“Cream of Tomato Soup" Blood: What's the Skinny on FCS and Other Chylomicronemic States?

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Duality of Interest

Dr. Brinton has received:

• **Research** funding: Amarin, Aurora Foundation, Kowa, National Institutes of Health

• Honoraria as **consultant/advisor**: Akcea, Alexion, Amarin, Amgen, Araelez, Arisaph, AstraZeneca, Kastle, Kowa, Merck, PTS Diagnostics, Regeneron, Sanofi-Aventis

• Honoraria as **speaker**: Akcea, Alexion, Amarin, Amgen, Boehringer-Ingelheim, Janssen, Kastle, Kowa, Lilly, Merck, Novo-Nordisk, Regeneron, Sanofi-Aventis
Educational Objectives

After this presentation, listeners will be able to

• Explain:
  – The clinical presentation, epidemiology and pathophysiology of fasting chylomicronemia (severe hypertriglyceridemia, S-HTG)
  – The similarities and differences between multifactorial S-HTG (polygenic) vs monogenic S-HTG (familial chylomicronemia syndrome, FCS)

• Discuss S-HTG comorbidities:
  – Pancreatitis
  – Atherosclerotic cardiovascular disease (ASCVD)
  – HTG categories and testing strategies

• Apply appropriate lifestyle & medical treatment for chylomicronemia
Chylomicronemia/S-HTG
Description, Epidemiology and Pathophysiology
Components, Size, and Density of Human Serum Lipoproteins

Apolipoproteins (A-I, A-II, A-IV, A-V, B48, B100, C-I, C-II, C-III, C-IV)
- Assist in structural integrity and solubility
- Serve as co-factors in enzymatic reactions
- Act as ligands

Lactescent Blood and Plasma in Hyperchylomicronemia

<table>
<thead>
<tr>
<th>TG (mg/dL)</th>
<th>Whole blood Unspun</th>
<th>Whole blood Spun</th>
<th>Plasma Severe HTG</th>
<th>Plasma Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>16,713</td>
<td>385</td>
<td>385</td>
<td>16,713</td>
<td>385</td>
</tr>
</tbody>
</table>


Lipemia Retinalis in Chylomicronemia

Normal fundus

Lipemia retinalis

Eruptive Xanthomas in Chylomicronemia

Usually transient, seen on trunk, buttocks and thighs

Prevalence of HTG in the USA

~40 Million Americans have TG >200 mg/dL

TG=Triglycerides

*On the basis of the 2010 US population of 226,082,000 persons ≥20 years of age.

# Prevalence and Clinical Relevance of TG Categories

<table>
<thead>
<tr>
<th>TG Range (mg/dL)</th>
<th>ATP-III &amp; AHA Statement</th>
<th>Prevalence in US Adults</th>
<th>Disease Risk</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Optimal ²</td>
<td>68% (134M)</td>
<td>None</td>
<td>No Rx interest</td>
</tr>
<tr>
<td>&lt;150</td>
<td>Normal ¹</td>
<td>14% (28M)</td>
<td>“Athero Dyslip”</td>
<td></td>
</tr>
<tr>
<td>150-199</td>
<td>Borderline</td>
<td>16% (32M)</td>
<td>More dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>200-499</td>
<td>High</td>
<td>1.7% (3M)</td>
<td>↑CVD</td>
<td>Approve if reasonable safety</td>
</tr>
<tr>
<td>≥500 ³</td>
<td>Very High</td>
<td></td>
<td>↑CVD &amp; sl ↑pancreatitis³ (esp ↑if &gt;2000)</td>
<td></td>
</tr>
</tbody>
</table>

3. ↑Risk of acute pancreatitis starting at >500 mg/dL likely due to association with far higher TG.
Obesity and DM2 Drive (Most) HTG

PREVALENCE OF OBESITY AND DIABETES INCREASES AS TG LEVEL INCREASES

![Chart showing prevalence of overweight/obese and diabetes with increasing serum TG levels](chart_image)

- Overweight/Obese
  - <150: 57.3% (n=3812)
  - 150-199: 79.9% (n=839)
  - 200-499: 83% (n=939)
  - 500-2000: 89.6% (n=87)
- Diabetes
  - <150: 5.2%
  - 150-199: 10%
  - 200-499: 12.5%
  - 500-2000: 14.6%

N=5,680, age ≥20 y, National Health and Nutrition Examination Survey (NHANES) 2001-2006 with fasting TG levels.

