Clinical Management of Hypertriglyceridemia: State of the Art 2015

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Eliot A. Brinton, MD, FAHA, FNLA
President, American Board of Clinical Lipidology
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
President, Utah Lipid Center
Salt Lake City
eliot.brinton@utah.edu
Speaker Disclosures

Dr. Brinton has received:

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• Honoraria as **consultant/advisor**: Amarin, Amgen, Arisaph, AstraZeneca, Atherotech, Janssen, Kowa, Lilly, Merck, Novartis, Sanofi-Aventis, Synageva

• Honoraria as **speaker**: Aegerion, Amarin, AstraZeneca, Genzyme, Janssen, Kowa, Merck, Synageva, Takeda
Learning Objectives

Participants should be able to:
1. Discuss the prevalence and pathophysiology of hypertriglyceridemia (HTG)
2. Appreciate the likely causal connection of HTG with acute pancreatitis and atherosclerotic cardiovascular disease (ASCVD)
3. Diagnose HTG and its atherogenic sequelae
4. Acknowledge TG-lowering medications in development
5. Implement appropriate management of HTG
TG Categories: Names, Disease Risks, and Drug Approval Pathways

<table>
<thead>
<tr>
<th>TG Range (mg/dL)</th>
<th>NCEP ATP-III ¹</th>
<th>AHA Statement ² NLA Statement ³</th>
<th>Disease Risk</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Desirable</td>
<td>Optimal</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>Normal</td>
<td>Dyslipidemia</td>
<td>No Rx interest</td>
<td></td>
</tr>
<tr>
<td>150-199</td>
<td>Borderline High</td>
<td>Borderline</td>
<td>More dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>200-499</td>
<td>High</td>
<td>High</td>
<td>↑CVD</td>
<td>Approve if ↓CVD likely</td>
</tr>
<tr>
<td>≥500</td>
<td>Very High</td>
<td>Very High</td>
<td>↑CVD &amp; sl ↑pancreatitis ⁴ (esp ↑ if &gt;2000)</td>
<td>Approve if reasonable safety</td>
</tr>
</tbody>
</table>

4. ↑Risk of acute pancreatitis at this level is mainly due to ↑TG variability.
Prevalence of HTG in US Adults

3.4 million Americans have very high TG

Triglyceride Level (mg/dL)

Increasing Prevalence of HTG Parallels Increased Obesity in the US

Very-High and Severe HTG are Usually Genetic


**“Very High” cutoff per AHA Consensus Panel Statement. **“Severe” cutoff per EAS Consensus Panel.

Metabolism of TG-Rich Lipoproteins
Normal Metabolism of TGRLp: Exogenous (Dietary Origin)


Normal Metabolism of TGRLp: Endogenous (Hepatic Origin)

TG within VLDL:
- derived from glycerol + fatty acids from plasma
- newly synthesized in the liver (fructose driven)

Apo, apolipoprotein; VLDL, very low-density lipoprotein; CE, cholesteryl ester

Normal Plasma Metabolism of TGRLp: Hepatic Origin

IDL, intermediate-density lipoproteins; LDL, low-density lipoprotein

- LDL receptor clears VLDL remnants, IDL & LDL
Cholesterol Enrichment of VLDL and Shrinkage of LDL & HDL Promoted by CETP in HTG

- CETP-mediated exchange affects composition and metabolism of VLDL, LDL, and HDL
- Occurs at all TG levels but is greatly increased w/ HTG, causing “Atherogenic Dyslipidemia”

HDL, high-density lipoprotein; LDL, low-density lipoprotein; CETP, cholesteryl ester transfer protein
Lipid Measurements in HTG Patients
Increasing Inaccuracy of Friedewald LDL-C with Increasing TG

On routine lipid panel, LDL-C is calculated using the Friedewald Formula:

\[ LDL-C = \text{Total Cholesterol} - \text{HDL-C} - \frac{\text{TG}}{5} \]

Absolute underestimation of LDL-C (by Friedewald) by Fasting TG level

Even modest increases in TG result in LDL-C underestimation using Friedewald formula

Increasing Inaccuracy of Friedewald LDL-C with Increasing TG

On routine lipid panel, LDL-C is calculated using the Friedewald Formula:

\[ \text{LDL-C} = \text{Total Cholesterol} - \text{HDL-C} - \frac{\text{TG}}{5} \]

Even modest increases in TG result in LDL-C underestimation using Friedewald formula.

