Clinical Management of Hypertriglyceridemia: State of the Art 2015

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Dr. Brinton has received:

- **Research** funding: Aurora Foundation, Health Diagnostic Laboratory

- 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</th>
<th>AHA Statement</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>Borderline High</td>
<td>Normal</td>
<td>Dyslipidemia</td>
<td>No Rx interest</td>
</tr>
<tr>
<td>150-199</td>
<td></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>&gt;500</td>
<td>Very High</td>
<td>Very High</td>
<td>↑CVD &amp; sl ↑pancreatitis (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

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
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:

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

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 lipos
- 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?
- 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**

Does HTG Cause Disease?
Pancreatitis Risk $\uparrow \uparrow$ w/ TG $>500$ mg/dL

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

*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*


- Large, TG-rich chylomicrons
  - Impaired pancreatic capillary blood flow
  - Modest pancreatic lipase leak $\rightarrow$ ↑FFA production

- Ischemia
- Inflammation ($\rightarrow$↑FFA)

- Pancreatic acinar cell injury

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>

Overall CHD Risk Ratio*

- Decreased Risk
- Increased Risk

CHD Risk Ratio* (95% CI)

1.72 (95% CI, 1.56-1.90)

*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

↑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

Adjusted Incidence Rate Ratio

Triglycerides (mg/dL)


Similar CHD Results from Copenhagen 4y f/u; N= 75,725.

HTG As a \textit{Cause} of Atherosclerosis & CVD

**Biological mechanisms** (selected)

- TGRLp Remnants $\rightarrow$ senescence of endothelial precursors ($\rightarrow$ impaired endothelial repair) \(^1\)
- Post-prandial TG $\rightarrow$ ↑ endothelial microparticles, \(^2\) inflammatory cytokines, \(^3\) apoptosis\(^4\)
- TG lipolysis $\rightarrow$ FFA $\rightarrow$ ↑ endothelial cell inflammation\(^5^*\)
- ↑ Apo C-III $\rightarrow$ HTG \textit{AND} $\rightarrow$ vascular endothelial activation & monocyte adhesion (pro-inflam.)\(^6\)
- HTG $\rightarrow$ ↓ LDL size, ↓ HDL size/loss of apo A-I
- ↑ VLDL prod. $\rightarrow$ HTG and ↑ apo B (pro-athero.)

\(^3\) Norata GD. \textit{Atherosclerosis}. 2007;193:321–327.

\*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 Al

Endothelial Dysfunction/Inflammation

Atherosclerotic Cardiovascular Disease

LPL, lipoprotein lipase; TRL, triglyceride-rich lipoprotein; NO, nitric oxide; TLR2, toll-like receptor, 2 (an immune receptor which produces cytokines when activated).

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

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 hypertriglyceridermia (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

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**
- Fewer Particles &
- Less Risk/Particle

**Small, Dense LDL**
- More Particles &
- More Risk/Particle

**Apo B**

**Cholesterol Ester (CE)**

**Lipid profile:**

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>130 mg/dL</td>
<td>198 mg/dL</td>
<td>90 mg/dL</td>
<td>50 mg/dL</td>
<td>148 mg/dL</td>
</tr>
<tr>
<td>Second</td>
<td>130 mg/dL</td>
<td>210 mg/dL</td>
<td>250 mg/dL</td>
<td>30 mg/dL</td>
<td>180 mg/dL</td>
</tr>
</tbody>
</table>

Less CE/particle so **more particles and ↑↑CVD Risk!**

Basic lipid panel shows differences

↑ 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>R²</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>Patients Experiencing Major CHD Events, %</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S Group</td>
<td></td>
<td>4444</td>
</tr>
<tr>
<td>LIPID Study</td>
<td>19.4</td>
<td>9014</td>
</tr>
<tr>
<td>CARE</td>
<td>10.2</td>
<td>4159</td>
</tr>
<tr>
<td>HPS Collaborative Group</td>
<td>8.7</td>
<td>20,536</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5.5</td>
<td>6595</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>6.8</td>
<td>6605</td>
</tr>
</tbody>
</table>

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>WOSCOPS (TG ≥148) (Pravastatin)</td>
<td>–31%</td>
<td>–32%</td>
</tr>
<tr>
<td>CARE (TG ≥144) (Pravastatin)</td>
<td>–24%</td>
<td>–15%</td>
</tr>
<tr>
<td>PPP Project (TG ≥200) (Pravastatin)</td>
<td>–23%</td>
<td>–15%</td>
</tr>
<tr>
<td>4S (TG &gt;159, HDL-C &lt;39) (Simvastatin)</td>
<td>–34%</td>
<td>–52%</td>
</tr>
<tr>
<td>JUPITER (TG ≥150) (Rosuvastatin)</td>
<td>–44%</td>
<td>–21%</td>
</tr>
<tr>
<td>CTT (TG &gt;177) (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)

**Statin monoRx is not enough in HTG/lowHDL-C Patients!**

*CHD = Death, MI, and recurrent ACS. HR = Hazard Ratio
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><strong>Drug/class</strong></th>
<th>↓<strong>Triglycerides</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>20-50%</td>
</tr>
<tr>
<td>Omega-3 oil (EPA +/- DHA; EE vs FFA) <em>(pharmacologic doses)</em></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

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

**After:**
<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</td>
<td>Good</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>(short-term)</td>
<td></td>
<td></td>
<td></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 Om-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>
<td>↓ to ↓↓</td>
</tr>
<tr>
<td>Δ Non-HDL-C</td>
<td>→ to ↓</td>
<td>→ to ↓</td>
<td>↓ to ↓↓</td>
</tr>
<tr>
<td>Δ HDL-C</td>
<td>→ to ↑</td>
<td>→ to ↑</td>
<td>↑ to ↑↑</td>
</tr>
<tr>
<td>↓ CVD Efficacy</td>
<td>0 to +</td>
<td>0 to +++</td>
<td>0 to +</td>
</tr>
<tr>
<td>↓ Mortality</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Non-CVD Benefits</td>
<td>0 to ++</td>
<td>0 to ++?</td>
<td>0</td>
</tr>
<tr>
<td>Access (cost/month)</td>
<td>$60-250</td>
<td>$90-300</td>
<td>$10-400</td>
</tr>
<tr>
<td>“Natural”</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Safety</td>
<td>+ to –</td>
<td>+++</td>
<td>– – – to 0</td>
</tr>
<tr>
<td>Tolerability</td>
<td>++ to –</td>
<td>++ to –</td>
<td>– – – to 0</td>
</tr>
<tr>
<td>Ease of use</td>
<td>+++</td>
<td>+++</td>
<td>– – to ++</td>
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### Fenofibrate vs Om-3 vs Niacin as TG/HDL Statin Adjuncts

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<td>0 to ++?</td>
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</tr>
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<td>$90-300</td>
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<tr>
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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_{Rx}: 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 (Essentiais)

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)