
<td>111</td>
</tr>
</tbody>
</table>

AIM-HIGH Primary Outcome

HR 1.02, 95% CI 0.87, 1.21
Log-rank $P$ value = 0.79

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Monotherapy at risk</th>
<th>Combination Therapy at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1696</td>
<td>1718</td>
</tr>
<tr>
<td>1</td>
<td>1581</td>
<td>1606</td>
</tr>
<tr>
<td>2</td>
<td>1366</td>
<td>1381</td>
</tr>
<tr>
<td>3</td>
<td>903</td>
<td>910</td>
</tr>
<tr>
<td>4</td>
<td>428</td>
<td>436</td>
</tr>
</tbody>
</table>

16.2% vs. 16.4%
Effect of High-risk Groups on Primary Outcome

<table>
<thead>
<tr>
<th># Pts. with Events (% of Category)</th>
<th>ERN Better</th>
<th>ERN Worse</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-val.** Int.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG ≥ 198 and HDL &lt; 33</strong> *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Yes</em> 48 (17.0) 54 (22.4)</td>
<td></td>
<td></td>
<td>0.74 (0.50, 1.09)</td>
<td>0.073</td>
</tr>
<tr>
<td><em>No</em> 234 (16.3) 220 (15.1)</td>
<td></td>
<td></td>
<td>1.09 (0.91, 1.31)</td>
<td></td>
</tr>
<tr>
<td><strong>TG ≥ 200 and HDL &lt; 32</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Yes</em> 40 (16.7) 50 (25.0)</td>
<td></td>
<td></td>
<td>0.63 (0.40, 0.98)</td>
<td>0.017</td>
</tr>
<tr>
<td><em>No</em> 242 (16.2) 224 (15.0)</td>
<td></td>
<td></td>
<td>1.11 (0.93, 1.33)</td>
<td></td>
</tr>
</tbody>
</table>

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

Treating Hypertriglyceridemia: Fibrate Therapy
# Reduction in CV Events: Fibrate Studies

<table>
<thead>
<tr>
<th>Study (fibrate)</th>
<th>Primary endpoint (all patients)</th>
<th>Lipid criteria (mmol/L)</th>
<th>Primary endpoint (lipid subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD (fenofibrate/simvastatin)</td>
<td>-8% ((P=0.32))</td>
<td>TG(\geq2.3 ) + HDL-C (\leq0.88)</td>
<td>-31%</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>-11% ((P=0.16))</td>
<td>TG(\geq2.3 ) + Low HDL-C ($)</td>
<td>-27% ((P=0.005))</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>-7.3% ((P=0.24))</td>
<td>TG(\geq2.3 ) + HDL-C (\leq0.9)</td>
<td>-39.5% ((P=0.02))</td>
</tr>
<tr>
<td>HHS (gemfibrozil)</td>
<td>-34% ((P&lt;0.02))</td>
<td>TG(\geq2.3 ) + LDL/HDL (&gt;5.0)</td>
<td>-71% ((P&lt;0.005))</td>
</tr>
</tbody>
</table>

*Comparator treatments: simvastatin in ACCORD Lipid and placebo in other studies; § <1.03 in men and <1.29 in women

**SAFARI: Combination Therapy in Patients With Combined Hyperlipidemia**

SAFARI = Simvastatin plus fenofibrate for combined hyperlipidemia trial.

*P<0.001 vs. simvastatin.*
Treating Hypertriglyceridemia: Omega-3 Fatty Acid Therapy
Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels: Physicians' Health Study

GISSI-Prevenzione: Time Course of Clinical Events

- > 11,300 post-MI patients were given usual care with or without 850 mg EPA+DHA for 3.5 years
  - Total mortality ↓ 28% ($P = 0.027$)
  - Sudden death ↓ 47% ($P = 0.0136$)
- Benefit discernable early during treatment period
- Lipid profiles show reduction in TG with no change in TC, LDL-C, or HDL-C

**Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis**

- \( n > 18,000 \) (Japan)
- All administered statins
- Primary and secondary prevention
- 5-year followup
- 1800 mg EPA/day
- Mean TG = 150 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=9319)</th>
<th>EPA Treatment (N=9326)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61 (9)</td>
<td>61 (8)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>2908 (31%)</td>
<td>2951 (32%)</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td>24 (3)</td>
<td>24 (3)</td>
</tr>
<tr>
<td><strong>Cardiovascular History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>502 (5%)</td>
<td>548 (6%)</td>
</tr>
<tr>
<td>Angina</td>
<td>1484 (16%)</td>
<td>1419 (15%)</td>
</tr>
<tr>
<td>CABG or PTCA</td>
<td>433 (5%)</td>
<td>462 (5%)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1700 (18%)</td>
<td>1830 (20%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1524 (16%)</td>
<td>1516 (16%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>3282 (35%)</td>
<td>3329 (36%)</td>
</tr>
<tr>
<td><strong>Serum lipid values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.11 (0-68)</td>
<td>7.11 (067)</td>
</tr>
<tr>
<td>LDL-c (mmol/L)</td>
<td>470 (0-75)</td>
<td>4-69 (0-76)</td>
</tr>
<tr>
<td>HDL-c (mmol/L)</td>
<td>1.51 (0-44)</td>
<td>1-52 (0.46)</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.74 (1-25—2.49)</td>
<td>1.73(1-23-2.48)</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>135 (21)</td>
<td>135 (21)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>79 (13)</td>
<td>79 (13)</td>
</tr>
<tr>
<td><strong>HMG COA RI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>5553 (60%)</td>
<td>5523 (60%)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3417 (37%)</td>
<td>3272 (36%)</td>
</tr>
<tr>
<td>Other statin</td>
<td>128 (1%)</td>
<td>110 (1%)</td>
</tr>
</tbody>
</table>

• But…minimal (5%) Net TG lowering effect
  – 19%↓ in the cumulative incidence of major coronary events at 6 years in the statin + EPA group relative to statin use alone ($P = 0.011$)
    ▪ Benefit discernable at about 6 months of therapy

Addition of Eicosapentaenoic Acid (EPA) to Statin Therapy in Japanese Patients

Major CHD Events*

<table>
<thead>
<tr>
<th></th>
<th>Statin Alone</th>
<th>Statin + EPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event rate (%)</td>
<td>3.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

19% Reduction
P=0.011

Lipid Effects

Change from Baseline:
- No change in LDL-C
- No change in TC
- TG reduced by ~50% (P<0.0001)

* Sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or CABG.
CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol.
Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)

- 53%↓ in the cumulative incidence of major coronary events in the EPA group relative to controls
  - HR: 0.47, 95% CI: 0.23-0.98, $P=0.043$

Patient Subgroup – TG > 150 mg/dL and HDL < 40 mg/dL: JELIS

Prescription Omega-3 Fatty Acids (EPA and DHA Ethyl Esters)

- **Omega-3-acid ethyl esters** are a combination of ethyl esters of omega-3-fatty acids containing 465 mg EPA and 375 mg DHA in 1 gram capsule.

- **Omega-3-acid ethyl esters** are FDA approved for very high TG (> 500 mg/dL).

- The daily dose of **omega-3-acid ethyl esters** is 4 g per day taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily).

http://www.pdr.net/full-prescribing-information?druglabelid=211
Prescription Omega-3 Fatty Acids (EPA and DHA Free Fatty Acids)

- **Omega-3-carboxylic acids** are a fish oil-derived mixture of free fatty acids, with at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids (EPA and DHA being the most abundant)

- **Omega-3-carboxylic acids** are FDA approved for very high TG (> 500 mg/dL)

- The daily dose of **omega-3-carboxylic acids** is 2 g (2 capsules) or 4 g (4 capsules) once daily.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205060s000lbl.pdf
Prescription Omega-3 Fatty Acids (EPA Ethyl Esters Only)

- **Icosapent ethyl** is a 96% pure ethyl ester of eicosapentaenoic acid (EPA)
- **Icosapent ethyl** is FDA approved for very high TG (> 500 mg/dL)
- The daily dose is 4 g per day taken as 2 capsules twice daily