Direct LDL-C solves this problem, but there may be a better solution...

What is Non-HDL-C?

Non-HDL-C = Total cholesterol – HDL-C
Non–HDL-C Is Stronger than LDL-C in Predicting CHD Risk

Non-HDL-C Advantages vs other Lipid Parameters

• **Stronger CVD risk** predictor than TG (less variable, less loss w/ adjustments)
• Measures chol content of TG-rich lipoproteins
• **Stronger CVD risk** predictor than LDL-C
• More stringent than LDL-C (only ~ ½ of pts at LDL-C goal also at Non-HDL-C goal)
• Valid non-fasting (not true for LDL-C)
• Valid in HTG (not true for LDL-C)
• ~**Comparable** to apo B/LDL-P, yet
• **Free** with basic lipid panel
• Guideline goal consensus (IAS, NLA, etc.)
TG Measurement: Summary

- **Fasting TG** is standard (12 hr, water ok)
- Non-fasting TG predicts CVD risk in populations\(^1\) but too variable in individuals?\(^2\)
- If NF TG <200 mg/dL fasting TG not neces.\(^2\)
- SD LDL remains important (see below)
- Remnant particle testing *controversial*
  - Post-prandial (cumbersome, no standards)
  - RLP-C—easy but ?accuracy ?validation
  - DGUC—apo A-I/Rem ratio?\(^3\)
  - **Beta-quant best to R/O type III**\(^4\)
  - Other: NMR? ion mobility?
  - Friedewald VLDL-C (=TG/5) is NOT remnants!\(^5\)
- **Non-HDL-C incl. all**, is free, has consensus

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Does HTG Cause Disease?
Pancreatitis Risk ↑↑ w/ TG >500 mg/dL

- HTG is the 3rd biggest cause of acute pancreatitis (~10%) after alcohol & gallstones\(^1,\text{2}\)
- Acute pancreatitis risk ↑4%/100 mg/dL ↑ TG* (HR, 1.04)\(^3\)

Incidence of Acute Pancreatitis by TG\(^3\)

<table>
<thead>
<tr>
<th>Triglycerides (mg/dL)</th>
<th>Crude Incidence (Cases/1000 Patient-Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>0.5</td>
</tr>
<tr>
<td>150–499</td>
<td>2.0</td>
</tr>
<tr>
<td>≥500</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*After adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure, and other biliary disease.

Proposed Mechanisms of VHTG-Induced Acute Pancreatitis*

HTG Predicts CHD Risk  
(Meta-analysis of 29 Studies, N=262,525*)

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Follow-up</td>
<td></td>
</tr>
<tr>
<td>≥10 years</td>
<td>5902</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>4256</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7728</td>
</tr>
<tr>
<td>Female</td>
<td>1994</td>
</tr>
<tr>
<td>Fasting Status</td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>7484</td>
</tr>
<tr>
<td>Nonfasting</td>
<td>2674</td>
</tr>
<tr>
<td>Adjusted for HDL-C</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4469</td>
</tr>
<tr>
<td>No</td>
<td>5689</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall CHD Risk Ratio*</th>
<th>1.72 (95% CI, 1.56-1.90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Risk</td>
<td>Increased Risk</td>
</tr>
</tbody>
</table>

*3rd vs 1st tertile, adjusted for at least age, sex, smoking, other lipids & BP.  

