Hypertriglyceridemia: Epidemiology, Metabolism, and Management

Peter P. Tóth, MD, PhD, FAAFP, FICA, FCCP, FAHA, FACC
Director of Preventive Cardiology
Sterling Rock Falls Clinic
Sterling, Illinois
Clinical Professor
University of Illinois School of Medicine
Peoria, Illinois

National Cholesterol Education Program
Adult Treatment Panel III NCEP-ATP III
Risk of Triglycerides

- Several causes underlie elevated Triglycerides in the general population
  - Overweight and obesity
  - Physical inactivity
  - Cigarette smoking
  - Excess alcohol intake
  - Very high carbohydrate diets (>60% of energy)
  - Other disease (diabetes, renal failure, nephrosis)
  - Drugs: steroids, protease inhibitors, estrogen, etc
  - Genetic factors

National Cholesterol Education Program
Adult Treatment Panel III NCEP-ATP III
Risk of Triglycerides: Lipoprotein Remnants

Renewed interest in the importance of elevated triglycerides has been stimulated by the publication of meta-analyses that found that raised triglycerides are in fact an independent risk factor for CHD.

This independence suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

The most likely candidates for atherogenic TGRLP are remnant lipoproteins. These lipoproteins include small very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). They are cholesterol enriched particles and have many of the properties of LDL.

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Adult Treatment Panel III NCEP-ATP III
Risk of Triglycerides

When triglyceride levels are ≥200 mg/dL, the presence of increased quantities of atherogenic remnant lipoproteins can heighten CHD risk substantially beyond that predicted by LDL cholesterol alone.

For these reasons, ATP III modified the triglyceride classification to give more attention to moderate elevations.

Study (PROCAM) Risk of CHD by Triglyceride
8-Year Follow-Up

- Elevated triglyceride levels significantly increase CHD risk
- Significant correlation remains between triglyceride level and CHD risk after adjustment for LDL-C and HDL-C
- 6-fold increased CHD risk in patients with triglycerides >200 mg/dL and LDL-C/HDL-C >5


Triglycerides

The Framingham Heart Study

Women

Castelli WP. Am J Cardiol. 1992;70:3H-9H.

The Baltimore Coronary Observational Long-Term Study

N=740 with angiographic CHD at baseline

What is the prevalence without new CAD event after 18 years

According to standard baseline risk factors

Miller, M J Am Coll Cardiol 1998;31:1252-7

The Copenhagen Male Study

2906 men free of CVD 8 year follow up 229 men had first CHD event

For the trend \( p > 0.001 \)


Copenhagen Male Study

Risk of Ischemic Heart Disease (IHD) Associated With Higher TG and Lower HDL-C

Adjusted for all possible confounders


CAD Risk in European Concerted Action on Thrombosis (ECAT)-Angina Pectoris Study

Thromb Haemost 2000;84:955-960

Thomas Dayspring MD, FACP
TG >150 mg/dL Increases CHD Events\(^a\) in Patients With ACS on Statins\(^b\)

**Framingham Offspring Study**

As TG rise so does LDL particle concentration.

Above TG of 150 to 175 mg/dl LDL-C starts to fall.

\(^a\) Each 10 mg/dL, \( \Delta \) in TG = 1.8% \( \Delta \) in CHD risk (\( \text{P}<0.0001 \))

\(^b\) Pravastatin Pooling Project

**NCEP Guidelines: Patient Types Based on Fasting TG Levels**

<table>
<thead>
<tr>
<th>Patient Type (category)</th>
<th>Fasting TG Level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>( \geq 500 )</td>
</tr>
<tr>
<td>High</td>
<td>200-499</td>
</tr>
<tr>
<td>Borderline high</td>
<td>150-199</td>
</tr>
<tr>
<td>Normal</td>
<td>(&lt; 150 )</td>
</tr>
</tbody>
</table>

\* Continue TLC even if lipid-lowering drug therapy is started

Pravastatin treatment is effective in reducing coronary heart disease events in patients with high or low risk factor status and across a wide range of pretreatment lipid concentrations, but efficacy is less as TG rise.

**Pravastatin Pooling Project**

Concentration:

**Elevated Triglycerides Are Associated With Altered Metabolism of LDL and HDL Particles**

**Trials of Fibrates: Effects on Cholesterol and Triglyceride**

**Adapted from Bays H, et al. Circulation 2003;4:1901-1938.**

**Triglycerides**

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Triglycerides

HHS: Marked Reduction of CHD Events in Patients With High Triglyceride Levels and LDL/HDL Ratio


71% Reduction

LDL/HDL > 5

Triglyceride values are in mg/dL

BIP: Baseline Triglyceride Determinant of Response to Bezafibrate


Baseline LDL-C: Placebo, 148 mg/dL; Bezafibrate, 149 mg/dL

39.5% Reduction

p=0.02

SAFARI: Combination Therapy in Patients With Combined Hyperlipidemia


*P <0.001 versus simvastatin.

