Clinical Significance and Treatment of Hypertriglyceridemia: Overcoming Challenging Patient Cases

SPEAKER
Alan Brown, MD, FACC, FNLA
Kevin Maki, PhD, FNLA, CLS

Presenter Disclosure Information

Off-Label/Investigational Discussion

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Clinical Significance and Treatment of Hypertriglyceridemia

Overcoming Challenging Patient Cases

Dean Karalis, MD, FACC, FNLA
Kevin C. Maki, PhD, FTOS, FNLA
Eliot A. Brinton, MD, FAHA, FNLA

Learning Objectives

1. Assess patients with elevated triglycerides for risks of cardiovascular disease and/or pancreatitis
2. Explain the importance of managing both LDL-C and non-HDL-C in patients with elevated triglycerides
3. Diagnose secondary causes of hypertriglyceridemia
4. Develop treatment plans for patients with elevated triglycerides to achieve LDL-C and non-HDL-C targets both through lifestyle modification and drug therapy
5. Assess the benefits and risks of emerging therapeutic approaches for the management of hypertriglyceridemia
Two Main Lipids in the Body

- Triglyceride: Essential energy source for the body
- Cholesterol: Component of cell membranes and precursor for bile acids and steroid hormones

Composition of Plasma Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Chylomicrons</th>
<th>VLDL</th>
<th>IDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (g/mL)</td>
<td>&lt; 0.95</td>
<td>0.95-1.006</td>
<td>1.006-1.109</td>
<td>1.019-1.063</td>
<td>1.063-1.21</td>
</tr>
<tr>
<td>Apo B48, CII, CIII, E</td>
<td>Apo B100, CII, CIII, E</td>
<td>Apo B100, CII, E</td>
<td>Apo B100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Body Mass Index (BMI) Strongly Predicts Hypertriglyceridemia (HTG)

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>TG category by BMI category in adult US population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 (n=4057)</td>
<td>39.0</td>
</tr>
<tr>
<td>200 - 299 (n=937)</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Metabolic Syndrome: The NCEP ATP III Definition*

Three or more of the following five risk factors must be present:

- Abdominal obesity
  - Men: Waist circumference ≥ 102 cm (40 in)
  - Women: Waist circumference ≥ 88 cm (35 in)
- Triglycerides: ≥150 mg/dL (1.7 mmol/L)
- HDL cholesterol:
  - Men: <40 mg/dL (1.04 mmol/L)
  - Women: <50 mg/dL (1.30 mmol/L)
- Blood pressure: ≥130 / 85 mm Hg
- Fasting glucose: ≥100 mg/dL (5.6 mmol/L)

Classification of Serum TG Levels

<table>
<thead>
<tr>
<th>2011 AHA Scientific Statement*</th>
<th>2012 Endocrine Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG Designation**</td>
<td>TG Designation**</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Borderline-high</td>
<td>150 – 199</td>
</tr>
<tr>
<td>High</td>
<td>200 – 499</td>
</tr>
<tr>
<td>Very high</td>
<td>≥ 500</td>
</tr>
</tbody>
</table>

Causes of Hypertriglyceridemia

**Genetic Causes**
- Mild to moderate HTG is likely related to multigenic and 2nd factors while severe HTG is more likely due to monogenic disorders

**Genetic Disorders**
- Chylomicronemia syndrome
- Familial hypertriglyceridemia
- Familial combined hyperlipidemia
- Dysbetalipoproteinemia
- LPL, Apo CII and Apo AV deficiency

Genetic testing is not generally recommended and is not required to manage these conditions

Causes of Hypertriglyceridemia—cont.

**Secondary or Acquired Causes**

- Central obesity
- Diabetes mellitus
- Insulin Resistance
- Physical inactivity
- Hypothyroidism
- Renal disease
- Pregnancy
- Alcohol or calorie excess
- Increased fructose intake

**Medications**

- Oral estrogen
- Protease inhibitors
- Systemic glucocorticoids
- Retinoic acid drugs
- Beta blockers
- Thiazides
- Antipsychotics
- Bile acid sequestrants

Secondary causes of HTG are clinically important and treatment generally begins by addressing these. Clinically most important disorders shown in bold. After Miller et al. Circulation 2011; 123: 2292.