Also: 22% ↑CVD/ 88 mg/dL ↑TG (61 studies N=330,566)  
Liu, J. *Lipids in Health and Disease* 2013, 12:159.
TG Predicts CAD Risk Beyond HDL-C

Triglycerides mg/dL

Odds Ratio

HDL-C mg/dL

< 30
30 - 39
40 - 49
50+
< 200
200 - 299
300 +

5.7
2.2
1.3
1.0
17.2
4.3
6.7
7.9

↑CHD Risk w/ TG ≥ 200, ↑↑ if > 500 mg/dL

TGs are independently associated with premature familial CHD*

*Triglyceride odds ratio adjusted for HDL-C; n=653 (FHx early CHD), n=1029 (control)

Reduction of TG → ↓ Pancreatitis & ASCVD
(After Baseline TG >500 mg/dL)

Pancreatitis
<200
200-299
300-399
400-499

Cardiovascular Events
<200
200-299
300-399
400-499

Triglycerides (mg/dL)

Adjusted Incidence Rate Ratio


Similar CHD Results from Copenhagen 4y f/u; N= 75,725.
HTG As a *Cause* of Atherosclerosis & CVD

**Biological mechanisms** (selected)

- TGRLp Remnants → senescence of endothelial precursors (→impaired endothelial repair)¹
- Post-prandial TG → ↑endothelial microparticles,² inflammatory cytokines,³ apoptosis⁴
- TG lipolysis → FFA → ↑endothelial cell inflammation⁵*
- ↑Apo C-III → HTG AND → vascular endothelial activation & monocyte adhesion (pro-inflam.)⁶
- HTG → ↓LDL size, ↓HDL size/loss of apo A-I
- ↑VLDL prod. → HTG and ↑apo B (pro-athero.)


*Only factor specific for TG rather than TG-rich Lp*
ApoC-III is raises TG and is anti-endothelial, pro-inflammatory, and pro-atherogenic.

**ApoC-III**

- **TG & HDL metab**
  - LPL activity
  - TRL clearance
  - VLDL production
  - HDL catabolism

- **Endothelial cells**
  - adhesion molecules
  - NO production
  - vasoconstriction

- **Monocytes**
  - β1-integrin expression, TLR2 activation, and monocyte adhesion

**HTG↑ Remn↓ apo AI**

- Endothelial Dysfunction/Inflammation

- **Atherosclerotic Cardiovascular Disease**

HTG As a **Cause** of Atherosclerosis & CVD (cont)

### Genetic Evidence
- Mendelian randomization studies strongly suggest HTG causes CVD\(^1\)-\(^3\)

**Conclusion**: “In mild-to moderate [HTG], intervention can be indicated to prevent cardiovascular disease, dependent on triglyceride concentration, concomitant lipoprotein disturbances, and overall cardiovascular risk.”\(^2\)

Mechanisms of Remnant Lipoprotein (RLP) Atherogenicity

- Cholesterol-rich remnant Lipoprotein (RLP)
- CETP & LPL
- Inflammatory FFA
- Lipoprotein Lipase
- Lipid & Protein Oxidation
- Dysfunctional Endothelium
  - ↓NO production
  - ↑Adhesion Molecules
  - ↑Permeability
  - ↑Plt activation
- Macrophage (MΦ) Foam Cell
  - MΦ Uptake → foam cells
  - Lipoprotein Lipase
  - Inflammatory FFA
  - Lipid & Protein Oxidation

and Wang L J Lipid Res. 2009;50;204-213
Genetic Causes of HTG

Somewhat Common but Controversial
• Familial combined hyperlipidemia (FCH)
  – ↑TG and Cholesterol levels (possibly also w/ HBP) believed due to genetic defects in one or more factors of lipoprotein metabolism (including Apo C-II, Apo C-III & CETP?)
• Familial hypertriglyceridemia (FHT)
  – ↑TG levels only (nl cholesterol), related to ↑hepatic VLDL production and/or polygenic vs environmental ↓LPL activity