### Simplified TG Categories

Proposed by EAS

<table>
<thead>
<tr>
<th>Category</th>
<th>TG level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal TG</td>
<td>&lt;175</td>
</tr>
<tr>
<td>Mild to Moderate HTG</td>
<td>175-885</td>
</tr>
<tr>
<td>Severe HTG (S-HTG)</td>
<td>&gt;885</td>
</tr>
</tbody>
</table>

EAS Consensus Statement. Genetics of HTG vs CVD.
Hegele R Lancet Diabetes & Endocrin 2014, 2(8)655-666.
Classification and Genetics of Severe Hypertriglycerideridemia (Chylomicronemia)

**FCS; Monogenic, recessive, rare**

<table>
<thead>
<tr>
<th>WHO ICD number</th>
<th>Fredrickson hyperlipoproteinaemia phenotype</th>
<th>OMIM number</th>
<th>Main lipid change</th>
<th>Primary lipoprotein change</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial hyperchylomicronaemia</strong> E78.3</td>
<td>Type 1</td>
<td>238600</td>
<td>↑Triglyceride</td>
<td>↑Chylomicrons</td>
<td>Monogenic; autosomal recessive due to two mutant alleles of LPL, APOC2, APOA5, LMF1, GPIHBP1, or GPD1; presentation mainly paediatric or early adulthood</td>
</tr>
<tr>
<td><strong>Mixed hypertriglyceridaemia</strong> E78.3</td>
<td>Type 5</td>
<td>144650</td>
<td>↑Total cholesterol, ↑triglyceride</td>
<td>↑VLDL, ↑chylomicrons</td>
<td>Polygenic; high GRS for hypertriglyceridaemia, excess of rare variants in hypertriglyceridaemia-associated genes, with higher burden of risk alleles than for hyperlipoproteinaemia type 4</td>
</tr>
</tbody>
</table>

GRS was created by unweighted tallying of risk alleles from single nucleotide polymorphisms associated with increased plasma concentrations of triglyceride and hypertriglyceridaemia. Adapted from Hegele (2009).\(^8\) ICD=International Classification of Diseases. OMIM=Online Mendelian Inheritance in Man database. VLDL=very low-density lipoprotein. GRS=polygenic genetic risk score. IDL=intermediate-density lipoprotein.

**Multifactorial S-HTG; Polygenic + Environmental, uncommon**

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Normal Metabolism of TGRLp: Exogenous (Dietary Origin)

Normal Metabolism of TGRLp: Exogenous (Dietary Origin)

Fasting chylomicronemia (TG > ~800 mg/dL) seen only if ↓↓ or no LPL activity (monogenic=FCS, or multifactorial = polygenic + environmental)

Familial Chylomicronemia Syndrome (FCS) vs Multifactorial Severe HTG (S-HTG)
# Multifactorial vs Monogenic Chylomicronemia

## Multifactorial Chylomicronemia
- **Uncommon** (2-10/100,000?)
- ↑↑↑Chylomicrons (↓↓↓LPL → ↓↓↓ chylo clearance)
- **Environmental** > genetic
- ~Always **adult**-onset
- **Insulin resistance** → ↓↓↓ LPL
- **Obesity**-related
- **Diabetes**-related
- Some LPL→↑TGRL Remnants →↑**Atherosclerosis**
- Acute/recur/chronic pancr.
- Eruptive xanth/lipemia retinalis
- Neuropathy, memory loss
- Moderate benefit of ↓sugar/carb
- EtOH & oral estrogen worsens
- Dietary-fat-inducible
- Fatty liver (↑Hepatic VLDL Synth → & ↑↑VLDL levels)
- Multifactorial LPL deficiency (↓↓ severity, sl ↑**resp. to meds**)

## Monogenic LPL-defic. (FCS)
- **Rare** (1-2/million)
- ↑↑↑Chylomicrons (**absent** LPL → ↓↓↓ chylo clearance)
- **Genetic** >> environmental
- Often presents in **childhood**
- **Not** rel. to insulin resistance
- Obesity-**un**related
- Diabetes-**un**related
- No LPL→**no** ↑TGRL Remnants →**no** ↑Atherosclerosis
- Acute/recur/chronic pancr.
- Eruptive xanth/lipemia retinalis
- Neuropathy, memory loss
- Some benefit of ↓sugar/carb?
- EtOH & oral estrogen worsens
- Dietary-fat-inducible
- Fatty liver (sl ↑Hepatic VLDL Synth → sl ↑VLDL levels?)
- Absolute LPL deficiency (↑↑ severity, ↓↓**resp. to meds**)
~40 Million Americans have TG >200 mg/dL

Estimated US prevalence of Severe HTG:
- FCS: 300-600?
- Multifactorial: Thousands to tens of Thousands?

TG=Triglycerides

*On the basis of the 2010 US population of 226,082,000 persons ≥20 years of age.

