## Hypertriglyceridemia and CVD: to Treat or Not to Treat?

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### Disclosures

- None

### Objectives

- Review the physiology and pathophysiology of triglycerides  
- Discuss the role of hypertriglyceridemia as a risk factor for ASCVD  
- Summarize the data regarding treatments for hypertriglyceridemia on CVD outcomes  
- Develop a treatment paradigm for the management of moderate hypertriglyceridemia
Case:

- 66 y/o woman with h/o of ASCVD (NSTEMI with stent at age 63, TIA at age 65) and hypertension. Doing well.
- Medications: atorvastatin 80 mg, metoprolol, lisinopril, aspirin, levothyroxine, omeprazole
- Family Hx: no clear premature ASCVD
- Social: heart healthy diet, walks 45 min/d, non-smoker

Exam: BP 124/80  BMI 25  otherwise normal exam
Labs: TChol 171, TG 235, HDL 46, LDL 78, non-HDL 125
CMP wnl, A1c 5.6%

Audience Participation

- Which of the following is most true about her lipids and ASCVD?
  1. LDL is well controlled on high-intensity statin therapy and further LDL lowering would not be indicated.
  2. Her elevated triglycerides are a clear cause to her ASCVD.
  3. Adding a fibrate and lowering her triglycerides would clearly reduce her risk for another ASCVD event.
  4. High dose icosapent ethyl may reduce her risk for another ASCVD event.
Audience Participation

Which of the following is true about triglycerides?
1. Triglycerides all come from the diet.
2. Severe hypertriglyceridemia (>500) is associated with acute ASCVD events.
3. Elevated triglycerides can be due to over production and/or reduced clearance.
4. Moderate hypertriglyceridemia is not associated with increased risk for ASCVD.
5. Hypertriglyceridemia is rarely due to "secondary" causes.

Secondary Prevention in Patients with Clinical ASCVD

ASCVD at very high-risk†

High-Intensity or Maximal Statin

If on maximal statin therapy and LDL ≥70, consider adding ezetimibe

If PSCK9-I is considered, add ezetimibe first before adding PCSK9-I

If on clinically judged maximal LDL lowering therapy and LDL ≥70 or non-HDL-C ≥100, consider adding PCSK9-I

Grundy et al. Circulation 2018
Case:

- **ASCVD and Hypercholesterolemia:**
  - Why did she have premature and recurrent ASCVD?
  - Consider checking an Lp(a)
  - Per the new guidelines she is at "very high risk":
    - multiple major ASCVD events and multiple high risk conditions
    - While she is on high intensity statin therapy, her LDL is >70 so consider more aggressive therapy.
  - Options include:
    - Intensify statin therapy: switch to rosuvastatin 40mg
    - Add ezetimibe or bempedoic acid
    - Go straight to adding a PCSK9 inhibitor
  - Guidelines are meant to be exactly that: "guidelines"
  - But what about her triglycerides?

What about “Residual Risk”?

- We don’t start with LDL-C lowering early enough?
- Studies are not long enough?
- We have not been aggressive enough?
- There’s only so much one can do with LDL-C lowering, so are we missing other targets?
  - Lipoprotein(a)
  - Triglycerides
  - “fish oil deficiency”
  - HDL-C
  - Inflammation
  - Others
What About Hypertriglyceridemia?

- Severe hypertriglyceridemia
  - Associated with acute pancreatitis
- Moderate hypertriglyceridemia
  - "Risk factor" for ASCVD
  - Associated with insulin resistance, metabolic syndrome, type 2 diabetes
  - But unclear whether triglyceride lowering is beneficial

Lipid Physiology

- Triglycerides
  - Structure:
  - Fuel source for muscle use and adipose tissue storage

Fatty Acid and Triglyceride Flux
Lipoprotein Lipase

- Breaks down TGs from TG-rich lipoproteins (Chylomicrons, VLDL) into FFA’s
- Activated by Apo CII, insulin?
- Inhibited by Apo CIII and ANGPTL3
- Requires transport to the lumen by GPIHBP1 (glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1)
Causes of Hypertriglyceridemia

- Can be isolated
  - Familial Chylomicronemia Syndrome (Class I)
    - LPL or apoC-II deficiency/mutations
  - Familial Hypertriglyceridemia (Class V)
- Can by part of a “mixed-hyperlipidemia”
  - Familial/Genetic
    - Familial Combined Hyperlipidemia (Class IIb)
    - Dysbetalipoproteinemia (Class III - apoE2 mutation)
- Secondary causes
- Usually associated with low HDL
  - Except with estrogens and alcohol

Causes of Hypertriglyceridemia

- Increased VLDL Production:
  - Insulin Resistant states
  - Drugs (alcohol, estrogens)
  - Familial Hypertriglyceridemia (autosomal dominant)
  - Familial Combined Hyperlipidemia
- Decreased Triglyceride Catabolism
  - Lipoprotein Lipase (LPL) Deficiency
  - ApoE2 Deficiency (activator of LPL)
  - Circulating inhibitors to LPL
  - Familial Dysbetalipoproteinemia
  - Secondary Causes: Diabetes, Alcohol
- Polygenic/Multifactorial

Exam Findings Associated with Severe Hypertriglyceridemia

- Lipemia Retinalis
- Eruptive Xanthomas
- Lipemic Serum
### Rule Out and Treat Secondary Causes of Hypertriglyceridemia