Relatively Rare to Very Rare
• Familial dysbetalipoproteinemia (Fredrickson Type III)
• Lipoprotein lipase (LPL) deficiency
• Apo C-II deficiency
• GPIHBP1 deficiency
• Others

Note: genetic testing for HTG is rarely useful clinically and is not recommended for routine use

CETP=cholesteryl ester transfer protein
Does LDL Size Contribute to HTG Management?
LDL-C Doubly *Underestimates* ↑CVD Risk With HTG/low HDL-C & Small, Dense LDL

Large LDL
- Fewer Particles & Less Risk/Particle
- Same LDL-C (130 mg/dL)

Small, Dense LDL
- More Particles & More Risk/Particle
- More Apo B
- Less CE/particle so more particles and ↑↑CVD Risk!

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

LDL-C Doubly *Underestimates* ↑CVD Risk With HTG/low HDL-C & Small, Dense LDL

Large LDL

- Same LDL-C (130 mg/dL)
- Fewer Particles & Less Risk/Particle

Small, Dense LDL

- More Apo B
- Less CE/particle so more particles and ↑↑CVD Risk!

Basic lipid panel shows differences

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>198 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>130 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>90 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>50 mg/dL</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>148 mg/dL</td>
</tr>
</tbody>
</table>

↑SD LDL Even at TG <100 mg/dL!

SD LDL Predicts CVD Regardless of LDL-C

Hoogeveen, RC. ATVB 2014;34:1069-77. ARIC Study, N≈11,000.
Non-HDL-C best predicts SD LDL

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Pearson R</th>
<th>$R^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>0.721</td>
<td>0.520</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.706</td>
<td>0.498</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TG (log)</td>
<td>0.641</td>
<td>0.411</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.543</td>
<td>0.392</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.291</td>
<td>0.085</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hoogeveen, RC. ATVB 2014;34:1069-77. ARIC Study, N≈11,000.
SD LDL Summary

Biology: SD LDL is pro-atherogenic
• Easier into subendothelial space
• Stickier to subendothelial matrix
• More readily oxidized
• Carries atherogenic proteins (e.g. apo C-III)
• Harder to clear via LDL-R

Epidemiology: SD LDL predicts ASCVD
• SD LDL was discounted since not predictive of ASCVD w/ LDL-P; however,
• Discordance between LDL-P and LDL-C makes sense only re: LDL size, and
• LDL-P is “weighted” towards SD LDL, and
• SD LDL by new assay strongly predicts ASCVD; however,
• Non-HDL-C captures much of this assoc.

Bottom line: LDL size is important mechanistically
How to measure? Non-HDL-C, LDL-P, LDL sizing, new assay?
Management of HTG Patients
Statins do NOT Prevent All CHD Events
(Residual Risk ~50-70%)

CHD events occur frequently in patients taking statins

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>28.0</td>
<td>19.4</td>
</tr>
<tr>
<td>LIPID</td>
<td>15.9</td>
<td>12.3</td>
</tr>
<tr>
<td>CARE</td>
<td>13.2</td>
<td>10.2</td>
</tr>
<tr>
<td>HPS</td>
<td>11.8</td>
<td>8.7</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>7.9</td>
<td>5.5</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>10.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