Population TG Distribution by Genetic Causes & Consequences

Multigenic:
LPL, APOA5, GCKR, APOB, LMF1, GPIHBP1, CREBH1, APOC2, APOE, and small-effect variants

Can be monogenic:
LPL, APOC2, APOA5, LMF1, GPIHBP1, and GPD1

- Mild-to-moderate triglycerides increase
- Increased CVD risk

- Severe triglycerides increase
- Chylomicronaemia
- Pancreatitis risk
- Increased CVD risk likely

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### Genetics: Known mutations responsible for FCS

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<th>Gene product function</th>
<th>Molecular features</th>
<th>% of Monogenic mutations</th>
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<tr>
<td><strong>LPL</strong></td>
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<td>Severely reduced or absent LPL enzyme activity</td>
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<td><strong>APOC2</strong></td>
<td>Required cofactor of LPL</td>
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<td>Enhancer of LPL activity</td>
<td>Absent or defective apoA-V</td>
<td>0.6%</td>
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<tr>
<td><strong>LMF1</strong></td>
<td>Chaperone molecule required for proper LPL folding</td>
<td>Absent or defective LMF1</td>
<td>0.4%</td>
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Adapted from Brahm, Nat Rev Endocrinol, 2015.

Abbreviations: FCS=familial chylomicronemia syndrome, LPL=lipoprotein lipase, APOC2=gene for apolipoprotein C-II, APOA5=gene for apolipoprotein A-V, GPIHBP1= Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1, LMF1=lipase maturation factor 1, FFA=free fatty acid; TG=triglyceride.

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Severe-HTG-Related Morbidity: Acute Pancreatitis
Pancreatitis Risk ↑↑w/ TG >500 mg/dL

Pancreatitis Risk by TG

Cases/1000 pt –y

Why ↑Risk at TG > 500?
Fasting TG is tip of iceberg!

VHTG is the third greatest cause of acute pancreatitis (after EtOH & gallstones)

After adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure, and other biliary disease
Mechanisms of Chylomicron-Induced Acute Pancreatitis*

* Proposed mechanisms. LPL, lipoprotein lipase; FFA = free fatty acids.

Hypertriglyceridemia is likely the third leading cause of acute pancreatitis.

Alcoholism

Idiopathic

Hypertiglyceridemia

Gallstones

Worse outcomes in patients with Acute Pancreatitis with severe HTG

Clinical outcomes in AP: Normal vs severe TG levels

- Persistent organ failure: 17% TG <150 mg/dL vs 48% TG ≥1000 mg/dL
- Need for intensive care: 23% TG <150 mg/dL vs 60% TG ≥1000 mg/dL
- Mortality: 3% TG <150 mg/dL vs 8% TG ≥1000 mg/dL
- Pancreatic necrosis: 36% TG <150 mg/dL vs 50% TG ≥1000 mg/dL

Median hospital stay (days):
- TG <150 mg/dL: 7 days
- TG ≥1000 mg/dL: 17 days

Abbreviations: HTG, hypertriglyceridemia; TG, triglyceride.

Adapted from Nawaz H, Koutroumpakis E, Easler J, et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. Am J Gastroenterol. 2015;110(10):1497-1503. doi:10.1038/ajg.2015.261. Patients were neither evaluated or diagnosed with FCS.
Severe-HTG-Related Morbidity: Atherosclerosis
All-cause Mortality Risk Increases as TG Levels Increase

15,355 patients who were screened for the Bezafibrate Infarction Prevention (BIP) trial. 22-year mortality data were obtained from the national registry.

**Adjusted Hazard Ratio**

- <100 mg/dL: 1 (CI 1.01-1.12)
- 100-149 mg/dL: 1.06 (CI 1.09-1.23)
- 150-199 mg/dL: 1.16 (CI 1.22-1.37)
- 200-499 mg/dL: 1.29 (CI 1.38-2.06)
- >500 mg/dL: 1.68 (CI 1.38-2.06)

Baseline TG Predicts 20-y CV Mortality in Familial Endogenous HTG

Age-standardized rate of cardiovascular mortality per 1000 person-years

<table>
<thead>
<tr>
<th>Triglyceride Quintile</th>
<th>Age (mg/dL)</th>
<th>Concentration (mmol/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>0.91</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>1.29</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td>167</td>
<td>1.89</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td>246</td>
<td>2.78</td>
<td>2.78</td>
<td>p &lt; 0.02</td>
</tr>
</tbody>
</table>


Very High TG Strongly Associated With ↑CAD Risk

Higher TG Level = Higher CAD Odds Ratio

Relationship Between TG Levels and CAD Risk

Odds ratio for CAD with high TG rose progressively even after correction for HDL-C, other elements of the metabolic syndrome, and other CAD risk factors

CAD=coronary artery disease.