N = 618

HDL-C < 42 mg/dl

-27%

ACCORD (Fenofibrate) - 8% (0.32)

TG > 204 mg/dl

HDL-C < 34 mg/dl

-31%

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>175</td>
</tr>
<tr>
<td>Women %</td>
<td>31</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>101</td>
</tr>
<tr>
<td>Women %</td>
<td>31</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>38</td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White %</td>
<td>68</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)*</td>
<td>162</td>
</tr>
<tr>
<td>Black %</td>
<td>15</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>134/74</td>
</tr>
<tr>
<td>Hispanic %</td>
<td>7</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9</td>
</tr>
<tr>
<td>Secondary prevent %</td>
<td>37</td>
</tr>
<tr>
<td>Current smoking %</td>
<td>15</td>
</tr>
<tr>
<td>DM duration (yrs)*</td>
<td>9</td>
</tr>
<tr>
<td>On a statin %</td>
<td>60</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>8.3</td>
</tr>
<tr>
<td>On another LLA %</td>
<td>8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32</td>
</tr>
<tr>
<td>On Insulin %</td>
<td>33</td>
</tr>
</tbody>
</table>

*Median value

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### Primary Outcome by Treatment Group and Baseline Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Primary Endpoint: Subgroup (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.1% (0.2)</td>
<td>11.2% (0.2)</td>
</tr>
<tr>
<td>HHS</td>
<td>Gemfibrozil -34% (0.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG &gt; 200 mg/dl</td>
<td>-39.5%</td>
</tr>
<tr>
<td></td>
<td>LDL-C/HDL-C &gt; 5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BIP</td>
<td>Bezafibrate -7.3% (0.24)</td>
</tr>
<tr>
<td></td>
<td>TG &gt; 200 mg/dl</td>
<td>-39.5%</td>
</tr>
<tr>
<td></td>
<td>FIELD</td>
<td>Fenofibrate -11% (0.16)</td>
</tr>
<tr>
<td></td>
<td>TG &gt; 204 mg/dl</td>
<td>-27%</td>
</tr>
<tr>
<td></td>
<td>HDL-C &lt; 42 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACCORD</td>
<td>Fenofibrate -8% (0.32)</td>
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<td>-31%</td>
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<tr>
<td></td>
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### Comparison of ACCORD subgroup results with those from prior fibrate studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: Subgroup (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS</td>
<td>Simvastatin</td>
<td>LDL-C/HDL-C &gt; 5.0</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>(Gemfibrozil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG &gt; 200 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td>Bezafibrate</td>
<td>HDL-C ≤ 42 mg/dl</td>
<td>39.5%</td>
</tr>
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<td></td>
<td>(Bezafibrate)</td>
<td></td>
<td></td>
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<tr>
<td>FIELD</td>
<td>Fenofibrate</td>
<td>HDL-C ≤ 42 mg/dl</td>
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</tbody>
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### Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS)

- Open label study of ~15000 Japanese in a primary prevention study and 3600 others for secondary prevention
- AI received either 5-10 mg of Simvastatin or 10-20 mg of Pravastatin and then randomized to 1800 mg/day of eicosapentaenoic acid ethyl ester (EPA)
- Blinded adjudication of outcomes
- After 4 years of study the composite endpoint (sudden cardiac death, MI, unstable angina and/or coronary revascularization)
- 18% reduction in primary (ns) and 19% in secondary prevention (significant)


### Japan EPA Lipid Intervention Study (JELIS)

- Source: Lipids Online Slide Library, www.lipidsonline.org
- Yokoyama M. Presented at American Heart Association Scientific Sessions, Dallas, Texas, November 14, 2005

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Triglycerides

Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS)

Effects of EPA on MCE incidence for the high TG/low HDL-C Group

Saito Y et al. Atherosclerosis 2008;

GISSI-Prevenzione: Time Course of Clinical Events

EPA Group

0 1 2 3 4 5
Cumulative incidence of major coronary events (%)

HR: 0.47
95% CI: 0.23-0.98
p=0.043

-53%

Cumulative Incidence of major coronary events (%)

Total mortality reduced by 28%
(P=0.027)

Sudden death reduced by 47%
(P=0.0136)


CONCLUSIONS

• Hypertriglyceridemia adversely impacts lipoprotein physiology by stimulating HDL catabolism and promoting an increase in the numbers of small, dense LDL particles. It is associated with elevations in VLDL and remnant particles (i.e., incompletely digested VLDL and chylomicrons).

• Hypertriglyceridemia is associated with insulin resistance, familial combined hyperlipidemia, and a large number of genetic polymorphisms.

• Serum triglycerides can be lowered by a diet reduced in saturated fat, statins, fibrates, fish oils, TZDs, and the pancreatic lipase inhibitor orlistat.

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