- Diet: high carb diets, high intake of refined carbohydrates, high saturated diets, excessive alcohol intake
- Weight gain, obesity, lipodystrophy
- Hyperglycemia, insulin resistance, uncontrolled diabetes
- Pregnancy
- Hypothyroidism
- Nephrotic syndrome, chronic renal failure
- Drugs: oral estrogens, SERMS (raloxifene, tamoxifen), glucocorticoids, anabolic steroids, bile acid sequestrants, beta blockers (not carvedilol), thiazides, protease inhibitors, atypical antipsychotics, retinoic acid, sirolimus

### Treatment of “Severe” Hypertriglyceridemia

If TG ≥ 400-500 mg/dL, primary goal is to prevent pancreatitis:
- Treat/Eliminate Secondary Causes
- Reduce “chylomicronemia” with a very low fat diet (< 10% calories from fat) or NPO in hospital
- No alcohol
- Weight Management, Physical Activity
- Medical Therapy: Fibrates, high dose Fish Oil
- when TG < 500 mg/dL,…

### Treatment of “Moderate” Hypertriglyceridemia

If TG 150-500 mg/dL:
- Use elevated TG as a risk marker and treat LDL with statin therapy if indicated per guidelines
- Treat/Eliminate secondary causes of dyslipidemia
- Intensify weight management, physical activity
- Consider higher mono-, poly-unsaturated fat diet
- Unclear if medical therapy targeting triglycerides (fibrates, fish oil) is beneficial in addition to statin therapy
Fibric Acid Derivatives (Fibrates)

- Gemfibrozil, Fenofibrate
- Mechanisms:
  - Activate lipoprotein lipase
  - Inhibit VLDL production
  - Proven reduction in CV events esp in obesity, diabetes
  - Lower TG’s 30-50%
- First line drug for severe hypertriglyceridemia
- Raises HDL moderately (5-10%)
- Can raise LDL!
- Few side effects (GI, cholelithiasis)
- Caution when combined with statins?

Fibrate Outcome Studies Evaluating Hypertriglyceridemic Subgroups

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (p-value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: HTG Subgroup (p-value)</th>
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</thead>
<tbody>
<tr>
<td>Helsinki Heart</td>
<td>-34% (0.02)</td>
<td>TG &gt;= 204 mg/dL, LDL-C/HDL-C &gt; 5.5</td>
<td>-71% (?0.005)</td>
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<td>Study (Gemfibrozil)</td>
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<tr>
<td>Pre-Statin Era</td>
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<tr>
<td>VA HPT (Gemfibrozil)</td>
<td>-22% (&lt;0.004)</td>
<td>TG &gt;= 204 mg/dL, LDL-C/HDL-C &gt; 5.5</td>
<td>-71% (?0.005)</td>
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<tr>
<td>Pre-Statin Era</td>
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<tr>
<td>Some Statin Use</td>
<td>-11% (0.16)</td>
<td>TG &gt;= 204 mg/dL, HDL-C &lt; 42 mg/dL</td>
<td>-27% (0.67)</td>
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<td>FIELD (Fenofibrate)</td>
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<td>Statin Add-On</td>
<td>-8% (0.32)</td>
<td>TG &gt;= 204 mg/dL, HDL-C &lt; 34 mg/dL</td>
<td>-31% (?0.057)</td>
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<td>ACCORD (Fenofibrate)</td>
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So, what's the stink about fish oil?
Fish Oils

- Primarily lowers triglycerides (~30%)
- Need large doses to be effective
  - 6-12 g daily with OTC preparations
  - 4-6 g daily with Rx preparations (Lovaza, Vascepa)
- Safe to combine with statins/fibrates
- Generally well tolerated
  - GI SEs: fishy taste, eructation, nausea, diarrhea
- Slight increased risk of bleeding due to decreased platelet aggregation
- Benefits of “supplement” doses (500-1000 mg) of fish oil are unclear based on RCTs
- Then there’s REDUCE-IT…

JELIS Study:
CVD Risk Reduction of EPA in Patients with ↑ TG and ↓ HDL-C

![Graph showing CVD risk reduction in patients with increased triglycerides and decreased HDL-C.](image)


Methods:
- Icosapent ethyl 4 g/day vs placebo (corn oil)
- 8,179 patients with:
  - either CVD or DM plus one or more other CVD risk factors
  - moderate hypertriglyceridemia (150-499, mean 216 mg/dl)
  - controlled LDL-C (41-100, mean 75 mg/dl) on statin therapy
**REduce-IT Trial Results**

- More effective in secondary prevention
- Baseline TG and change in TG did not predict the response, suggesting a non-TG lowering mechanism?

**STRENGTH Trial**

A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EPANova in High Cardiovascular Risk Patients With Hypertriglyceridemia

So, is it all about EPA?

According to a press release from the company, the trial's data monitoring committee recommended the trial be closed because of a statistically significant reduction in cardiovascular events with the addition of omega-3 fatty acids (EPANova) demonstrating a benefit in the trial population.

The academic leadership of the STRENGTH trial is obviously disappointed in this result, but we are very proud to have had the opportunity to answer this important scientific question. Cardiology Today's Editorial Board Member Steven L. Houser, MD, MACC, senior chief of the trial and chief academic officer of the trial and...
Case:

- ASCVD and Hypercholesterolemia:
  - We added ezetimibe and her LDL came down to 62 mg/dl, so at “goal”, but is that sufficient?
  - Her triglycerides remained persistently (moderately) elevated without clear secondary cause
  - Consider adding icosapent ethyl
    - what if not covered?
  - Guidelines are meant to be exactly that: "guidelines"

Thank You!