N
Secondary: 4444 9014 4159
High Risk: 20,536
Primary: 6595 6605

### Statins Reduce CVD Events in HTG Patients

**HOWEVER…**

<table>
<thead>
<tr>
<th>Trial (Subgroup, mg/dL) (Drug)</th>
<th>Risk difference vs placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Main Study</td>
<td>HTG Subgroup</td>
</tr>
<tr>
<td><strong>WOSCOPS (TG ≥148)</strong> (Pravastatin)</td>
<td>–31%</td>
<td>–32%</td>
</tr>
<tr>
<td><strong>CARE (TG ≥144)</strong> (Pravastatin)</td>
<td>–24%</td>
<td>–15%</td>
</tr>
<tr>
<td><strong>PPP Project (TG ≥200)</strong> (Pravastatin)</td>
<td>–23%</td>
<td>–15%</td>
</tr>
<tr>
<td><strong>4S (TG &gt;159, HDL-C &lt;39)</strong> (Simvastatin)</td>
<td>–34%</td>
<td>–52%</td>
</tr>
<tr>
<td><strong>JUPITER (TG ≥150)</strong> (Rosuvastatin)</td>
<td>–44%</td>
<td>–21%</td>
</tr>
<tr>
<td><strong>CTT (TG &gt;177)</strong> (Various)</td>
<td>–21%</td>
<td>–24%</td>
</tr>
</tbody>
</table>

Median follow-up: ≥5 yrs.

CARE=Cholesterol and Recurrent Events Trial; CTT=Cholesterol Treatment Trialists; JUPITER=Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; NS=not significant; PPP=Prospective Pravastatin Pooling; 4S=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study.

TG >150 mg/dL Increases CHD Risk* Even when LDL-C <70 on a Statin
(PROVE IT-TIMI 22 Subanalysis)

*CHD = Death, MI, and recurrent ACS. HR = Hazard Ratio
TG >150 mg/dL Increases CHD Risk* Even when LDL-C <70 on a Statin
(PROVE IT-TIMI 22 Subanalysis)

*CHD = Death, MI, and recurrent ACS. HR = Hazard Ratio

Statin monoRx is not enough in HTG/lowHDL-C Patients!
Treatment of HTG: Begin with 2° Causes

• **High fructose/sucrose/carbohydrate intake**
• Low fiber intake
• **Ethanol** (also tobacco? also THC?)
• **Sedentary** lifestyle/calorie excess
• **Central obesity/insulin resistance**
• **DM2** (or 1)—esp. if poor glycemic control
• Hypothyroidism (check **TSH!!**)
• Nephrotic syndrome
• Medications:
  – **Antiretrovirals**
  – **Oral estrogens**
  – **Systemic glucocorticoids**
  – Retinoic acid derivatives
  – Minor effects (some antipsychotics, nonselective beta-blockers, thiazide diuretics, etc.)

TG-Lowering Medications
**TG Medications: Which? When?**

- If TG ≥500 mg/dL: Rx all to prevent pancreatitis (& ASCVD)
- If TG 200-499 mg/dL: *consider* Rx to prevent ASCVD*

<table>
<thead>
<tr>
<th>Drug/class</th>
<th>↓ Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>20-50%</td>
</tr>
<tr>
<td>Omega-3 oil (EPA +/- DHA; EE vs FFA)</td>
<td>20-45%</td>
</tr>
<tr>
<td>Niacin</td>
<td>20-50%</td>
</tr>
<tr>
<td>Statins**</td>
<td>7-30%</td>
</tr>
</tbody>
</table>

**“TG-Lowering”**

- 1° for TG ≥500
- 2° for TG 200-499

- 1° for TG 200-499
- 2° for TG ≥500

**“TG-Lowering”**

- 1° for TG ≥500
- 2° for TG 200-499

- 1° for TG 200-499
- 2° for TG ≥500

**High-intensity statin Rx will ↓ TG 20-50% in pts with HTG**

*After:*
- Robinson JG, Stone NJ. Am J Cardiol 2006; 98(suppl):39i-49i.
## Fenofibrate Formulations: A Confusing Mess!
### Available Fenofibrate Doses (mg/day)

<table>
<thead>
<tr>
<th>Regular dose</th>
<th>Reduced dose*</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>67**</td>
<td>Lofibra®</td>
</tr>
<tr>
<td>160</td>
<td>54/50</td>
<td>Lofibra®/Triglide®</td>
</tr>
<tr>
<td>150</td>
<td>50</td>
<td>Lipofen®</td>
</tr>
<tr>
<td>145</td>
<td>48</td>
<td>Tricor®</td>
</tr>
<tr>
<td>135</td>
<td>45</td>
<td>Trilipix®***</td>
</tr>
<tr>
<td>130</td>
<td>43</td>
<td>Antara®</td>
</tr>
<tr>
<td>120</td>
<td>40</td>
<td>Fenoglide®</td>
</tr>
<tr>
<td>90</td>
<td>30</td>
<td>Antara®</td>
</tr>
</tbody>
</table>