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202057s002lbl.pdf
### Icosapent Ethyl 4 g/day vs Icosapent Ethyl 2 g/day

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl 4 g/day</th>
<th>Reduction from Baseline</th>
<th>Icosapent Ethyl 2 g/day</th>
<th>Reduction from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG</strong></td>
<td>265</td>
<td>-21.5****</td>
<td>254</td>
<td>-10.1***</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>128</td>
<td>-13.6****</td>
<td>128</td>
<td>-5.5**</td>
</tr>
<tr>
<td>ApoB</td>
<td>93</td>
<td>-9.3****</td>
<td>91</td>
<td>-3.8*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>82</td>
<td>-6.2**</td>
<td>82</td>
<td>-3.6 (NS)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>37</td>
<td>-4.5**</td>
<td>38</td>
<td>-2.2 (NS)</td>
</tr>
</tbody>
</table>

****P<0.0001; ***P<0.001; **P<0.01; *P<0.05; NS = not significant (P≥0.05), icosapent ethyl vs placebo

### Bottom line:
- EPA+DHA better for ↓TG & ↑HDL-C.
- EPA better for ↓LDL-C, ↓Non-HDL-C, ↓Apo B (↓CVD?)

### Statin + EPA/DHA (TG 200-500 mg/dL): COMBOSOS Lipid Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Median Change from Baseline (%)</th>
<th>Omega-3 4 g/d + simvastatin 40 mg/d</th>
<th>Placebo + simvastatin 40 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>-9.0*</td>
<td>-2.2</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>-29.5*</td>
<td>-6.3</td>
<td></td>
</tr>
<tr>
<td>VLDL-C</td>
<td>-27.5*</td>
<td>-7.2</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.7†</td>
<td>-2.8</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>3.4*</td>
<td>-1.2</td>
<td></td>
</tr>
<tr>
<td>ApoB</td>
<td>-4.2†</td>
<td>-1.9</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001 between groups; †P=0.0232 between groups; ‡P=0.0522 between groups.
TG 200-500 baseline on statin.

Lipid Effects of Prescription Omega-3 in TG > 500 mg/dL

**EVOLVE (EPA+DHA FFA)**

- **LS Mean Change from Baseline (%)**
  - OMG3CA 2g (N=215)
  - OMG3CA 4g (N=216)
  - Olive Oil (N=216)

**MARINE (EPA EE)**

- **Median Change from Baseline (%)**
  - Icosapent ethyl 4g (N=76)
  - Placebo Corrected (N=76)
  - Placebo (N=75)

**EPA+DHA EE**

- **Median Change from Baseline (%)**
  - OMG3EE4g (N=42)
  - Placebo Corrected (N=42)
  - Placebo (N=42)

**LDL-C ∆**

- OMG3CA 2g: +19.4%*
- OMG3CA 4g: +19.2%*
- Olive Oil: +3%

- Icosapent ethyl 4g: -4.5%
- Placebo Corrected: -7.5%
- Placebo: +3%

- OMG3EE4g: +45%*
- Placebo Corrected: +49.8%
- Placebo: -4.8%

ApoC-III Inhibits the Conversion of VLDL to LDL and Causes Small Dense LDL and Low HDL

Hypertriglyceridemia

Liver

DGAT

Glycerol

Small, dense HDL

Apo A-I

VLDL

TG

TG

TG

TG

CE

ApoC-III

CETP

TG

CE

Small, dense LDL

LDL

Apo B-100

ApoC-III Promotes Dyslipidemia and Atherosclerosis

- ApoC-III is a liver-derived apolipoprotein present on TG-rich lipoproteins and HDL
- ApoC-III promotes hypertriglyceridemia by inhibiting lipoprotein lipase and inhibiting binding of apoE to hepatic receptors, thus reducing lipolysis and clearance of TG-rich lipoproteins
- ApoC-III-containing LDL are more strongly associated with cardiovascular risk than LDL without apoC-III
- Mutations that reduce apoC-III plasma concentrations are associated with reduced TG, increased HDL-C, and reduced coronary atherosclerosis
- ApoC-III is of considerable interest as a validated target for therapeutic inhibition
- Some small studies have suggested that omega 3 fatty acids (fish oils) may reduce apoC-III
Apolipoprotein C-III has Significant Consequences for Lipoprotein Metabolism

