Hypertriglyceridemia, Remnants, and Cardiovascular Disease

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Faculty Disclosures*

Dr. Paul D. Rosenblit reported the following relevant financial relationships with commercial interests:

<table>
<thead>
<tr>
<th>Speaker / Teaching Faculty:</th>
<th>Esperion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Research Site Trials:</td>
<td>Dexcom, Ionis(Akcea), Novo Nordisk, Novartis</td>
</tr>
</tbody>
</table>

* 12 months: July 1, 2021 – June 30, 2022
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

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Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society 2021

Lipoprotein Sub-Classes

1.20
1.10
1.06
1.02
1.006
0.95

Density (g/ml)

Triglyceride
HDL-C
LDL-C

Apolipoprotein B (Apo B)-Containing Particles or Non-HDL-C

Directly atherogenic (found in plaque)

Traditional Lipid Panel
Total Cholesterol
Triglyceride
HDL-C
LDL-C
Major Lipoproteins as Carriers of Various Lipids (Cholesterol, Triglycerides, Phospholipids, and Apolipoproteins)

<table>
<thead>
<tr>
<th></th>
<th>Density, g/mL</th>
<th>Diameter, nm</th>
<th>VLDL Remnants</th>
<th>LDL</th>
<th>IDL</th>
<th>VLDL</th>
<th>Chylomicron-Remnants</th>
<th>Chylomicrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>1.063-1.21</td>
<td>8-13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a)</td>
<td>1.006-1.125</td>
<td>25-30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LDL</td>
<td>1.019-1.063</td>
<td>22-25.5--28.5</td>
<td>25-30</td>
<td></td>
<td></td>
<td>30-80</td>
<td></td>
<td>50-74</td>
</tr>
<tr>
<td>IDL</td>
<td>1.006-1.019</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Small--Large</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>0.95-1.006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylom</td>
<td>0.94-1.010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylomi</td>
<td>&lt;0.95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90-95%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Apo AI, II, IV, V
Apo Cl, CII, CIII, CIV
Apo E
Apo B 100
Apo B 100
Apo B 100
Apo B 100
Apo B 48
Apo B 48

Cholesterol
Triglyceride-rich Lipoproteins

‘Number’ of Atherogenic particles

Total Cholesterol minus HDL-C = Atherogenic cholesterol


Normal Conversion by Lipoprotein Lipase (LPL) of Chylomicrons to Chylomicron Remnants and VLDL to VLDL Remnants and by Hepatic Lipase (HL) to LDL-C & Ultimate Uptake by Liver


‘Normal’ $T_{1/2}$ 15-20 mins clearance completion ~2hrs
Normo-Triglyceridemia

Production

Clearance

Hypertriglyceridemia

↑TG Pool

↓Clearance

↑Production
### Various Classification Schemes for Levels of Triglyceride (TG)’mia Introduced or Adopted by Selected Organizations in the Last 2 Decades

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Classification,</th>
<th>TG, mg/dL</th>
<th>TG, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 ESC/EAS 2013 EAS</td>
<td>Normal</td>
<td>&lt;150</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td></td>
<td>HTG</td>
<td>150-885</td>
<td>1.7-9.9</td>
</tr>
<tr>
<td></td>
<td>Severe HTG</td>
<td>≥885</td>
<td>≥10</td>
</tr>
<tr>
<td>2012 Endocrine Society</td>
<td>Normal</td>
<td>&lt;150</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td></td>
<td>Mild HTG</td>
<td>150-199</td>
<td>1.7-2.3</td>
</tr>
<tr>
<td></td>
<td>Moderate HTG</td>
<td>200-999</td>
<td>2.3-11.2</td>
</tr>
<tr>
<td></td>
<td>Severe HTG</td>
<td>999-1999</td>
<td>11.2-22.4</td>
</tr>
<tr>
<td></td>
<td>Very severe HTG</td>
<td>≥2000</td>
<td>≥22.4</td>
</tr>
<tr>
<td>2011 AHA</td>
<td>Optimum</td>
<td>&lt;100</td>
<td>&lt;1.13</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>100-150</td>
<td>1.13-1.7</td>
</tr>
<tr>
<td></td>
<td>Borderline high</td>
<td>150-199</td>
<td>1.7-2.3</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>200-499</td>
<td>2.26-5.6</td>
</tr>
<tr>
<td></td>
<td>Very high</td>
<td>≥500</td>
<td>≥5.6</td>
</tr>
<tr>
<td></td>
<td>Borderline high</td>
<td>150-199</td>
<td>1.7-2.3</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>200-499</td>
<td>2.3-5.6</td>
</tr>
<tr>
<td></td>
<td>Very high</td>
<td>≥500</td>
<td>≥5.6</td>
</tr>
<tr>
<td>2011 NHLBI supported NCEP Expert Panel on CV Health in Children and Adolescents</td>
<td>Normal (Acceptable)</td>
<td>0-9 yrs</td>
<td>&lt;75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-19 yrs</td>
<td>&lt;90</td>
</tr>
<tr>
<td></td>
<td>Borderline 75th %’tile</td>
<td>0-9 yrs</td>
<td>75-99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-19 yrs</td>
<td>90-129</td>
</tr>
<tr>
<td></td>
<td>High 95th %’tile (Abnormal)</td>
<td>0-9 yrs</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-19 yrs</td>
<td>≥130</td>
</tr>
<tr>
<td>Category</td>
<td>Triglyceride level</td>
<td>mg/dL</td>
<td>mmol/L</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Extreme</td>
<td>&gt;880</td>
<td></td>
<td>&gt;10</td>
</tr>
<tr>
<td>Severe</td>
<td>500-880</td>
<td></td>
<td>5.7-10.0</td>
</tr>
<tr>
<td>Moderately Elevated</td>
<td>150-500</td>
<td></td>
<td>1.7-5.7</td>
</tr>
<tr>
<td>Borderline</td>
<td>100-150</td>
<td></td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Optimal</td>
<td>&lt;100</td>
<td></td>
<td>&lt;1.2</td>
</tr>
</tbody>
</table>

**Hypertriglyceridemia: Population Distribution/Frequency**

### Optimal "Ideal"

- **Population**: 333 million
- **World**: 7.9 billion

### Borderline

- **Population**: 243 million
- **World**: 5.8 billion

### Mild-to-moderate HTG (formerly Types 4, 3, 2b HLP)

- **Population**: ~27%
- **World**: 2.1 billion
- **US**: 90 million

### Moderately Elevated

- **Population**: ~27%
- **World**: 2.1 billion
- **US**: 90 million

### Severe

- **Population**: ~1.7%
- **World**: 23 million
- **US**: 3-4 million

### Extreme Monogenic (BI-Allelic) Chylomicronemia (formerly HLP Type 1 or Familial Chylomicronaemia Syndrome, FCS)

#### Extreme

- **Population**: 0.1%
- **World**: 7.9 million
- **US**: 0.333 million

#### Extreme Monogenic Bi-Allelic (FCS)

- **Population**: ~0.0001%
- **World**: 7,900-15,800
- **US**: 333-666

### Multifactorial or polygenic Chylomicronemia (MCS)

- **Population**: 27%
- **World**: 2.1 billion
- **US**: 90 million

### Non-Fasting Triglyceride Level

- **Mild-to-moderate HTG** (formerly Types 4, 3, 2b HLP)
  
  (TG 2.0–9.9 mmol/L, 180–499 mg/dL)

- **Moderately Elevated**
  
  (>176-880 mg/dL, 27%)

- **Severe**
  
  (>500 mg/dL, ~1.7%)

- **Extreme**
  
  (>880 mg/dL, 0.1%)

---

Causes and Distribution of Hypertriglyceridemia, in the Population.