**Clinical Significance**

**Moderate HTG Consistently Predicts ↑CHD**

Meta-analysis of 29 studies in 262,525 individuals in the top vs. bottom third of TG levels (>181 vs <120 mg/dL, respectively)

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of Cases</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7128</td>
<td>1.72 (1.56–1.90)</td>
</tr>
<tr>
<td>Female</td>
<td>1994</td>
<td>1.58 (1.39–1.79)</td>
</tr>
<tr>
<td>Fasting</td>
<td>7484</td>
<td>1.59 (1.44–1.76)</td>
</tr>
<tr>
<td>Nonfasting</td>
<td>2674</td>
<td>1.45 (1.27–1.66)</td>
</tr>
<tr>
<td>Adjusted for HDL-C</td>
<td>4469</td>
<td>1.73 (1.64–1.82)</td>
</tr>
<tr>
<td>Not adjusted for HDL-C</td>
<td>5689</td>
<td>1.58 (1.42–1.77)</td>
</tr>
</tbody>
</table>

From Sarwar et al. Circulation 2007; 115: 450

**CAD Risk Is Further Increased with Greater TG Elevations**

TG is independently associated with premature familial CAD

**Small, Dense Low-density Lipoprotein (sdLDL) Caused by HTG**

Liver

TG ≥ 100 (1 TG)

Larger TG-rich VLDL

Apo CIII + Apo E

CETP (TG/CE exchange)

LPL

IDL

Remnant

Pattern B

Atherogenic Dyslipidemia

HDL= High-density Lipoprotein
FFA= Free Fatty Acids

Hepatic Lipase

VLDL → LDL

Liver

↑ Central Adiposity

Insulin Resistance

Hepatic Lipase

FFA

LDL

HDL

sdLDL

sdHDL

Rapid renal Apo-AI excretion


Genetic Studies Support a Causal Relationship between HTG and CVD Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Myocardial Infarction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubling of TG concentration</td>
<td>1.6</td>
<td>1.3-1.9</td>
</tr>
<tr>
<td>Causal using genetics</td>
<td>1.9</td>
<td>1.4-2.7</td>
</tr>
</tbody>
</table>

Noorderstjgaard BS, Yavus A. Lancet 2014;384:626-635.

Pathophysiologic Links for the Association between Hypertriglyceridemia and CVD

Elevated TGs are a marker for increased concentrations of atherogenic particles (Apo B-containing, Apo CIII-containing, LDL-P, sdLDL)

Atherogenicity of TG-rich remnant lipoprotein particles (especially postprandially)

Association with other metabolic disturbances
- Insulin resistance
- Inflammation
- Endothelial dysfunction
- Hypercoagulability
- Lower reverse cholesterol transport


Pathogenesis of Hypertriglyceridemic Pancreatitis

Excess of TG-rich lipoproteins

Hyperviscosity impairs capillary blood flow

Leak of pancreatic lipase and increased FFA

Ischemia, inflammation and acidosis leads to pancreatic acinar cell injury

Acute Pancreatitis


Risk of Acute Pancreatitis by TG Level

Acute pancreatitis risk increased 4% per 100 mg/dL increase in TG from a crude rate in those with TG <=150 mg/dL of 0.95 per 1000 person-years. (after adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related comorbidities, renal failure and other biliary diseases)

From Murphy et al. JAMA Intern Med 2013; 173: 162

Endocrine Society Clinical Practice Guidelines on the Evaluation of Hypertriglyceridemia

- Recommend screening adults for hypertriglyceridemia as part of a lipid panel at least every 5 years
- The diagnosis should be based on fasting triglyceride levels
- Individuals found to have any elevation of fasting triglycerides should be evaluated for secondary causes of hyperlipidemia
- Patients with primary hypertriglyceridemia should be assessed for other CV risk factors and for a family history of dyslipidemia and CV disease to assess genetic causes and future CV risk

From Berglund et al. J Clin Endocrino/Metab 2012; 97: 2969
Clinical Case

- 26 year old white female
- She is in good health
- She is sedentary and admits to moderate alcohol consumption. She is not compliant with a low fat diet.
- Her only meds are oral contraceptives
- Her father has a history of hyperlipidemia, but there is no family history of premature CHD
- Her physical exam is normal
- Her thyroid and renal function studies are normal

<table>
<thead>
<tr>
<th>Clinical and Lipid Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Fasting glucose</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>LDL-C (direct)</td>
</tr>
<tr>
<td>HDL-C</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Non-HDL-C</td>
</tr>
<tr>
<td>Apo B</td>
</tr>
</tbody>
</table>