Increasing TG Levels Increases CVD and All-cause Mortality

Hazard ratios were estimated by Cox proportional hazard regression models, and were adjusted for age, sex, and trial group. Nordestgaard BG et al. *Lancet*. 2014;384:626-35.
Increasing TG Levels Increases CVD and All-cause Mortality

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**Copenhagen City Heart Study and Copenhagen General Population Study**

**Myocardial Infarction**
N=96,394 (events=3287); Median follow-up 6 years

**Ischemic heart disease**
N=93,410 (events=7183); Median follow-up 6 years

**All-cause mortality**
N=98,515 (events=14,547); Median follow-up 6 years

**Ischemic stroke**
N=97,442 (events=2994); Median follow-up 6 years

**Non-fasting triglycerides (mg/dL)**

HTG (like all other MetSynd factors) → ↑ASCVD risk more in women than in men
Causes and Atherogenic Consequences of Severe HTG/Chylomicronemia

Moderate LPL deficiency causes ↑↑ chylo (& VLDL) remnant cholesterol leading to ↑↑ atherogenicity (even w/ normal VLDL synth & normal fat intake)

1. CE-rich TGLp remn
2. SD LDL/↑LDL-P
3. ↓HDL-C & Apo A-I
Remnants of TG-Rich Lipoproteins (TGRLp) Can be Atherogenic

- TG is the major component of TG-Rich Lipoproteins, including both VLDL and chylomicrons
- TG and TG-Rich Lipos appear to be causal factors in atherogenesis and ASCVD events

Remnants of TG-Rich Lipoproteins (TGRLp) Can be Atherogenic

Atherogenesis: S-HTG>>FCS (FCS has few TGRLp)

Remnants of TG-Rich Lipoproteins (TGRLp) Can be Atherogenic

- Enter artery wall & cause
- ↑↑↑ Macrophage Ingestion

LPL

- Hepatic Lipoprotein Receptors
- apoC-III

LDL

- ANGPTL3
- ANGPTL4

VLDL Remnant

- apoC-III

Chylomicron Remnant

- apoA-V

Small Intestine

- TG is the major element
- TG and TG-Rich Lipoproteins appear to be causal factors in atherogenesis and ASCVD events

Apparent Mechanisms for ↑CVD in Patients with Severe HTG

- TG lipolysis by lipoprotein lipase causes **pro-inflammatory** ↑free-fatty-acids (MFSHTG>>FCS)
- ↑TG-rich lipoprotein **remnants** (CE-enriched) appear to be **atherogenic** (MFSHTG>>FCS)
- HTG causes **atherogenic** changes in **LDL and HDL** particles (MFSHTG≈FCS)
- HTG associates w/ hyper-Apo B (MFSHTG>FCS)
- **Apo C-III** (esp. on TG-rich Lp) inhibits LPL + other ↑TG effects + other **pro-athero** effects: ↑inflammation via endothelial “activation”, monocyte adhesion, etc. (MFSHTG≈FCS?)
- Strong **genetic** evidence for causality via Mendelian randomization (MFSHTG>>FCS)

Apparent Mechanisms for ↑CVD in Patients with Severe HTG

- TG lipolysis by lipoprotein lipase causes pro-inflammatory ↑free-fatty-acids (*MFSHTG>>FCS*)
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- HTG causes atherogenic changes in LDL and HDL particles (*MFSHTG≈FCS*)
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- Apo C-III (esp. on TG-rich Lp) inhibits LPL + other ↑TG effects + other pro-athero effects:
  ↑inflammation via endothelial “activation”, monocyte adhesion, etc. (*MFSHTG≈FCS?*)
- Strong genetic evidence for causality via Mendelian randomization (*MFSHTG>>FCS*)

Management of Chylomicronemia (FCS and Multifactorial)
TG Measurement
To Fast or Not to Fast?

Fasting Lipid Panel
- Better TG accuracy
- TG cutoffs are based on fasting values
- Slightly better for LDL-C
- Can get fasting glucose

Non-Fasting Lipid Panel
- Can get on any visit
- OK TG accuracy
- Good Non-HDL-C accuracy
- Other lipids reasonably accurate
- Could do A1c to follow DM2

Bottom line: fasting panel is often better but non-fasting is often easier
To Fast or Not to Fast?