Uptake of Chylomicron Remnants by the Liver

LDL receptors (LDLR) and/or LDL receptor-related protein (LRP)—mediated remnant endocytic process requires apoE.

Sequestration of the apoB-48 particle remnants on Heparin-Sulfated Proteoglycans (HSPG) followed by receptor-mediated endocytosis.

Lipolysis of TG-rich Lipoproteins: Interactions of Chylomicrons, VLDL, Remnants and Lipoprotein Lipase (LPL): Multiple Proteins are at Play in Regulating Lipolytic Pathways

**Activators of LPL**
(lipolysis)
- Apo C-II
- Apo A-V

**Inhibitors of LPL**
(lipolysis)
- Apo C-III
- ANGPTL 3
- ANGPTL 4

**Apo E**
(required for hepatic clearance)

**ANGPTL** = angiopoietin-like proteins
LMF1 = Lipase maturation factor-1
GPIHBP = glycosyl-Phosphatidyl-Inositol-anchored HDL binding protein

Adapted from Ballantyne CM. *Clinical Lipidology*. Saunders 2009, Chapter 2.
Primary Causes of Hypertriglyceridemia

A. Extreme HTG (TG >880 mg/dL, >10mmol/L)

1. Monogenic Chylomicronemia

   (formerly HLP Type1 or Familial Chylomicronaemia Syndrome, FCS)

   a) Lipoprotein lipase deficiency (Bi-allelic LPL gene mutations)

   b) Apo C-II deficiency (Bi-allelic APOC2 gene mutations)

   c) Apo A-V deficiency (Bi-allelic APOA5 gene mutations)

   d) Lipase maturation factor 1 deficiency (Bi-allelic LMF1 gene mutations)

   e) GPIHBP1 deficiency (Bi-allelic GPIHBP1 gene mutations)

GPIHBP = glycosyl-Phosphatidyl-Inositol-anchored HDL binding protein.


Primary Causes of Hypertriglyceridaemia

A. Extreme Hypertriglyceridaemia (TG >10mmol/L, >880 mg/dL)

2. Multifactorial or polygenic chylomicronemia, MCS,
   (formerly HLP Type 5 or mixed hyperlipidemia)
   a) Complex genetic susceptibility, including
   b) Heterozygous rare large-effect gene variants for monogenic chylomicronaemia (see above); and/or
   c) Accumulated common small-effect TG-raising polymorphisms (e.g., numerous GWAS loci including APOA1, APOC3, APOA4, APOA5; RIB1, LPL, MLXIPL, GCKR, FADS1-2-3, NCAN, APOB, PLTP, ANGPTL3)
   a) Other: Transient infantile HTG (glycerol-3-phosphate dehydrogenase 1 deficiency) from bi-allelic GPD1 gene mutations

MCS = Multifactorial Chylomicronemia Syndrome
Extreme Hypertriglyceridemia: Population Distribution/Frequency, Pathophysiology

- **Non-Fasting Triglyceride Level**
  - **Population**
  - **Frequency**
  - **Mild-to-moderately elevated triglycerides**
    - 27%
  - **Extremely elevated triglycerides**
    - 0.1%
    - 0.0001%

- **Acute Pancreatitis risk**
  - (chylomicron particle dependent)

- **Equivalent Conversion**
  - 10 mmol/L = 880 mg/dL
  - 11 mmol/L = 968 mg/dL
  - 12 mmol/L = 1056 mg/dL
  - 13 mmol/L = 1144 mg/dL
  - 14 mmol/L = 1232 mg/dL
  - 15 mmol/L = 1320 mg/dL

- **Population (2021)**
  - US: 333 million
  - World: 7.9 billion

Adapted from:
Primary Causes of Hypertriglyceridaemia

B. Mild-to-moderate HTG (TG 2.0–9.9mmol/L, 180-499 mg/dL)

1. Multifactorial or polygenic HTG (formerly HLP Type 4 or familial HTG)
   a. Complex genetic susceptibility (see above)

2. Dysbetalipoproteinaemia (formerly HLP Type 3 or dysbetalipoproteinaemia)

3. Complex genetic susceptibility (see above), plus

4. APOE E2/E2 homozygosity or

5. APOE dominant rare variant heterozygosity

6. Combined hyperlipoproteinaemia (formerly HLP Type 2B or familial combined hyperlipidaemia) Complex genetic susceptibility (see above), plus accumulation of common small effect LDL-C-raising polymorphisms

Hypertriglyceridemia: Population Distribution/Frequency, Determinants, and Pathophysiology

Population Frequency

Mild-to-moderately elevated triglycerides

27%

Severely elevated triglycerides

0.1%

Atherosclerotic Disease risk → (cholesterol particle number dependent)

Non-Fasting Triglyceride Level

Population (2021)

US 333 million

World 7.9 billion

Adapted from:
The Secondary “Environmental’ Causes of Hypertriglyceridaemia Contribute to Overproduction &/or Reduced Clearance

- Diet with high positive energy-intake balance and high fat or high glycemic index
- Increased alcohol consumption (HTG risk increases with >2 & >1 drink(s)/day in ♂ & ♀, respectively)
- Obesity
- Metabolic syndrome
- Insulin resistance
- Diabetes mellitus (predominantly Type 2)
- Hypothyroidism
- Renal disease (proteinuria, uraemia, or glomerulonephritis)
- Pregnancy (particularly in the third trimester)
- Paraproteinaemia
- Systemic lupus erythematosus
- Medications, including corticosteroids, oral estrogen, tamoxifen, thiazides, non-cardioselective beta-blockers and bile acid sequestrants, cyclophosphamide, L-asparaginase, protease inhibitors, and second-generation antipsychotic agents (such as clozapine and olanzapine)

Cardiovascular Risk Begins Well Below the Designated “Normal TG<150 mg/dL)”

Atherosclerosis Risk in Communities & Framingham Offspring studies
N=15,792 study participants, aged 40–65 years, free of CVD.
Up to 10 yrs of follow-up
Time to-first CVD event, (3-point composite of ASCVD MI, stroke, or CV death)

Q4: >153.5 to max
Q3: 110.2 to 153.4
Q2: 81.8 to 110.1
Q1: <81.8 (mg/dL)

Unadjusted linear association (Model 1) of baseline triglyceride (TG) levels with the primary composite cardiovascular outcome (CV death, MI and stroke) in Patients with Type 2 Diabetes and CAD and Histogram of TG levels correspond to right Y-axis.