Non-HDL-C Schematic

Non-HDL-C Is Stronger than LDL-C in Predicting ASCVD Risk

Non-HDL-C Is Stronger than LDL-C in Predicting ASCVD Risk

With HTG, LDL-C Underestimates ↑CVD Risk but Non-HDL-C Captures the Excess Risk

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
NHLBI Charge to the Expert Panel

Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk

- Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
- RCTs and systematic reviews/meta-analyses of RCTs independently assessed for quality
- Less expert opinion than in prior guidelines

3 Clinical Questions (CQ’s)

1. What is the evidence for LDL-C and non-HDL-C goals for secondary prevention of ASCVD?
2. What is the evidence for LDL-C and non-HDL-C goals in primary prevention?
3. For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific lipid meds, in general and in specific subpopulations

Synopsis of Recommendations*

1. Encourage adherence to a healthy lifestyle
2. Statin therapy recommended for adult groups demonstrated to benefit
3. Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored
4. Engage in a Clinician-Patient Discussion Before Initiating Statin Therapy –especially for Primary Prevention in Patients with Lower ASCVD Risk

Synopsis of Recommendations

1. Use the Newly Developed Pooled Cohort Equations for Estimation 10-Year ASCVD Risk
2. Initiate proper intensity of statin therapy
3. Evidence is inadequate to Support Treatment to Specific LDL-C or Non-HDL-C Goals
4. Regularly Monitor Patients for Adherence to Lifestyle and Statin Therapy

Synopsis of Recommendations*

1. Use the Newly Developed Pooled Cohort Equations for Estimation 10-Year ASCVD Risk
2. Initiate proper intensity of statin therapy
3. Evidence is inadequate to Support Treatment to Specific LDL-C or Non-HDL-C Goals
4. Regularly Monitor Patients for Adherence to Lifestyle and Statin Therapy

4 Statin Benefit Groups

High risk groups:
- 1. Clinical atherosclerotic cardiovascular disease (ASCVD)
- 2. LDL–C ≥190 mg/dL, Age ≥21 years (FH)
- 3. Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL

4. Primary prevention – Clinician-patient risk discussion required.
- No Diabetes and ≥7.5% 10-year ASCVD risk
- Age 40-75 years, LDL–C 70-189 mg/dL

Focus on Appropriate intensity of statin therapy to reduce ASCVD risk

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
- Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit
- Quantitative comparison of statin benefits with statin adverse effects
- Nonstatin therapies –did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy
**Why Not Continue to Treat to Target?**

**Major difficulties:**
1. Current RCT data do not indicate what the target should be.
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another.
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal.
4. Therefore, unknown net benefit from treat-to-target approach.

**To Reduce ASCVD by treating blood cholesterol**
1. Favor proven therapy for those shown to benefit.
2. Use statins as drugs of choice; they are inexpensive (most are generic) & safe when taken as tolerated.
3. Focus on proper intensity of statin therapy & monitor for adherence to optimal lifestyle and statin Rx.
4. Insist on a clinician-patient discussion in primary prevention:
   a. Discuss a global risk reduction strategy.
   b. Discuss potential for benefit and adverse effects of statin therapy including drug-drug interactions.
   c. Patient preferences (shared decision making).

**Classifications of Cholesterol and Triglyceride Levels in mg/dL**

<table>
<thead>
<tr>
<th>Non-HDL-C</th>
<th>HDL-C</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130</td>
<td>Desirable</td>
<td>&lt;150</td>
</tr>
<tr>
<td>130-159</td>
<td>Above desirable</td>
<td>150-199</td>
</tr>
<tr>
<td>160-189</td>
<td>High</td>
<td>200-499</td>
</tr>
<tr>
<td>≥220</td>
<td>Very high</td>
<td>≥500</td>
</tr>
</tbody>
</table>

**Individuals Not in a Statin Benefit Group**

In those for whom a risk decision is uncertain:
- These factors may inform clinical decision making in context of clinician-patient discussion.
  - LDL-C ≥160 mg/dL
  - Elevated lifetime risk of ASCVD (below added from risk assessment guideline)
  - Family history of premature ASCVD
  - hs-CRP ≥2.0 mg/L
  - Coronary artery calcium score ≥300 Agatston units
  - Ankle brachial index (ABI)<0.9

**Triglycerides as a Target of Lipid-Altering Therapy**
- For TG ≥500 mg/dL (especially ≥1000), TG-lowering is the primary goal of therapy.
- For TG 200-499 mg/dL, lipid treatment targets are non-HDL-C and LDL-C.