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- Better TG accuracy
- TG cutoffs are based on fasting values
- Slightly better for LDL-C
- Can get fasting glucose

**Non-Fasting Lipid Panel**
- Can get on *any* visit
- OK TG accuracy
- Good Non-HDL-C accuracy
- Other lipids reasonably accurate
- Could do A1c to follow DM2

*Bottom line: fasting panel is often better but non-fasting is often easier*

TG-Lowering Treatment
VHTG and S-HTG Remain Undertreated

Treatment Patterns at 6 mo Follow-up of TG-Treatment-Naïve Patients*

Baseline TG (mg/dL) | \( \geq 1500 \) n=1964 | \( \geq 750 \) and \( <1500 \) n=7432 | \( >500 \) and \( <750 \) n=17,500

- 45.6% “TG-Lowering”
- 44.7% “TG-Lowering”
- 37.8% “TG-Lowering”

*“Other” therapies and combination therapies are not plotted; “other” therapy accounted for ≤6.2% of each cohort and combination therapy was prescribed for ≤9% of each cohort.

At baseline: 82.2% of patients with TG >500 and <750 were treatment naïve; 76.4% of patients with TG ≥750 and <1500 were treatment naïve; 66.5% of patients with TG ≥1500 were treatment naïve.

Data derived from a retrospective claims study of commercially insured patients with an index TG >500 mg/dL and at least 12 months of follow-up. Toth PP. Atherosclerosis. 2014;237(2):790-797.
Despite Decreased Levels, TG Remains High at 1 Year, and Few Are Diagnosed or Referred

HTG diagnosed in only ~20% at follow-up.

<20% saw specialist* (ABCL or cardiologist/endocrinologist/gastroenterologist at follow-up).

*“Specialist” includes American Board of Clinical Lipidology (ABCL)-certified lipidologists and American Board of Medical Specialties (ABMS)-certified cardiologists, endocrinologists, and gastroenterologists.

Data derived from a retrospective claims study of commercially insured patients with an index TG >500 mg/dL and at least 12 months of follow-up.

**Proposed**

**Lipid & Apolipoprotein Rx Goals**

in Patients w/ ↑ASCVD Risk & HTG

<table>
<thead>
<tr>
<th>Factor</th>
<th>Goal* (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Apo B (in high-risk)</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Apo B (in very-high-risk)</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

*“Desirable concentrations”, but *unclear if apply to S-HTG*

EAS Consensus Statement. Genetics of HTG vs CVD.

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Aims of FCS Management

Reduce plasma triglyceride levels

Prevent abdominal pain and recurrent acute pancreatitis

Alleviate signs and symptoms/physical manifestations of FCS\(^1,2,3\)

Reduce risk of long term consequences\(^1,4,5\)

## Always Look for and Treat Secondary Causes of HTG (Multifactorial>>FCS)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinically useful details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td><strong>↑Calories (↑Saturated fat? ↑glycemic index?), ethanol</strong></td>
</tr>
<tr>
<td></td>
<td><strong>↑Simple sugars, esp. fructose (sucrose, etc.) &amp; ↓dietary fiber</strong></td>
</tr>
<tr>
<td><strong>Adiposopathy</strong></td>
<td>Especially if with ↑<strong>visceral adiposity</strong></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>Especially if <strong>insulin resistant</strong> and/or <strong>hyperglycemic</strong></td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>Only if inadequately controlled</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
<td><strong>Nephrotic syndrome</strong>, <strong>ESRD</strong>, glomerulonephritis</td>
</tr>
<tr>
<td><strong>Systemic Inflammation</strong></td>
<td>Lupus, rheumatoid arthritis, paraproteinemias, etc.</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td><strong>Antiretroviral agents</strong> (for HIV), asparaginase (for leukemia)</td>
</tr>
<tr>
<td></td>
<td>2nd-generation anti-Ψ, phenothiazines, anti-seizure meds</td>
</tr>
<tr>
<td></td>
<td>Nonselective beta-blockers &amp; thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td>Bile-acid sequestrants</td>
</tr>
<tr>
<td></td>
<td>Pregnancy (especially 3rd trimester)</td>
</tr>
<tr>
<td></td>
<td><strong>Oral contraceptives, oral hormone replacement</strong>, tamoxifen</td>
</tr>
<tr>
<td></td>
<td><strong>Glucocorticoids, isotretinoin</strong></td>
</tr>
<tr>
<td><strong>Recreational drugs</strong></td>
<td><strong>Ethanol</strong>, marijuana (↑ApoC-III)</td>
</tr>
</tbody>
</table>

*Strong dose-gene interaction (polygenic); HIV=human immunodeficiency virus.
# Fat-Inducible vs Carbohydrate-Inducible Hypertriglyceridemias