**CV Death, MI, Stroke at 4 Years**

*primary composite outcome time to CV death, MI, or stroke*

*secondary outcome was CV death*


**BARI-2D Trial** 2,307 patients with T2DM and CAD

HR (95% CI): 1.032 (1.001-1.065)

- In the unadjusted model, every 50 mg/dL increase in TG level was associated with
  - a 3.2% (HR 1.032, 95% CI 1.001–1.065) increase in CV death/MI/stroke
  - a 5.8% (HR 1.058, 95% CI 1.014–1.105) increase in CV death.

- In the fully adjusted model, each 50 mg/dL increase in TG was associated with
  - a 3.8% (HR 1.038, 95% CI 1.004–1.072) increase in CV death/MI/stroke
  - a 6.4% (HR 1.064, 95% CI 1.018–1.113) increase in CV death.

Shaded region represents the upper and lower bounds of the 95% confidence intervals.
Triglycerides (TG) and TG-Rich Lipoprotein (TGRL) remnants are in the Causal Pathway for CVD and Treatment May Result in ASCVD Benefit

**Epidemiological Data**
*(Strong, Consistent)*
Elevated TG (>100 mg/dL or >88 mg/dL) correlates with elevated CV risk

- Women’s Health, Bansal 2007
- Asia Pacific Cohort, Patel 2004
- MIRACL, Schwartz 2001
- Austin 1998, meta
- Baltimore COLTS, Miller 1998
- Copenhagen Male, Jeppesen 1998
- Hokanson 1996 meta
- Patsch 1992
- PROCAM Assman 1992, 1996
- Framingham Heart Castelli 1986, 1992
- Nelson 2020
- Aberra 2020
- Toth 2018
- TNT, Vallejo-Vaz 2018
- Nordesgtgaard 2014, 2015
- Schwartz 2015
- Kasai 2013 -meta
- Sarwar 2007, 2010 metas
- Di Angelantonio, ERFC 2009; meta

**Genetic Data**
*(Strong, Consistent)*
TG/TG-rich lipoproteins are in the causal pathway of CVD

- Do 2013
- Willer (GLGC) 2013
- Jørgensen 2013
- Varbo (Circ) 2013
- Varbo (JACC) 2013
- Johanssen 2012
- Schunkert 2011
- Teslovich 2010
- Pollin 2008
- Wittrup 1999

- Ference (JAMA, 2018)
- Van Iperen 2016
- Do 2015
- Crosby 2014
- Jørgensen 2014
- Holmes 2014, (Eur Heart J. 2015
- Thomsen 2014
Genetic Data Supports ‘Triglycerides’ in the Causal Pathway of Atherosclerotic Cardiovascular Disease

### Genetic data supporting causative role of TGs in ASCVD: mutational analyses

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Variable</th>
<th>Effect on TGs</th>
<th>Effect on CV Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollin 2008</td>
<td>809</td>
<td>ApoC-III R19X null mutation</td>
<td>-46% (P = 4 X 10^{-13})</td>
<td>CAC: OR=0.35 (95% CI: 0.21 to 0.60; P=0.002)</td>
</tr>
<tr>
<td>Jorgensen 2014</td>
<td>75,725</td>
<td>ApoC-III null mutations</td>
<td>-44% (P&lt;0.001)</td>
<td>IVD: HR=0.59 (95% CI: 0.41-0.86; P=0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IHD: HR=0.64 (95% CI: 0.41-0.99; P=0.04)</td>
</tr>
<tr>
<td>Crosby 2014</td>
<td>3,734</td>
<td>ApoC-III null mutations</td>
<td>-39% (P=6 x 10^{-9})</td>
<td>CHD: OR=0.60 (95% CI: 0.47-0.75; P=4 x 10^{-6})</td>
</tr>
<tr>
<td>Nataraj 2015</td>
<td>6,699</td>
<td>ApoC-III null mutations</td>
<td>-43.7% (P=1.83 x 10^{-21})</td>
<td>CAC: -27.9 U (95% CI: -51.1 to -4.7; P=0.019)</td>
</tr>
<tr>
<td>Dewey 2016</td>
<td>42,930</td>
<td>ANGPTL4 variants</td>
<td>-13% (P=2 x 10^{-23})</td>
<td>CAD: OR=0.81 (95% CI: 0.70-0.92; P=0.002)</td>
</tr>
<tr>
<td>Stitziel 2016</td>
<td>120,575</td>
<td>ANGPTL4 variants</td>
<td>-0.3 SD per allele</td>
<td>CAD: OR=0.86 (P=4.0 x 10^{-8})</td>
</tr>
<tr>
<td>Do 2015</td>
<td>13,432</td>
<td>ApoA-V mutations</td>
<td>+61% (P=0.007)</td>
<td>MI/CAD: OR=2.2 (P=5 x 10^{-7})</td>
</tr>
<tr>
<td>Sarwar 2010</td>
<td>302,430</td>
<td>ApoA-V variant</td>
<td>+16% (P=4.4 x 10^{-24})</td>
<td>CHD: HR=1.10 (95% CI: 1.08-1.12; P=2.6 x 10^{-7})</td>
</tr>
</tbody>
</table>

### Genetic data supporting causative role of TGs in ASCVD: genome-wide association analyses

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Study Type</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teslovich, 2010</td>
<td>96,598</td>
<td>Meta-analysis of 46 lipid GWAS</td>
<td>Identified 95 loci, including regions encoding ANGPTL3 and ANGPTL4; 4 novel CAD-associated loci related to HDL-C or TGs, but not LDL-C</td>
</tr>
<tr>
<td>Schunkert 2016</td>
<td>147,733</td>
<td>Meta-analysis of 14 GWAS of CAD</td>
<td>Identified 13 novel loci associated with 6 to 17% increase in risk of CAD; included regions associated with increased TGs</td>
</tr>
<tr>
<td>Willer 2013</td>
<td>188,578</td>
<td>Linear regression of 149 lipid SNPs</td>
<td>TG effect size correlated with CAD (Pearson r=0.46; P= -0.02)</td>
</tr>
<tr>
<td>Do 2013</td>
<td>188,577</td>
<td>Multivariate analysis of 185 lipid SNPs</td>
<td>TG effect size correlated with CHD after adjusting for LDL-C and HDL-C effect sizes (P=1 x 10^{-9})</td>
</tr>
</tbody>
</table>