**Triglyceride Treatment in AHA/ACC Guidelines**
- Treat TG> 500mg/dl to avoid pancreatitis.
- For those with TG < 500 mg/dl, assess risk and focus on appropriate intensity of statin therapy as well as aggressive lifestyle modification.
- NLA recommendations suggest further consideration for those patients with TG between 200 mg/dl and 499 mg/dl.
Non-HDL-C as a Target of Lipid-Altering Therapy

- Non-HDL-C treatment goal for patients at low, moderate and high ASCVD risk is <130 mg/dL, and is <100 mg/dL for patients with ASCVD and very high risk.
- Non-HDL-C comprises cholesterol carried by all potentially atherogenic particles:
  - LDL
  - IDL
  - VLDL and VLDL remnants
  - chylomicron remnants
  - lipoprotein (a)

For Diet/Diseases/Disorders/Altered Metabolism

- Excess energy density
- Diabetes mellitus
- Metabolic syndrome (obesity, insulin resistance)
- HIV infection
- Autoimmune disorders
- Hypothyroidism
- Pregnancy
- Polycystic ovary syndrome
- Menopause transition

For Patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

NLA Recommendations

Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at Which to Consider Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 or 1 of major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥100</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 or 3 of major ASCVD risk factors</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td>High</td>
<td>4 or more of major ASCVD risk factors</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Very High</td>
<td>5 or more of major ASCVD risk factors</td>
<td>&lt;70</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Secondary Hypertriglyceridemia - Drugs

<table>
<thead>
<tr>
<th>Drugs That Elevate Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral estrogens, tamoxifen, raloxifene</td>
</tr>
<tr>
<td>Retinoids</td>
</tr>
<tr>
<td>Immunosuppressive drugs (cyclosporine, sirolimus)</td>
</tr>
<tr>
<td>Interferon</td>
</tr>
<tr>
<td>Beta-blockers (especially non-beta 1-selective)</td>
</tr>
<tr>
<td>Atypical antipsychotic drugs (fluphenazine, clozapine, olanzapine)</td>
</tr>
<tr>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Rosiglitazone (but not pioglitazone)</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
</tr>
<tr>
<td>Ciprofibrate</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
</tr>
</tbody>
</table>

Secondary Hypertriglyceridemia – Diet/Diseases/Disorders/Altered Metabolism

<table>
<thead>
<tr>
<th>Diet</th>
<th>Diseases/Disorders/Altered Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive energy balance</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>High glycemic load</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Excess alcohol</td>
<td>Metabolic syndrome (obesity, insulin resistance)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td></td>
<td>Menopause transition</td>
</tr>
</tbody>
</table>

Metabolic Syndrome

- Metabolic syndrome is recognized as a multiplex risk factor for both ASCVD and type 2 diabetes mellitus.
- Increased adiposity and insulin resistance appear to be central pathophysiologic features of this cluster of interrelated metabolic and hemodynamic disturbances.
- The presence of the metabolic syndrome indicates high potential to benefit from lifestyle therapies, particularly weight loss if overweight/obese and increased physical activity.
  - Successful lifestyle intervention will reduce adiposity and insulin resistance, improving multiple physiological disturbances that may contribute to risk, including the metabolic syndrome components, as well as indicators of inflammation and thrombogenicity.
**Triglyceride-Lowering Drug Therapies**

- A drug targeting triglyceride reduction should be considered for first-line therapy in those with triglycerides ≥500 mg/dL.
  - Triglyceride-lowering drug therapies include fibric acids, high-dose long-chain omega-3 fatty acids and nicotinic acid.
  - A statin may be a reasonable first-line agent if the triglyceride concentration is ≥500 mg/dL, but <1000 mg/dL, if no history of pancreatitis.

**Drugs Affecting Lipoprotein Metabolism**

<table>
<thead>
<tr>
<th>Drug Class, Agents, and Daily Doses</th>
<th>Lipid/Lipoprotein Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Fibrate Class</strong></td>
<td></td>
</tr>
<tr>
<td><em>Cholesterol absorption inhibitors</em></td>
<td>LDL-C</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>≥15-30%</td>
</tr>
<tr>
<td>Nicotinic acids</td>
<td>≥5-25%</td>
</tr>
</tbody>
</table>

*TG reduction with statins, particularly high potency statins, is higher in patients with hypertriglyceridemia, producing reductions in the range of 20-50%.