Apo C-III Effects

- ApoC-III modifies particle composition\(^1\)
  - Inhibits the conversion of VLDL to LDL
  - Causes an increase in small, dense LDL and a decrease in HDL-C

- Glucose increases apoC-III gene expression and therefore may link diabetes and TGs\(^2\)

- ApoC-III-enriched LDL can increase monocyte binding to endothelial cells\(^3\)

- ApoC-III in VLDL+LDL is a marker of increased risk of recurrent coronary events\(^4\)

LSR=lipolysis stimulated lipoprotein receptor; SR-B1=scavenger receptor class B1; LCAT=lecithin-cholesterol acyltransferase; CETP=cholesteryl ester transfer protein; LPL=lipoprotein lipase; LDLr=low-density lipoprotein receptor.

CARE Trial, ApoC-III in VLDL + LDL Was a Marker of Increased Risk of Recurrent Coronary Events

- ApoC-III content in VLDL and LDL particles increased relative risk for coronary events 2.25 fold ($P=0.001$)

Omega 3 Significantly Reduced ApoC-III Concentrations

In Clinical Trials, Reductions in ApoC-III Are Associated with Omega-3 Products That Contain DHA

EPA alone

- EPA 2.7 g/d

Baseline | Week 4 | Week 12
--- | --- | ---
-15 | 0 | 5

Change (%)

N= 15

DHA vs. PBO

- DHA 3 g/day
- Placebo

Baseline | Day 45 | Day 90
--- | --- | ---
-15 | -5 | 0

Change (%)

N= 17, 17
P<0.01

DHA vs. EPA vs. PBO

- EPA 5 g/d
- DHA 5 g/d
- PBO

Baseline | EPA 5 g/d | DHA 5 g/d | PBO
--- | --- | --- | ---
-15 | 6 | 0

Change (%)

N= 15, 12, 15
Event-driven CV Outcome Trials with Omega-3 FA

Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT)
- Enrolling 8000 men and women ≥45 years; prior CHD (70% patients) or T2DM + > 1RF; atherogenic dyslipidemia (Hx of increased TC (at LDL-C goal on statin), TG 150-500 mg/dL
- Treatment: icosapent ethyl 4 g/d or placebo
- Primary outcome measure: composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by non-invasive testing and requiring emergent hospitalization
- Follow-up: 4-6 years
- Estimated primary completion date: November 2016

Outcome Study to Assess Statin Residual Risk Reduction With Omega-3 Carboxylic Acids in Hypertriglyceridemia (STRENGTH)
- Estimated enrollment: 13,000 high risk adults for CVD on statin therapy
- Treatment: Omega-3 carboxylic acids 4 g/d or placebo
- Primary outcome measure: cardiovascular death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina
- Follow-up: 5 years

Conclusions

• Hypertriglyceridemia is an important risk factor for atherosclerotic disease and contributes to residual risk after statin therapy.
• HTG is a marker for elevated serum levels of remnant lipoproteins, all components of non-HDL cholesterol.
• Niacin and fenofibrate have the capacity to reduce hepatic VLDL secretion; fenofibrate also promotes TG lipolysis by activating lipoprotein lipase.
• Subgroup analyses from niacin and fibrate trials suggest they may impact CV risk in patients with HTG and low HDL.
Conclusions

• The omega-3 fish oils are long-chain fatty acids that activate key pathways for triglyceride disposal and reduce serum levels of triglyceride.

• The omega-3 fish oils are indicated for the treatment of severe HTG (> 500 mg/dL).

• Outcomes trials (STRENGTH, REDUCE-IT) are underway to establish if these agents reduce risk for CV events in patients with moderate HTG.
Severe Hypertriglyceridemia
Confronting the Complex Issues in Etiology and Treatment

Course Chair
Peter P Toth, MD, PhD