## Genetic Data Supports ‘Triglycerides’ in the Causal Pathway of Atherosclerotic Cardiovascular Disease

### Genetic data supporting causative role of TG IN ASCVD: Mendelian randomization studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Variable</th>
<th>Effect on TGs</th>
<th>Effect on Cardiovascular Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorgensen 2013</td>
<td>60,113</td>
<td>10 combinations of 3 APOA5 variants</td>
<td>Stepwise increase up to 56%</td>
<td>MI: causal OR=1.94 (95% CI: 1.40-1.85); observational OR=1.57 (95% CI: 1.32-2.68)*</td>
</tr>
<tr>
<td>Jorgensen 2013</td>
<td>73,513</td>
<td>3 non-fasting cholesterol-increasing alleles</td>
<td>Correlated with remnant cholesterol ($r^2=0.96$)</td>
<td>IHD: causal OR=2.8 (95% CI: 1.9-4.2); observational OR=1.4 (95% CI: 1.3-1.5)†</td>
</tr>
<tr>
<td>Varbo 2013</td>
<td>60,608</td>
<td>6 non-fasting cholesterol-increasing alleles</td>
<td>Not measured</td>
<td>IHD: causal OR=3.3 (95% CI: 2.1-5.2); observational OR=1.3 (95% CI: 1.2-1.4)†</td>
</tr>
<tr>
<td>Thomsen 2014</td>
<td>10,208</td>
<td>4 LPL genetic variants</td>
<td>Stepwise decrease up to 31%</td>
<td>All-cause mortality: HR=0.86 for 6 LPL alleles vs 0-3 LPL alleles (95% CI: 0.83-0.88)</td>
</tr>
<tr>
<td>Holmes 2015</td>
<td>62,199</td>
<td>67 triglyceride-related SNPs</td>
<td>Mean increase of 28.5%</td>
<td>CHDx: OR (unrestricted)=1.62 (95% CI: 1.24-2.11); OR (restricted)=1.61 (95% CI: 1.00-2.59)</td>
</tr>
</tbody>
</table>

Genetic Epidemiology: Evidence that the Cholesterol Content of Triglyceride-Rich Lipoproteins (Remnant-Cholesterol) is Causally Linked to ASCVD

15 selected genetic variants
N=66,000 (12,000 IHD)

Remnant cholesterol ↑
Observational
Genetic: Causal

HDL cholesterol ↓
Observational
Genetic: Causal

LDL cholesterol ↑
Observational
Genetic: Causal

Genome wide 185 SNPs
N=87,000 (22,000 IHD)

Triglycerides ↑
Genetic unadjusted
Genetic LDL+HDL adj.

HDL cholesterol ↓
Genetic unadjusted
Genetic LDL+TG adj.

LDL cholesterol ↑
Genetic unadjusted
Genetic TG+HDL adj.

IHD=ischemic heart disease;
SNP=single nucleotide polymorphism.

HR/OR (95% CI) for IHD per 1 mmol/L ↑ or ↓

Effect size [b(95% CI)] for IHD per 1 SD ↑ or ↓


LDL Fractionation via Gradient Gel Electrophoresis


High Triglycerides Are Associated with LDL Subclass Pattern B, Elevated Apo B, and TG-Rich Remnant Cholesterol (large VLDL, IDL)

Adapted from
Distinct Biological Features of Small Dense LDL

- Prolonged plasma residence time reflecting low LDL receptor binding affinity.
- Increased affinity for LDL receptor-independent cell surface binding sites.
- Small particle size favoring enhanced arterial wall penetration.
- Elevated binding affinity for arterial wall proteoglycans favoring enhanced arterial retention.
- Elevated susceptibility of PL and CE components to oxidative modification, with the formation of lipid hydroperoxides.
- Elevated susceptibility to glycation.
- Enrichment in electronegative LDL.
- Preferential enrichment in lipoprotein-associated phospholipase A2.
- Preferential enrichment in apoC-III.

Boren J. et al. References: 54,55,64,66,69–75,78,79,81–85,105,111–113

LDL = low density lipoprotein; PL = phospholipid; CE = Cholesterol ester; Apo CIII = apolipoprotein CIII

Framingham Offspring Study: Nuclear Magnetic Resonance, NMR, Spectroscopy, LDL Particle Numbers (LDL-P) & LDL Cholesterol (LDL-C): Relationships to Levels of HDL Cholesterol and Triglycerides

Modified from
The movement of lipoprotein particles, from the circulation, into the arterial wall, is gradient driven.

A ‘large concentration’ of atherogenic lipoprotein particles is most predictive of IHD.
Lipoprotein Cholesterol as a Function of Increasing Levels of Non-Fasting Triglycerides: Copenhagen General Population Study (n=36,160)

Liver
Bloodstream
LDL
HDL
Hepatic Lipase

⬆️ Small, dense HDL particles
⬆️ Small, dense LDL particles

Hepatic Lipase
Rapid degradation
& Renal loss

Lipid and Lipoprotein Metabolism Pathways are Enhanced in Progressive Hypertriglyceridemia:

- ↑ Cholesterol-enriched, Triglyceride-depleted, abnormal VLDL-remnants
- ↑ VLDL remnants
- ↑ Large VLDL
- ↑ Apo-B
- ↑ Cholesterol
- ↑ Triglycerides
- ↑ Liver Fat
- ↑ Free fatty acids
- Dietary Free fatty acids
- Non-esterified fatty acids released from adipose tissues
- → CETP

Bloodstream

- CETP = Cholesterol ester transfer protein

Berneis KK, Krauss RM. J Lipid Res. 2002;43:1363–1379
Choi SH, Ginsberg HN. Trends Endocrinol Metab. 2011;22(9):353-363.
Triglyceride-Rich (Remnant) Lipoproteins and ASCVD: New Insights from Epidemiology, Genetics, and Biology

97,962 participants from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) combined. 10,668 individuals were diagnosed with IHD between 1977 and 2011.

7% higher CRP level
For each 39-mg/dL increase in LDL-C

37% higher CRP level
For each 39-mg/dL increase in non-fasting Remnant cholesterol

Triglycerides (TG) and TG-Rich Lipoprotein (TGRL) remnants are in the Causal Pathway for CVD and Treatment May Result in ASCVD Benefit

**‘Residual increased risk’ with high TG in statin-treated high risk**

- PROVE-IT (Miller 2008)
- IDEAL & TNT (Faergeman 2009)

Inconsistent large CVOTs with drugs that lower TG levels; however, trial populations mean TG <2mmol/L (<188 mg/dL)

- Positive: VA-HIT (Rubins 1999); HHS (Manninen 1992)
- Negative: FIELD (Scott 2009); BIP (Haim 2006); ACCORD-Lipid (Ginsberg 2010)

**Eicosapentanoic acid (EPA)**

- JELIS (JELIS [Yokoyama 2008; 1.8 grams EPA open-label -19% RRR any major coronary event, p<0.011])

**Nicotinic acid (TG <180 mg/dL)**

- Negative: AIM-HIGH (Boden 2011)
- Negative: HPS2-THRIVE (Armitage 2013, 2014)

**Omega-3 ethyl esters trials of low (1 gm) dose:** Negative

**Clinical Data**

Reducing TG in ‘high’ TG Subgroups consistently reduces CV risk

- **Eicosapentanoic acid**
  - JELIS (Saito 2008 +; & subgroup+)