**Case Study**

- Male, 46 yr, weight stable (>10 yr) at 214 lb, BMI 31.5 kg/m²
- Executive in a consulting firm, works long hours and travels a great deal
- Family history unknown (adopted)
- Non-smoker (never smoked)
- History of hypertension well controlled with ramipril 10 mg qd (office BP = 118/76 mm Hg)
- History of GERD well controlled with omeprazole
- Taking simvastatin 40 mg hs
- Jogs 3-4 times per week, 30 min per session (2.5 to 3.0 miles) and lifts weights 2-3 times per week

**Case Study (continued)**

- Fasting lipid profile and indicators of glucose homeostasis
  - Total-C = 188 mg/dL
  - HDL-C = 38 mg/dL
  - Triglycerides = 323 mg/dL
  - LDL-C = 85 mg/dL
  - Non-HDL-C = 150 mg/dL
  - Glucose = 112 mg/dL, HbA1c = 6.2%
  - Waist = 104 cm (41 in)
- According to the 2014 NLA recommendations for patient-centered management of dyslipidemia, this patient has 3 risk factors (age, low HDL-C, and hypertension) classifying him as high risk for ASCVD.

**Case Study Questions**

1. What are the lipid and non-lipid treatment goals for this patient based on the NLA Recommendations?
2. Does this patient need a change in his drug therapy to reach his treatment goals?
Treatment

TREATMENT SECTION OUTLINE
• HTG Guidelines: American Heart Assoc. (AHA 2011) vs. European Society of Card. (ESC 2011)
• Identify and treat any secondary causes (e.g. hypothyroid, medication causes, EtOH excess)
• Lifestyle management
  – Diet
    • Differences between TG ≥ 500 vs < 500
  – Exercise
    • Duration?
    • Type?
• TG-Lowering Medications
  – Fenofibrate
  – Prescription Omega-3
  – Niacin
  – Other?

Treatment of HTG: 2° Causes – Treat These First
• High fructose/sucrose/carbohydrate intake
• High fat intake (need to ↓ only if TG >~700 mg/dL)
• Low fiber intake
• Ethanol (may ↑ TG even in moderation)
• Sedentary lifestyle/central obesity/insulin resistance, DM (poorly controlled)
• Hypothyroidism
• Nephrotic syndrome
• Pregnancy – Gestational diabetes, toxemia
• PCOS
• Medications:
  – Oral estrogen (contraceptives or HRT – not transdermal)
  – Systemic glucocorticoids
  – Antiretrovirals (for HIV)
  – Retinoic acid derivatives
  – Other (some antipsychotics, nonselective beta-blockers, thiazide diuretics, etc.)

Non-Medication Treatment of HTG

Dietary Measures to Lower TG Levels

<table>
<thead>
<tr>
<th>Change</th>
<th>TG Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (5-10% ↓ body weight : 1 kg ↓→2% TG ↓)</td>
<td>10% – 20%</td>
</tr>
<tr>
<td>&quot;Mediterranean&quot; diet (fiber, fish, fruits/veg) (vs. high-carb/low-fiber diet)</td>
<td>10% – 15%</td>
</tr>
<tr>
<td>Marine-derived omega 3 (EPA/DHA)gram (herring=salmon&gt;trout&gt;tuna)</td>
<td>5% – 10%</td>
</tr>
<tr>
<td>↓ Carbohydrates by 5-10% of energy (1-2% ↓ per 1% energy replacement w/MUFA or PUFA)</td>
<td>5% – 20%</td>
</tr>
<tr>
<td>Eliminate trans fats (1% ↓ per 1% energy replacement with MUFA/PUFA)</td>
<td>1% – 3%</td>
</tr>
</tbody>
</table>

MUFAs = monounsaturated FA; PUFAs = polyunsaturated FA.