**Fat-Inducible (S-HTG only: FCS or Multifactorial)**
- Chylomicronemia (+VLDL) after 12-hour+ fast
- Due to ↓chylomicron clearance (related to LPL ↓ or absence)
- Fasting TG > ~800 mg/dL
- Pancreatitis dominates clinical presentation (+eruptive xanth)
- ↑CVD (multifactor. only, VLDL)
- Rx:
  - Decrease/eliminate EtOH, glycemia, oral estrogen
  - **Very low fat diet,**
  - Low sugar/carb diet?
  - Medications (↑ w/ ↑ baseline TG, except FCS—responds poorly)

**Carbohydrate-Inducible (HTG & S-HTG, also FCS?)**
- VLDL excess (+ variable chylos after 12-hour+ fast)
- Due to ↑ VLDL production (related to fatty liver, insulin resistance)
- Fasting TG usu. < ~800 (higher?)
- No characteristic acute Sx (if TG<800)
- ↑CVD rel. to ↑ apo B, rem & sdLDL
- Rx:
  - Treat 2º factors (any/all)
  - **Low fructose/sugar/carb** diet
  - High-fiber intake
  - ↑ Physical activity
  - Medications
## Treatment of Severe HTG (EAS Consensus)

<table>
<thead>
<tr>
<th>Treatment priority</th>
<th>High (≥10 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment priority</td>
<td>Prevent acute pancreatitis</td>
</tr>
<tr>
<td>Primary therapeutic goal</td>
<td>Reduce triglyceride concentrations</td>
</tr>
<tr>
<td>Secondary therapeutic goals</td>
<td>Goals: achieve LDL cholesterol and non-HDL cholesterol goals once pancreatitis risk is decreased, as described above; rule out and treat secondary factors</td>
</tr>
<tr>
<td>Non-pharmacological therapeutic strategies</td>
<td>Eliminate oral intake during acute pancreatitis with intravenous rehydration, then slowly re-introduce foods with small frequent meals, then longer-term strict fat-reduced diet (&lt;20% of calories as fat), reduce bodyweight, reduce alcohol intake, reduce simple sugar intake, reduce total carbohydrate intake, replace trans and saturated fats with monounsaturated fats; increase dietary omega-3 fatty acids; increase aerobic activity</td>
</tr>
<tr>
<td>Pharmacological therapeutic strategies</td>
<td>Consider fibrate, nicotinic acid, and omega-3 fatty acids</td>
</tr>
</tbody>
</table>
Management of FCS: Dietary Guidance

**Lifelong Dietary Restrictions**

- Extremely low-fat diet (≤15% of energy)
- Very-low added-sugar (<100/150 calories, or ~≤7% of energy)
- Complete Avoidance of Alcohol

**Although generally very difficult, these dietary therapies will ↓TG and can ↓clinical manifestations**

- ↓Frequency of eruptive xanthomas
- ↓Risk of acute & chronic pancreatitis
- ↓Other abdominal pain
- ↓Hepatosplenomegaly
- ↓Peripheral neuropathy, CNS abnormalities

Major TG-Lowering Agents

- Fenofibrate
- Prescription Omega-3 oil
- (Niacin)
- (Statins)
National Lipid Association (NLA): Drug Therapy For TG Reduction

• “TG ↓med” 1st-line if TG ≥500 mg/dL
  – Fibrate, Rx omega-3 fatty acids, and/or nicotinic acid
  – Statin ok if TG <1000 mg/dL, and no pancreatitis

• Statin + “TG ↓med” for non-HDL-C > goal (and residual TG 200-500?), especially high & very high ASCVD risk

### Fenofibrate Formulations: Complicated!
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**
**Omega -3 Dietary Supplements are NOT Intended for Treating Disease!**

<table>
<thead>
<tr>
<th></th>
<th>Demonstrated Efficacy and Safety</th>
<th>FDA Approved</th>
<th>Regulated Manufacturing</th>
<th>Regulated Claims</th>
<th>FDA Safety Monitoring</th>
<th>Intended to Treat Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription drugs¹</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>OTC drugs² (No OTC omega-3!)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dietary supplements³</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Registration of manufacturing facilities only.
**Structure, function and qualifying health claims only.
***Serious AER reporting “required”, but how enforced?