- **Nicotinic acid**
  - AIM-HIGH (Guyton 2013; subgroup +)

- **Fibrate trials inconsistent**
  - Jun 2010 small and large trial meta-analysis +
  - ACCORD-Lipid Ginsberg 2010(-); subgroup +
  - FIELD Scott 2009; subgroups +
  - BIP Haim 2006; subgroups +
  - VA-HIT Rubins 1999 & subgroup +
  - HHS Manninen 1992 & subgroup +

- **3 Positive Independent fibrate meta-analyses**

- **Combination Fibrate+Nicotinic acid**

- **Stockholm Ischaemic Heart Dis. Sec. Prev. (Carlson 1988)**

**Recent Trials dedicated only to HTG populations; i.e., where inclusion TG levels >2 mmol/L, >188 mg/dL) in participants**

- **REDUCE-IT** [4 gms omega-3 EE (EPA only, icosapent ethyl) vs. mineral oil]. Completed -25-30% RRR MACE; p=0.0000001

- **STRENGTH** [4 gms omega-3-carboxylic acids (EPA/DHA), vs. PUFA (corn oil)], PEP 1st MACE, completed: Negative or Neutral

- **PROMINENT** (SPPARM, Pemafibrate in T2DM, dedicated HTG (200-499 mg/dL) population, (n=10,000 randomized) completion: 11/2022: “stopped early by the DSMB primary endpoint was unlikely to be met”. Negative or Neutral
Once Significance is Recognized, What Therapeutic Approaches Should Be Taken to Reduce Hypertriglyceridemia and Triglyceride-rich Lipoproteins?

Which is (are) the target(s) of therapy:
- TG molecules per se,
- FFA components of TG (trans, cis, sat’d, unsat’d, PUFA, MUFA, DHA, EPA)
- TG-rich lipoprotein (TRL) particles,
  • TRL remnant, or
  • Cholesterol contained in these particles

Austin MA.


Hazard Ratios for Coronary Heart Disease across Quantiles (= Deciles) of Usual Concentrations of Triglycerides.

302,430 participants, involving 12,785 cases) from 68 studies.
For TG analysis ‘further adjustments’ included: age, BPsys, smoking status, hx DM, BMI, total cholesterol, HDL-C and non-HDL levels.
Referent groups are lowest decile for TG.

Interpretation:
It is NOT the triglycerides per se that causes ASCVD, but the cholesterol in the triglyceride-rich lipoprotein remnant particles.

? Will lowering of triglyceride-rich lipoproteins and remnant cholesterol particles result in a reduction of major adverse cardiovascular events?

Association of Apolipoprotein B-Containing Lipoproteins and Risk of Myocardial Infarction in Individuals With and Without Atherosclerosis

Primary prevention cohort from UK Biobank cohort analyzed baseline lipids, no lipid-lowering Tx (n=389,529 individuals, statin use 0%, 42% ♂, median age 56). Baseline Apo B, 105; LDL, 142; Non-HDL, 168, TG, 127.

Secondary prevention cohort from both FOURIER and IMPROVE-IT trials (n= 40,430, statin use 99.95%, 76% ♂, median age 63). Baseline Apo B, 68; LDL, 61; Non-HDL, 86, TG, 115.

Lipid Parameters and Risk of Myocardial Infarction

After Adjusting for Apolipoprotein B concentration, the amount of lipid (cholesterol or TG) carried on the apoB-containing lipoprotein particles, or the type of apoB-containing lipoprotein particle (either TG-rich lipoprotein or LDL) did not confer additional risk beyond apoB concentration.
## Modifiable Secondary Causes of Dyslipidemia (↑TG & LDL-C)

Evaluate for contributing factors, then modify: Eliminate, Minimize or Optimize Management

### Lifestyles Contributing to ↑TG
- Calorie dense excess, including high saturated fat; trans fats → increase LDL-C
- Increased simple CHO, (sugar, fructose intake
- Lack of aerobic exercise
- Alcohol excess/abuse

### Co-Morbidities Contributing to ↑TG
- Central obesity
- Insulin Resistance
- Pre-Diabetes
- Fatty liver disease
- Diabetes mellitus
- Cushing’s Syndrome
- Pregnancy
- Hypothyroidism
- Chronic Kidney Disease
- Nephropathy, especially Nephrotic syndrome, Stage IV, ESKD
- Chronic Inflammatory Disorders
- HIV

### Medications Contributing to ↑TG
- Oral estrogen, tamoxifen, raloxifene
- Protease inhibitors
- Systemic glucocorticoids
- Immunosuppressive drugs ➢ i.e., cyclosporine, sirolimus
- Retinoic acid drugs
- Beta blockers
- Thiazides
- Atypical antipsychotics
- Bile acid sequestrants
- Cyclophosphamide
- L-asparaginase

### Poor Glycemic Control in Diabetes
Consider pioglitazone for reduction of insulin resistance and fatty liver; beta cell preservation and TG-lowering (i.e., Pre-DM or DM). [AACE]
If ASCVD, SGLT2i (HF) &/or GLP-1 RA. [AACE, ADA, EASD]

---

‘Saturated’ Compared with ‘Unsaturated’ Fats and Different Carbohydrate Sources in Relation to CHD Risk: Fatty Acid Components of Triglycerides or Phospholipids May Play a Part in Their Benefits or Risks.


Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study.


Brigham and Women’s Hospital & Harvard T.H. Chan School of Public Health: 84,628 women (Nurses’ Health Study, 1980 to 2010), and 42,908 men (Health Professionals Follow-up Study, 1986 to 2010); Baseline Exclusion: diabetes, CV disease, & cancer.

-- Diet was assessed by a semiquantitative food frequency questionnaire every 4 years.

-- During 24 to 30 years of follow-up, 7,667 incident cases of CHD were documented.
## Effect of Lipid-Lowering Therapies on Triglyceride Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Triglyceride Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>30-50</td>
</tr>
<tr>
<td>Immediate-release niacin</td>
<td>20-50</td>
</tr>
<tr>
<td>Omega-3 (DHA + EPA), 4 gm</td>
<td>20-50</td>
</tr>
<tr>
<td>Icosapent Ethyl (EPA), 4 gm</td>
<td>ANCHOR 264 mg/dL 33%</td>
</tr>
<tr>
<td></td>
<td>MARINE 680 mg/dL 27%</td>
</tr>
<tr>
<td>Extended-release niacin</td>
<td>10-30</td>
</tr>
<tr>
<td>Statins</td>
<td>10-30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5-10</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Lifestyle Interventions Impacting Lipid Levels</th>
<th>↓ TG-rich Lipoproteins</th>
<th>↑ HDL-C levels</th>
<th>↓ TC and LDL-C levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce excessive body weight</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Reduce alcohol intake</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase habitual physical activity</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Reduce total amount of dietary carbohydrates</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Reduce intake of mono- and disaccharides</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Replace saturated fats with mono- (MUFA) or polyunsaturated (PUFA) fats</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Use supplements of n-3 polyunsaturated (Omega-3 PUFA) fats</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid dietary trans fats</td>
<td></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Modest consumption in those who take alcohol may be continued</td>
<td>-</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Quit smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase dietary fiber</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Use functional foods enriched with phytosterols</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Reduce dietary cholesterol</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

High-risk Patients from the Whole Population VOYAGER \( n = 20,539 \), Individual Patient Data Meta-Analysis

Mean Baseline Lipids (in mg/dL) LDL-C, 168.1 \( (+32.5) \); TG, 161.2 (Median Q1-Q4 range 120.4–215.0); HDL-C 48.7 \( (+12.7) \).