*primarily for renal or geriatric patients
** also available at 134 mg
***fenofibric acid
(See FDA-approved prescribing information for further details)

**Bottom line:** pick the one that works best for your patient’s payer
## Choice of Prescription Om-3

<table>
<thead>
<tr>
<th></th>
<th>EE EPA+DHA*</th>
<th>EE EPA only**</th>
<th>FFA EPA+DHA***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic available?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EPA/DHA (total)</td>
<td>55/45 (84%)</td>
<td>100/0 (98%)</td>
<td>73/27 (75%)</td>
</tr>
<tr>
<td>Bioavailability (short-term)</td>
<td>Good</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Regimen</td>
<td>2 bid w/ meals</td>
<td>2 bid w/ meals</td>
<td>2 or 4 qd meal indep.</td>
</tr>
<tr>
<td>Tolerability issues</td>
<td>Fishy taste &amp; eruct, dyspeps</td>
<td>±Arthralgia only</td>
<td>Fishy eruct, dyspeps, diarrhea, nausea</td>
</tr>
<tr>
<td>TG-lowering</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>LDL-C effects</td>
<td>↑↑/±</td>
<td>±/↓</td>
<td>↑/±</td>
</tr>
<tr>
<td>HDL-C effects</td>
<td>↑</td>
<td>±/↓</td>
<td>↑</td>
</tr>
<tr>
<td>↓CVD?</td>
<td>Not at low dose, no ongoing trials</td>
<td>Probably (mid-dose) +ongoing trial</td>
<td>No data, but ongoing trial</td>
</tr>
</tbody>
</table>

## Fenofibrate vs Omega-3 vs Niacin as TG/HDL Statin Adjuncts

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate</th>
<th>Rx Omega-3</th>
<th>Niacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ TG</td>
<td>↓↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Δ LDL-C</td>
<td>↑↑↑↑ to →</td>
<td>↑↑↑↑ to → to ↓</td>
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**Bottom line:** Feno or Om-3 are 1st line for TG, Niacin for HDL, combos good.
Investigational TG-Lowering Agents

- **ISIS-APOCIII<sub>Rx</sub>:** apo C-III antisense (ISIS)
- **Pradigastat:** intestinal DGAT1 inhibitor (ISIS/Novartis)
- **ARI-3037MO:** Niacin analog (Arisaph)
- **CAT-2003:** oral ω-3 + niacin, intracellular (Catabasis)
- **Diazoxide Choline Controlled Release (DCCR):** $K_{ATP}$ channel agonist (Essentialis)

http://www.isispharm.com/Pipeline/index.htm
http://www.isispharm.com/Pipeline/Therapeutic-Areas/Metabolic-Disease.htm#ISIS-DGAT2Rx
http://www.Clinicaltrials.gov
HTG: Should We Treat? Yes!

• TG >~100: assume ↑ASCVD risk (statin Rx)
• TG 200-500—↑ASCVD risk even w/ statin!
  – Test for remnants if TC≈TG & both > ~250
  – Diet: ↓calories, ↓fructose, ↓EtOH (in ~all)
  – ↑Physical activity (in ~all)
  – ↓Glycemia (if DM or IR)
  – Rx w/ medications:
    • Statins (if ↑ASCVD risk), and
    • If HTG persists: consider fibrate, om-3, niacin

• TG >500—↑pancreatitis and ↑ASCVD!
  – Diet: ↓fat, ↓calories, ↓EtOH, (↓fructose)
  – ↑Physical activity
  – ↓Glycemia (if DM)
  – Rx: om-3, fibrate, (niacin, statin)