Omega-3 Dietary Supplements Often Have Low Potency

69% Had < 2/3 of Labelled EPA+DHA

Omega-3 Dietary Supplements Often are Highly Oxidized

81% Failed Peroxide Test;
92% Failed > 1 Oxidation Test

Leading Fish Oil Supplement

- 34% EPA
- 21% DHA
- 9% Saturated Fats
- 36% Unsaturated Fats

Leading Krill Oil Supplement

- 37% EPA
- 21% DHA
- 12% Saturated Fats
- 30% Unsaturated Fats

These chromatography findings have been noted by R. Preston Mason, PhD (unpublished data, 2015).
## 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 avail.?</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 g bid w/ meals</td>
<td>2 g bid w/ meals</td>
<td>2-4 g qd, meal indep.</td>
</tr>
<tr>
<td>Tolerability issues</td>
<td>Fishy taste &amp; eruct, dyspepsia</td>
<td>± Arthralgia</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>↑↑ (~45%)</td>
<td>± (no ↑)</td>
<td>↑ (~20%)</td>
</tr>
<tr>
<td>HDL-C effects</td>
<td>↑ (5-10%)</td>
<td>± (no ↑)</td>
<td>↑ (5-10%)</td>
</tr>
<tr>
<td>↓CVD?</td>
<td>Not at 1g/d, no ongoing trials</td>
<td>Probably (JELIS) +ongoing trial</td>
<td>No data, but ongoing trial</td>
</tr>
</tbody>
</table>

**Caveat: none of these comparisons are based on head-to-head data!**

# Fenofibrate vs Om-3 vs Niacin for Chylomicronemia

<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 → → ↓</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>↓ ASCVD data</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-ASCVD Benefits</td>
<td>0 to ++?</td>
<td>0 to ++?</td>
<td>0</td>
</tr>
<tr>
<td>Cost/month</td>
<td>$50-250</td>
<td>$9-300</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 +</td>
</tr>
<tr>
<td>Ease of use</td>
<td>+++</td>
<td>++</td>
<td>– – to +</td>
</tr>
</tbody>
</table>

_Bottom line: Feno or Om-3 are 1st-line for S-HTG, combos good._
Statins for Chylomicronemia/S-HTG?

• Quick rules of thumb
  – Rx HTG (200-500)
    • ↓TG is ½ ↓LDL-C
    • ↓ASCVD proven but resid. HTG → resid. ↑CVD
    • 1st choice Rx but often insufficient as monoRx
  – Rx S-HTG (>800 mg/dL)
    • ↓LDL-C is ½ and ≈ ↓TG
    • ↓ASCVD likely but ↓pancreatitis “insufficient”
    • OK as “TG-lowering” adjunct? (not 1st/monoRx?)

• Bottom line: yes for HTG, maybe for S-HTG
There are no medications with an FDA indication for TG-lowering specifically in FCS patients

### Mechanisms of action of “TG-Lowering Medications”

<table>
<thead>
<tr>
<th>Fibrates¹,²</th>
<th>Marine omega-3³,⁴</th>
<th>Niacin⁵</th>
<th>Statins⁶,⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Lipolysis and uptake of TG-rich particles <strong>by</strong> LPL activity</td>
<td>↑ Lipolysis and uptake of TG-rich particles <strong>by</strong> LPL activity</td>
<td>↑ Lipolysis and uptake of TG-rich particles <strong>by</strong> LPL activity</td>
<td>↓ Cholesterol synthesis</td>
</tr>
<tr>
<td>↑ LPL activity</td>
<td>↑ β-oxidation of FFA</td>
<td>↓ DGAT to ↓ Hepatic TG synthesis</td>
<td>↑ Hepatic LDL receptors to ↑ LDL catabolism</td>
</tr>
<tr>
<td>↑ β-oxidation of FFA</td>
<td>↑ DGAT to ↓ Hepatic TG synthesis</td>
<td>↓ Release of free fatty acids from adipose tissue</td>
<td>↓ Hepatic VLDL synthesis</td>
</tr>
<tr>
<td>↓ DGAT to ↓ Hepatic TG synthesis</td>
<td>↓ Hepatic VLDL synthesis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When LPL is absent, agents which upregulate LPL activity usually do not work, so FCS patients are often **unresponsive** to TG-lowering therapies⁸

---

Abbreviations: LPL, lipoprotein lipase; DGAT, diacylglycerol acyltransferase; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very low-density lipoprotein; VLDL-C, very low-density lipoprotein cholesterol.

Alternative HTG Medications in Development or Off-Label

In Development
- Flush-free niacin analogue (ARI-3037MO, Arisaph)
- Intracellular niacin/omega-3 preparation (Catabasis)
- Anti apo C-III antisense oligonucleotide (Ionis/Akcea)
- Alipogene tiparvovec—LPL gene therapy (uniQure, EMA-approved)

Approved but Off-Label
- Orlistat (pancreatic lipase inhib → ↓fat absorption → ↓chylo synthesis)
- Pioglitazone → ↓TG, ↑HDL-C, ↓ins. resist., ↓ASCVD
- PCSK9-I mAb → ↓ASCVD
- Lomitapide (MTP-I, ↓ chylo. & VLDL assembly)
- Mipomersen (apo B antisense, ↓ VLDL assembly)
Volanesorsen Ph2 FCS: 300 mg Reduced Fasting Plasma ApoC-III Levels