## Change in LDL-C and Triglycerides Levels with Increasing Dose of Each Statin

<table>
<thead>
<tr>
<th>Statin</th>
<th>LDL-C % Lowering</th>
<th>Triglycerides % Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>5</td>
<td>-39</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>-50</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20</td>
<td>-39</td>
</tr>
</tbody>
</table>

For every 3% LDL-C lowering, ~1% TG lowering

Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ.

Meta-analysis of comparative efficacy of increasing dose of Atorvastatin versus Rosuvastatin versus Simvastatin on lowering levels of atherogenic lipids (from VOYAGER).

Triglyceride (TG) and LDL Cholesterol-Lowering Effects of Atorvastatin and Simvastatin in Subjects With Hypertriglyceridemia


TG and LDL are lowered ~1:1, but with TG-lowering, VLDL-C is converted to LDL-C
Non-HDL-C

Apo B

Rosuvastatin Atorvastatin Simvastatin Rosuvastatin Atorvastatin Simvastatin

Dose (mg) 5 10 20 40 10 20 40 80 10 20 40 80

LSM % change (SE)

0 -10 -20 -30 -40 -50 -50 -40 -30 -20 -10 0 0

Generally: Statins lower LDL-C more than Non-HDL, and Non-HDL-C more than apo B;

(i.e., Rosuvastatin 40 mg Lowered LDL-C 55%, non-HDL-C 49.9%, and apo B 42.9%)
Effects of PCSK9 inhibitors on Blood Lipids at Different Levels of Triglycerides

<table>
<thead>
<tr>
<th>mg/dL:</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>&lt;1.70</td>
<td>1.70</td>
<td>2.3-5.63</td>
<td>&gt;5.64</td>
</tr>
<tr>
<td>150-203</td>
<td></td>
<td>2.3-5.63</td>
<td>500</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk Reduction (RRR) in Cardiovascular Events in Four Large ‘Monotherapy Fibrate’ Clinical Trials, and the One Combination ‘Statin+Fenofibrate’) ACCORD study

Primary End-Point for Populations:

In 3 of 5 trials, add-on fibrate did not reduce CV death, non-fatal MI, or stroke.

Hypothesis Generating

Baseline ‘Moderate Dyslipidemia’ [TG>200 mg/dL, HDL-C< 35-40 mg/dL] Predicts 26-35% Significant CVD Risk Reduction from PPAR-alpha Agonists (Fibrates = gemfibrozil, bezafibrate, fenofibrate)

CVD Events, Relative Risk Reduction, %

Low HDL | High TG | High TG, Low HDL | Neither
---|---|---|---
NR | NR | NR | NR
-17-16 | -28-25 | -35 | -6
p<0.001 | p<0.001 | p<0.001 | p=0.13

Sacks et al. Bruckert et al. Lee et al.


Independent Meta-analyses of Subgroups from Five Major Fibrate trials [HHS, BIP, VA-HIT, FIELD, ACCORD-Lipid] +/- moderate dyslipidemia

Hypothesis Generating
PROMINENT (Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN diabetic patiENTs) Trial

- Study Start Date: March 23, 2017; Avg. F-U 4 yrs, Estimated Completion Date: September 2022
- Aimed to recruit 10,000 patients with T2DM and elevated TGs (≥ 200 mg/dL or 2.3 mmol/L, and < 500 mg/dL or 5.7 mmol/L), and low HDL-C (≤ 40 mg/dL or 1.0 mmol/L), with and without established CVD.
- Patients randomized to treatment with Pemafibrate 0.4 mg/day or Placebo, against a background of aggressive, standard-of-care management of cardiovascular risk factors including treatment with high-intensity statins.
- The primary study endpoint is a composite of Non-Fatal MI, Non-Fatal Ischaemic Stroke, Hospitalization for unstable angina requiring unplanned coronary revascularization, or CV death.
- Data Safety Monitoring Board (DSMB) reviewed the results of a planned interim analysis and concluded that it was unlikely that the primary endpoint would be met.
- The Trial was stopped early April 8, 2022. There were no notable safety concerns.


Association Estimated by Meta-regression Between Extent of Triglyceride-lowering and Reduction in Risk of A Major Cardiovascular Event in Large Controlled Trials with Fibrates

- 0.1 mmol/L (8.9 mg/dL) decrease in TG caused a 5% (95% CI 1–10) reduction in coronary events
- a 1 mmol/L (89 mg/dL) reduction in TG reduced coronary events by 54% (5–78%) overall
- a 1 mmol/L (89 mg/dL) reduction in TG reduced by 43% (45 to 78%) in those with high triglycerides

...the totality of the scientific evidence favoring triglyceride reduction is less than the totality of the evidence favoring LDL reduction

Log-Linear Association Between Absolute Differences in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease (CHD)

A 10 mg/dL lower ApoB level is associated with a 23% reduction in CHD ($P = 1.42^{-170}$)

Associations Between the Lipoprotein Lipase (\textit{LPL}) Gene and LDL Receptor Gene (\textit{LDLR}) Genetic Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of CHD per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)–Containing Lipoproteins

A lifetime of 14 mg/dL lower LDL-C = a lifetime of 70 mg/dl lower TG = a lifetime of 10 mg/dL lower Apo B translates to a 23% lifetime lower CHD risk

Coronary Heart Disease Risk based on Genetic Background (up to 52 years), Prospective 12-year Observational, and 5-Year-Interventional CVOTs

Proportional Reduction in Risk of CHD (%)

Mendelian randomization studies median follow-up: 52 years (N = 194,427)
Prospective cohort studies median follow-up: 12 years (N = 403,501)
Randomized controlled trials median follow-up: 5 years (N = 196,552)

Consecutive Post-Myocardial Infarction Patients (Survivors at 4 months post-MI were randomized)

Allocated Combination* Clofibrate + Nicotinic acid, n=279 versus Control (no Rx, n=276)

Baseline TChol 241 mg/dL; TG 210 mg/dL

* Open-label Rx: Clofibrate, 1 gm, BID + Nicotinic acid, 1 gm up to TID

Effects of EPA on the Incidence of Major Coronary Events
Open Label, No Placebo, Blinded Endpoint Analysis
 Entire Cohort (N=18,645)


Effects of EPA on the Incidence of Major Coronary Events
for the high TG/low HDL-C Sub-group (n=957)

Combination THERapy of Eicosapentaenoic Acid (EPA, 1800 mg/day) and Pitavastatin (PTV, 4 mg/day) for CoRONary Plaque Regression Evaluated by Integrated Backscatter Intravascular UltrasonographY, CHERRY, Study

CHD patients (n=193) enrolled who underwent percutaneous coronary intervention (PCI) in six hospitals. A 6-8 month prospective, randomized, non-blinded, parallel, multicenter study, to investigate the effect of adding EPA (1.8 grams/day) to high-dose Pitavastatin (PTV, 4 mg/day) on coronary plaque volume and composition in non-stenting lesions analyzed by IB-IVUS.


Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REduce-IT)

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Key Secondary End Point:
CV Death, MI, Stroke

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite (ITT)</strong></td>
<td></td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68–0.83)</td>
<td>↓ 25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Key Secondary Composite (ITT)</strong></td>
<td></td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65–0.83)</td>
<td>↓ 26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular Death or Nonfatal Myocardial Infarction</strong></td>
<td></td>
<td>392/4089 (9.6%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66–0.86)</td>
<td>↓ 25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Fatal or Nonfatal Myocardial Infarction</strong></td>
<td></td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58–0.81)</td>
<td>↓ 31%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Urgent or Emergent Revascularization</strong></td>
<td></td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55–0.78)</td>
<td>↓ 35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular Death</strong></td>
<td></td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66–0.98)</td>
<td>↓ 20%</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Hospitalization for Unstable Angina</strong></td>
<td></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87)</td>
<td>↓ 32%</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Fatal or Nonfatal Stroke</strong></td>
<td></td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55–0.93)</td>
<td>↓ 28%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</strong></td>
<td></td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69–0.86)</td>
<td>↓ 23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total Mortality</strong></td>
<td></td>
<td>274/4089 (6.7%)</td>
<td>310/4090 (7.6%)</td>
<td>0.87 (0.74–1.02)</td>
<td>↓ 13%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

RRR denotes relative risk reduction.
Hazard Ratio Relative to EPA = 26µg/mL of Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality, MI, Stroke, Coronary Revascularization and Unstable Angina and by On-Treatment Serum EPA

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and sex¹, baseline diabetes², hsCRP³, statin compliance⁴, age⁵.

*P value is <0.001 for both non-linear trend and for regression slope.

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Icosapent Ethyl*, IPE (Highly Purified, Non-Oxidized, Eicosapentaenoic acid (EPA)), 4 grams: Proposed Multifactorial Mechanisms of Actions

* Relative to mixtures of: omega-3 EE (DHA + EPA) or DHA alone

<table>
<thead>
<tr>
<th>↑ Antioxidant effects</th>
<th>↓ IL-6</th>
<th>↑ Fibrous cap thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Cholesterol crystalline domains</td>
<td>↓ ICAM-1</td>
<td>↓ Plaque volume</td>
</tr>
<tr>
<td>↓ Ox-LDL</td>
<td>↓ IL-10</td>
<td>↓ Arterial stiffness</td>
</tr>
<tr>
<td>↓ RLP-C</td>
<td>↓ hsCRP</td>
<td>↑ Lumen diameter</td>
</tr>
<tr>
<td>↑ Improved endothelial function</td>
<td>↓ Lp-PLA₂</td>
<td>↑ Plaque stability</td>
</tr>
<tr>
<td>↓ Adhesion of monocytes</td>
<td>↑ EPA/AA ratio</td>
<td>↑ Plaque vulnerability</td>
</tr>
<tr>
<td>↓ Macrophages</td>
<td>↓ Inflammation</td>
<td>↓ Thrombosis</td>
</tr>
<tr>
<td>↓ Foam cells</td>
<td>↓ MMPs</td>
<td>↓ Platelet response</td>
</tr>
</tbody>
</table>

No significant relationship to triglyceride (TG) levels per se, but observed benefits may be due to the enrichment of non-oxidized eicosapentaenoic acid (EPA) that alters the fatty acid composition of TGs and/or phospholipids.

Icosapent Ethyl, IPE, Recommendations from Professional Society Guidelines

<table>
<thead>
<tr>
<th>Professional Society</th>
<th>Minimal Patient Pop. Recommendations (TG 135-499 mg/dL + maximally tolerated statin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACE/ACE, 2020</td>
<td>High-risk ASCVD</td>
</tr>
<tr>
<td>ADA, 2019</td>
<td>Diabetes mellitus with ASCVD or other risk factors</td>
</tr>
<tr>
<td>ACC, 2021</td>
<td>High-risk, TG ≥150 mg/dL</td>
</tr>
<tr>
<td>AHA, 2020</td>
<td>Clinical ASCVD after addressing lifestyle, medication adherence, and secondary causes</td>
</tr>
<tr>
<td>AHA/ASA 2021</td>
<td>Prior Ischemic Stroke or TIA; no hx pancreatitis, a fib, or HF</td>
</tr>
<tr>
<td>Endo Soc 2020</td>
<td>First-line therapy Rx with ASCVD, or DM + additional risk factors</td>
</tr>
<tr>
<td>ESC/EAS 2019</td>
<td>High- and very high-risk on statin therapy</td>
</tr>
<tr>
<td>NLA 2019</td>
<td>45 years old with clinical ASCVD or 50 years old with DM requiring medication + 1 or more additional risk factors</td>
</tr>
</tbody>
</table>


Icosapent Ethyl is a Pillar of Therapy for High-risk patients


ApoC-III Inhibits the Clearance of Triglyceride-rich Lipoproteins through LDL Family Receptors:
--- **LPL-Dependent** Pathways and
--- **LPL-Independent** (HL, LRP1, SDC1)* Pathways of Lipoprotein clearance

ApoC-III=apolipoprotein C-III;
CR=chylomicron remnant;
* HL=hepatic lipase;
IDL=intermediate-density lipoprotein;
LDL=low-density lipoprotein;
LDLR=LDL receptor;
LPL = lipoprotein lipase;
* LRP1 = LDL Receptor-Related Protein 1;
* SDC1 = Syndecan 1;
VLDL=very low-density lipoprotein.

Effect of Olezarsen (AKCEA-APOCIII-LRx) on Secondary Endpoints of Lipoprotein Cholesterol and Apolipoprotein CIII and B Levels

N=114 patients with fasting serum triglycerides 200-500 mg/dL (2.26-5.65 mmol/L), with established ASCVD (79.8%) or high ASCVD risk (20.2%), utilizing statin (96%), ezetimibe (14%), PCSK9i (7.9%), fibrates &/or omega-r fatty acids (39.5%)

<table>
<thead>
<tr>
<th>Baseline (mg/dL)</th>
<th>Apo C-III</th>
<th>TC</th>
<th>VLDL-C</th>
<th>non-HDL-C</th>
<th>Apo B</th>
<th>LDL-C</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.2</td>
<td>54.9</td>
<td>129.9</td>
<td>83.9</td>
<td>34.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Least squares mean percent changes from baseline

Apo B change

15 mg q 2 weeks: -14.3 mg/dL -17%
50 mg q 4 weeks: -10.1 mg/dL -12%
Effect of Olezarsen (AKCEA-APOCIII-LRx) on Primary Endpoint of Triglyceride-Lowering

Oleazersen (AKCEA-APOCIII-LRx) Percent of patients achieving fasting triglyceride levels <150 mg/dL (<1.7 mmol/L) and <100 mg/dL (<1.13 mmol/L)

The $P$-values of each oleazersen treatment group vs. the pooled placebo group were estimated using a logistic regression model with the treatment group as the fixed factor and log-transformed baseline value as the covariate.