Fat-Inducible vs. CHO-Inducible Hypertriglycerideremias

FAT (Types I & V)
• Chylomicronemia after 12-hour fast
• Defective chylomicron clearance
• Fasting TG > ~700
• Pancreatitis
• ↑ CVD in type V only ("atherogenic dyslip” +?)
• Rx very low fat diet (10-15%), + medication

Carb (Types IIa & IV)
• Few/no chylomicrons after 12-h fast
• Overproduction of VLDL (fatty liver, etc.)
• Fasting TG < ~700
• No specific acute Sx
• ↑ CVD risk in all ("atherogenic dyslip” +?)
• Rx low fructose, high fiber ↓ medication

physical exercise lowers TG

- ↓TG is usually the first/strongest lipid effect of ↑physical activity
- % ↓TG is directly proportional to:
  - Baseline TG
  - Amount of exercise (no minimum threshold)
- Aerobic activity better
- Frequency and intensity important
- Exercise can block CHO-induced ↑TG
- ↓VLDL production and ↑VLDL clearance

Recent HTG Guidelines:
AHA 2011 vs EAS 2011

<table>
<thead>
<tr>
<th>AHA 2011*</th>
<th>EAS 2011*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extensive review of diet and lifestyle treatment</td>
<td>• Extensive review of diet and lifestyle treatment</td>
</tr>
<tr>
<td>• Medical Rx for TG &gt;500 mg/dL</td>
<td>• Medical Rx for TG &gt;500 mg/dL</td>
</tr>
<tr>
<td><strong>No mention</strong> of medical Rx for TG 200-500 mg/dL</td>
<td><strong>Consider</strong> medical Rx for TG 200-500 mg/dL</td>
</tr>
</tbody>
</table>


Recent HTG/low HDL-C patients

- TG Medications: Which? When?

<table>
<thead>
<tr>
<th>Drug</th>
<th>TG-Lowering*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st for TG &gt;500</td>
<td>Omega-3 oil (EPA +/- DHA; EE vs FFA)</td>
</tr>
<tr>
<td>2nd for TG 200-499</td>
<td>Niacin (pharmacologic dose)</td>
</tr>
<tr>
<td>1st for TG 200-499</td>
<td>Statins</td>
</tr>
<tr>
<td>2nd for TG 2500</td>
<td>Statins</td>
</tr>
</tbody>
</table>

* High potency statins may ↓TG 20-50% in patients with HTG

Recent HTG Guidelines: AHA 2011 vs EAS 2011

<table>
<thead>
<tr>
<th>Trial (Subgroup, mg/dL)</th>
<th>Risk difference vs placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS (TG ≥115) (Prevention)</td>
<td>−31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CARE (TG ≥500) (Prevention)</td>
<td>−24</td>
<td>0.003</td>
</tr>
<tr>
<td>PPR Project (TG ≥200) (Prevention)</td>
<td>−23</td>
<td>0.029</td>
</tr>
<tr>
<td>4S (TG ≥200, HDL-C &lt;39) (Intervention)</td>
<td>−24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>JUPITER (TG ≥500) (Thromb)</td>
<td>−24</td>
<td>0.015</td>
</tr>
<tr>
<td>LLT-2 (TG ≥277) (Intervention)</td>
<td>−24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Statins Reduce CVD Events in HTG Patients

**Omega-3**

**Table: Lipid Effects of Prescription Om-3**

<table>
<thead>
<tr>
<th>Study</th>
<th>EPA/DHA FFA**</th>
<th>EPA EE</th>
<th>EPA/DHA EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Inclusion</td>
<td>TG 200-499 mg/dL</td>
<td>TG 200-499 mg/dL</td>
<td>TG 200-499 mg/dL</td>
</tr>
<tr>
<td>Duration</td>
<td>8 weeks</td>
<td>12 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-22.8%</td>
<td>-5.9%</td>
<td>-17.5%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.3%</td>
<td>1.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-4.2%</td>
<td>-0.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>TC</td>
<td>-7.2%</td>
<td>-2.1%</td>
<td>-5.2%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>3</td>
<td>2</td>
<td>-1*</td>
</tr>
<tr>
<td>Apo B</td>
<td>-2.1%</td>
<td>0.3%</td>
<td>-2.3%</td>
</tr>
</tbody>
</table>

**Currently Completed Om-3 CVD Studies**

**OMNIN**

<table>
<thead>
<tr>
<th>Risk &amp; Prevention*</th>
<th>JELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Om-3 Type/dose</td>
<td>EPA/DHA 1 g/day</td>
</tr>
<tr>
<td>Dose &amp; Kilcalories</td>
<td>12,380/1715</td>
</tr>
<tr>
<td>Risk profile</td>
<td>IGT, IFG, or DM2</td>
</tr>
<tr>
<td>Treatment</td>
<td>2x placebo, 2x FFA</td>
</tr>
</tbody>
</table>

| Statin Use | 54% | 6% | 100% |
| Statin Type/ Dose | Death from CVD | Death, Myocardial Infarction, Stroke | N/A |
| Result | HR=0.98 | P=0.72 | HR=0.97 P=0.30 |
| LVEF | 55% | 62% | 62% |