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Patient No.</th>
<th>Baseline</th>
<th>Primary Endpoint Day 85</th>
<th>Change from Baseline</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoC-III</td>
<td>1</td>
<td>18.9</td>
<td>5.5</td>
<td>-13.4</td>
<td>-70%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>35.1</td>
<td>3.4</td>
<td>-31.7</td>
<td>-90%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>19.8</td>
<td>3.5</td>
<td>-16.3</td>
<td>-83%</td>
</tr>
</tbody>
</table>

Volanesorsen Ph2 FCS: 300 mg Reduced Fasting Plasma Triglyceride Levels

Parameter (mg/dL) | Patient No. | Baseline | Primary Endpoint Day 85 | Change from Baseline | % Change from Baseline
--- | --- | --- | --- | --- | ---
Triglyceride     | 1          | 1,406    | 616.5                   | -789.5               | -56%                  
                  | 2          | 2,083    | 287.5                   | -1,795.5              | -86%                  
                  | 3          | 2,043    | 734.5                   | -1,308.5              | -64%                  

TREATMENT PERIOD

Study Day

△ = dose administered

Volanesorsen Clinical Safety Summary

Up to and Including Phase 2

- Exposure database
  - volanesorsen: n=99 / Placebo: n=37
- Well tolerated, favorable safety profile
  - No SAEs related to volanesorsen, no significant AEs
  - No flu-like symptoms
- Most frequent AEs were injection site reactions (pain, erythema)
  - Occurred in ~15% of injections
  - Nearly all were mild in nature and resolved without treatment
- No DDIs
- No lab abnormalities suggestive of an effect on renal or hepatic systems
- Reduction in platelets (<30% from baseline at PET) vs Placebo with mean nadirs above LLN which resolved after treatment
  - Not associated with bleeding
  - Considered not clinically significant

Summary: Hyperchylomicronemia Management (FCS and Multifactorial)

- **Pathophysiology**
  - ↑↑↑ Chylomicron half-life from ↓↓↓ or absent LPL activity
  - Monogenic recessive (FCS) vs polygenic + environ. (multifactorial)
  - ↑ VLDL from ↑ hepatic production (esp. in multifactorial) + ↓ VLDL clearance (↓/absent LPL)

- **Diagnosis (type/causes, severity, comorbidities)**
  - Age at Dx (adult, all multifact. & most FCS vs pediatric ~1/4 FCS)
  - H/O acute pancreatitis/severe abd. pain w/o other cause, or *not*
  - Careful Hx
    - DM2 or DM1
    - Use of EtOH, HTG-causing meds
    - Other secondary causes of HTG
  - Exam (*not* seen in all)
    - Lipemia retinalis
    - Eruptive xanthomas (mainly by Hx)
    - Hepatosplenomegaly
  - Labs
    - Fasting (or non-fasting) lipid panel, TG >500/>800
    - Advanced lipid and lipid-related testing—case-by-case
    - Genotyping for research *only*
Summary: Hyperchylomicronemia Management (FCS and Multifactorial)—continued

• Diagnosis—continued
  – FCS vs multifactorial—may be obvious, distinction may be useful re: ASCVD risk (but don’t bother to genotype)

• Diet and lifestyle
  – ↓↓↓ Dietary-fat (→↓chylomicron synth), also ↓sugar/carbs (→↓VLDL production)
  – ↓↓ or d/c Ethanol
  – ↓ Calories, ↑ Exercise, ↓ Excess weight
  – ↑ Dietary fiber?

• Meds—empiric trial
  – D/C or ↓ HTG-inducing meds, as possible
  – Treat to improve glycemic control, if indicated
  – Fenofibrate—easier (?)
  – Rx Omega-3—better in long term (?)
  – Niacin?
  – Statin?
  – MCT oil? Orlistat?
Chylomicronemia Take-Home Messages

**Dx**
- *Take seriously all* patients with $TG > 500$ mg/dL (fasting or not)—indicates \(↑↑\) risk of severe HTG/complics
- Degree of *TG elevation* → degree of *urgency* (acute pancreatitis happens quickly, is very painful, requires hospitalization, and can be fatal)
- *↑ASCVD* risk is likely if TG > 500 (or >800) mg/dL
- Distinction between monogenic FCS and multifactorial
  - May help determine CVD risk
  - Dx by clinical context (1°/peds/young adult vs 2° factors/adult)
  - Genotyping *not* clinically indicated

**Rx**
- 1st check for *treatable 2° causes*, especially *TG-raising meds*, *hyperglycemia* and *ethanol* use
- *Diet and lifestyle* treatment are ~always helpful
- Medications (*fibrate, Rx om-3*, etc.) are ~always needed, but may not *normalize* TG