FOURIER: Prespecified Analysis and a Post-Hoc Analysis of the Relationship Between the Achieved LDL-C Level at 4 weeks and the Risk of the Secondary Efficacy Composite* Endpoints

Lower Achieved LDL-C (mg/dL) & Greater Reduction of CV Outcomes among Highest Risk

**Subgroup Analyses:**
- Prespecified
- Post-hoc

**Meta-analysis RCT, Statin Trials**
- 8 STATIN RCTS
- CTT Collaboration (26 trials, 2010) [RR 0.78 (-22%) per 1 mmol/L (38.6 mg/dL) (RR 0.63 (-37%) per <1.8 mmol/L, <70]
- Septiles S1, <50
- Quartiles Q1, <62 (mean 49)

**Imaging:**
- POSCH (108)
- FATS (21), Post-CABG (114)
- Coronary IVUS trial
- Percent Arterial Volume (PAV) by Linear Regression Analysis (LRA)

**Targeted LDL-C Goal/Guideline**
- ATP I, <130
- ATP II, ATP III
- ATP III Update, <70
- AACE, <55
- ESC/EAS, <40
- LAI, <50
- LAI, <30

**Targeted LDL-C Goal/Guideline**
- ATP II, ATP III
- ATP III Update, <70
- AACE, <55
- ESC/EAS, <40
- LAI, <50
- LAI, <30

**RCTs**
- 4S (122)
- CARE (101)
- LIPID (113)
- PROVE-IT (62)
- IMPROVE-IT (53.2)
- FOURIER [30 (26)]
- O Dyss De Cal Outcomes (53.5)
- PROVE-IT (40)
- TNT (54)
- JUPITER (44)
- Palo Alto Healthcare (40)
- FOURIER (<30)
- FOURIER (<20)
- FOURIER (<10)
- ODYSSEY Outcomes Post-Hoc (<15)

**Imaging:**
- Angiographic studies

**Coronary IVUS**
- Percent Arterial Volume (PAV)

**Related Publications**
Management of Elevated Triglyceride-rich Lipoproteins

**Management Secondary Causes**
(eliminate, minimize or optimize)

- Poor Lifestyle
- Contributing Medications
- Co-Morbidities
- Uncontrolled Glycemia

### TG <135 mg/dL

**Cholesterol-Lowering Rxs**
- Statin
  - If LDL-C not at goal, add
    - Ezetimibe
  - If LDL-C not at goal, add
    - Bempedoic acid
  - If LDL-C not at goal, add
    - PCSK9i
- If non-HDL-C not at goal, add
  - BAS, only if on statin

See Risk-Dependent Targeted-Apo B, Non-HDL-C, LDL-C Goals; TG Goal <135 mg/dL (optimum <100 mg/dL)

### TG 135-500 mg/dL

**Cholesterol-Lowering Rxs**
- If LDL-C not at goal, add
  - Fibrate (Fenofibrate)
  - Cholesterol-Lowering Rxs
  - Prescription Omega-3 FA (Rx-Om-3)
    - 1st Choice: Pure EPA (IPE) 2 g BID
      [Rx-grade DHA-EPA mixture, only if IPE is inaccessible]

*Dietary Omega-3 Supplements are NOT a substitute; NOT to be used*

### TG >500; TG>880 mg/dL

**Triglyceride-lowering Rxs**
- Fibrates (Fenofibrate)
- Rx-Grade Omega-3 (4 grams)
  - EPA (IPE) 1st choice; DHA-EPA,)
- If TG/Non-HDL-C not at goal, add
  - Niacin (high dose)

**Cholesterol-Lowering Rxs**
- If TG/Non-HDL-C not at goal, add
  - LG-Grade Omega-3 FA (Rx-Om-3)

### TG >880 mg/dL

**Triglyceride-lowering Rxs**
- Fibrates (Fenofibrate)
- Rx-Grade Omega-3 (4 grams)
  - EPA (IPE) 1st choice; DHA-EPA,)
- If TG/Non-HDL-C not at goal, add
  - Niacin (high dose)

**GOALS:** Reduce ASCVD and Pancreatitis Risk

- To Reduce Risk of Pancreatitis
  - Minimum Targeted TG Goal <500 mg/dL
    [Even Lower TG (<200 mg/dL) is Better]

### TG >150 mg/dL with Persistent ↑↑ non-HDL-C or ↑↑ LDL-C

- Additional (LDL)-cholesterol-lowering
- See Risk-Dependent Targeted-Apo B, Non-HDL-C, LDL-C Goals; TG Goal <135 mg/dL (optimum <100 mg/dL)

### TG >500 mg/dL

**Additional LDL-cholesterol-lowering**
- If LDL-C not at goal, add
  - Fibrates (Fenofibrate)
  - Cholesterol-Lowering Rxs
- If non-HDL-C not at goal, add
  - Niacin (high dose)

**GOALS:** Reduce ASCVD and Pancreatitis Risk

- To Reduce Risk of Pancreatitis
  - Minimum Targeted TG Goal <500 mg/dL
    [Even Lower TG (<200 mg/dL) is Better]

### TG >880 mg/dL

**Triglyceride-lowering Rxs**
- Fibrates (Fenofibrate)
- Rx-Grade Omega-3 (4 grams)
  - EPA (IPE) 1st choice; DHA-EPA,)
- If TG/Non-HDL-C not at goal, add
  - Niacin (high dose)

**Cholesterol-Lowering Rxs**
- If non-HDL-C not at goal, add
  - BAS, only if on statin
- If LDL-C not at goal, add
  - Ezetimibe

### If Pre-DM or DM

Advise Pioglitazone

### If Refractory to management with Rx-Drug Tx (& secondary causes), i.e., Severe ↑↑↑ TG, >880 mg/dL

- Rare Monogenic (Familial) Chylomicronemia Syndrome (FCS), Lipoprotein Lipase deficiency or Fredrickson Type 1.

### Ultra-restrictive Fat diet (<10-15 grams fat/day)
- Avoid alcohol
- Limit simple sugars
- Volanesorsen\(^6\) / Olezarsen* (Clinical Trials in progress)
- Plasmapheresis

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\(^6\) European Medicines Agency (EMA)-approved only
*Clinical Trials in progress

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Thank you