**Low-dose Om-3 doesn’t CVD in statin-era: Mid-doseOm-3 does: CVD Failure of low-dose Rx Om-3 implies that dietary supplements don’t CVD**

*Reference from placebo; p=0.05  **p<0.05 compared to placebo; p=0.05

---

**Prescription Om-3**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>EPA/DHA**</th>
<th>EPA EE</th>
<th>EPA/DHA EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic?</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 (96%)</td>
<td>70/27 (75%)</td>
</tr>
<tr>
<td>Relevability</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, dyspepsia</td>
<td>Arthralgia only</td>
<td>Fishy eructs, dyspepsia, diarrhea, nausea</td>
</tr>
<tr>
<td>TG-lowering</td>
<td>++ +</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>LDL-C effects (HITG/HITG)</td>
<td>↑↑/↑</td>
<td>↑/↓</td>
<td>↑/↓</td>
</tr>
</tbody>
</table>

**CVD?**

| Low dose | No at low dose, no ongoing clinical trials | Probably (mid-dose) starting trials | No data, but planned trial |

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**Fibrates**

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**Notes:**


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**References:**

FIELD: Microvascular Benefit with Fenofibrate, Amputations and Albuminuria

Nontraumatic Amputations Progression and Regression of Albuminuria

38% Reduction (P=0.01)

14% Reduction 11% 15% Increase

*aProgression of albuminuria was defined as the proportion of patients who progressed either from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria.


First Laser Treatment for Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Years After Randomization</th>
<th>Placebo</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4900</td>
<td>4895</td>
</tr>
<tr>
<td>1</td>
<td>4784</td>
<td>4797</td>
</tr>
<tr>
<td>2</td>
<td>4674</td>
<td>4626</td>
</tr>
<tr>
<td>3</td>
<td>4559</td>
<td>4515</td>
</tr>
<tr>
<td>4</td>
<td>4485</td>
<td>4393</td>
</tr>
<tr>
<td>5</td>
<td>4274</td>
<td>4249</td>
</tr>
</tbody>
</table>

HPS2/THRIVE: Baseline Lipids

- LDL-C 63 mg/dL on statin
- HDL-C 44 mg/dL (no selection)
- TG 125 mg/dL (no selection)

No benefit from niacin

Niacin does not ↓↓↓↓ CVD in patients where it is not indicated (HTG/low HDL-C) given low LDL-C

Fenofibrate vs Om-3 vs Niacin for HTG: Summary

<table>
<thead>
<tr>
<th>Fenofibrate vs Om-3 vs Niacin for HTG: Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
</tr>
<tr>
<td>Δ TG</td>
</tr>
<tr>
<td>Δ LDL-C</td>
</tr>
<tr>
<td>Δ Non-HDL-C</td>
</tr>
<tr>
<td>Δ HDL-C</td>
</tr>
<tr>
<td>↓ CVD Efficacy</td>
</tr>
<tr>
<td>↓ Mortality</td>
</tr>
<tr>
<td>Non-CVD Benefits</td>
</tr>
<tr>
<td>Safety</td>
</tr>
<tr>
<td>“Natural”</td>
</tr>
<tr>
<td>Access (cost/generic)</td>
</tr>
<tr>
<td>Tolerability</td>
</tr>
<tr>
<td>Ease of use</td>
</tr>
</tbody>
</table>

Bottom line: Feno or Om-3 are usu. 1st line but any 2 or 3 may be needed
HTG Treatment Summary

When? After Rx, 2° factors & lifestyle, use meds for:
• TG ≥500 for pancreatitis & athero—treat all
• TG 200-499 mg/dL; Rx statin and non-statin (non-HDL-C to goal, esp. if 2° prevention or high CVD risk)

How?
• Review/eliminate 2° factors
• Diet (↓ sugar, fat, calories, & EtOH, ↑ fiber) ~ all!
• ↑ Exercise for ~ all
• Wt loss for obese and MONW
• Fenofibrate—easy and effective
• Prescription Om-3—exc. fibrate alternative/adjunct
• Niacin—good if low HDL-C & high LDL-C
• Statins—good if high LDL-C
• Combinations—any 2 or 3 for greater TG ↓