Title: Current & Future Triglyceride Pharmaceuticals

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Disclosures:

• In the past 12 months, Dr. Harold Bays has served as a consultant and/or speaker to Amarin, Amgen, Astra Zeneca, Bristol Meyers Squibb, Catabasis, Daiichi Sankyo, Eisai, Isis, Merck, Novartis, Omthera, VIVUS, WPU.

• In the past 12 months, Dr. Harold Bays’ research site has received research grants from Alere, Amarin, Amgen, Ardea, Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, California Raisin Board, Catabasis, Cymabay, Eisai, Elcelyx, Eli Lilly, Esperion, Forest, Gilead, Given, GlaxoSmithKline, Hanmi, Hisun, High Point Pharmaceuticals LLC, Hoffman LaRoche, Home Access, Janssen, Merck, Metabolex, Necktar, Novartis, Novo Nordisk, Omthera, Orexigen, Pfizer, Pronova, Regeneron, Sanofi, Takeda, TIMI, Transtech Pharma, Trygg, VIVUS, and Wpu Pharmaceuticals.
A new study questions the relationship between heart disease and saturated fat.

Many of us have long been told that saturated fat, the type found in meat, butter and cheese, causes heart disease. But a large and exhaustive new analysis by a team of international scientists found no evidence that eating saturated fat increased heart attacks and other cardiac events.
Fats = solid triglycerides
Oils = liquid triglycerides
Triglycerides

\[
\begin{align*}
\text{Glycerol} & \quad \text{3 Fatty Acids} & \quad \text{Triglyceride} \\
H_2C-OH & + & HO-C-R & \rightarrow & H_2C-O-C-R & + 3 H_2O \\
HC-OH & \quad & HO-C-R & \quad & HC-O-C-R & \\
H_2C-OH & \quad & HO-C-R & \quad & H_2C-O-C-R & \\
\end{align*}
\]
Types of Fatty Acids

**Saturated Fats:**

- Fully hydrogenated (no double bonds).
- From meat, dairy products, certain plant oils (palm, coconut).
- Usually solid at room temperature.

**Unsaturated fats**

- Not fully hydrogenated (some double bonds).
  - Monounsaturated (one alkene unit) or polyunsaturated (several alkene units).
  - Mostly *cis*-alkenes
- From fish, oily fruits & vegetables, nuts, certain plant oils (soybean, corn, canola, olive, sunflower).
- Often oily rather than solid.
- Tend to oxidize in air and become rancid.
Introduction / Outline

- Omega-3 fatty acids
- DGAT inhibitors
- Apo CIII inhibitors
### Statins Reduce CVD Events in HTG Patients (HTG Subgroup Data)

<table>
<thead>
<tr>
<th>Trial (Subgroup, mg/dL) (Drug)</th>
<th>Risk difference vs placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Main Study</td>
<td>Subgroup</td>
</tr>
<tr>
<td><strong>WOSCOPS (TG ≥148)</strong> (Pravastatin)</td>
<td>−31%</td>
<td>−32%</td>
</tr>
<tr>
<td><strong>CARE (TG ≥144)</strong> (Pravastatin)</td>
<td>−24%</td>
<td>−15%</td>
</tr>
<tr>
<td><strong>PPP Project (TG ≥200)</strong> (Pravastatin)</td>
<td>−23%</td>
<td>−15%</td>
</tr>
<tr>
<td><strong>4S (TG &gt;159, HDL-C &lt;39)</strong> (Simvastatin)</td>
<td>−34%</td>
<td>−52%</td>
</tr>
<tr>
<td><strong>JUPITER (TG ≥150)</strong> (Rosuvastatin)</td>
<td>−44%</td>
<td>−21%</td>
</tr>
<tr>
<td><strong>CTT (TG &gt;177)</strong> (Various)</td>
<td>−21%</td>
<td>−24%</td>
</tr>
</tbody>
</table>

Median follow-up: ≥5 yrs.

## Risk Difference vs Placebo of HTG Subgroups
### Large-scale, Primary and Secondary CVD Prevention Trials

<table>
<thead>
<tr>
<th>Trial (drug)</th>
<th>Primary endpoint: entire cohort (P)</th>
<th>Lipid subgroup criterion</th>
<th>Primary endpoint: subgroup post-hoc (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (gemfibrozil)</td>
<td>−34% (&lt;0.02)</td>
<td>TG &gt;204 mg/dL LDL-C/HDL-C ratio &gt;5.0</td>
<td>−72% (0.005)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>−9% (0.26)</td>
<td>TG ≥200 mg/dL</td>
<td>−39.5% (0.02)</td>
</tr>
<tr>
<td>VA-HIT (gemfibrozil)</td>
<td>−22% (0.006)</td>
<td>TG ≥150 mg/dL</td>
<td>−27% (0.01)</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>−11% (0.16)</td>
<td>TG ≥204 mg/dL HDL-C &lt;40 mg/dL (men) or &lt;50 mg/dL (women)</td>
<td>−27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (fenofibrate)</td>
<td>−8% (0.32)</td>
<td>TG ≥204 mg/dL HDL-C ≤34 mg/dL</td>
<td>Prespecified −31% (&lt;0.05)</td>
</tr>
<tr>
<td>JELIS (EPA)</td>
<td>−19% (0.011)</td>
<td>TG ≥150 mg/dL HDL-C &lt;40 mg/dL</td>
<td>−53% (.043)</td>
</tr>
<tr>
<td>AIM-HIGH (niacin)</td>
<td>+2% (0.79)</td>
<td>TG ≥200 mg/dL HDL-C &lt;32 mg/dL</td>
<td>−36% (0.032)</td>
</tr>
</tbody>
</table>

ACCORD=Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH=Atherothrombosis Intervention in MetS with Low HDL/High TG: Impact on Global Health Outcomes; BIP=Bezafibrate Infarction Prevention; FIELD=Fenofibrate Intervention and Event Lowering in Diabetes; HHS=Helsinki Heart Study; JELIS=Japan EPA Lipid Intervention Study; VA-HIT=Veterans Affairs HDL Intervention Trial.

Omega-3 fatty acids
Fig. 7. Chemical structures of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The omega-3 EPA has five double bonds, while DHA has six double bonds, with the first double bond being three carbons from the methyl ("omega") end.

Fig. 8. Comparison of omega-3 and omega-6 fatty acids. Omega-3 fatty acids have a double bond three carbons from the methyl end, while omega-6 fatty acids have a double bond six carbons from the methyl ("omega") end.
**Table X: Approximate levels of eicosapentaenoic acid and docosahexaenoic acid in dry-heat cooked fish** (2, 109, 142).

<table>
<thead>
<tr>
<th>Fish</th>
<th>EPA plus DHA (mg/100 g eaten)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon Atlantic wild</td>
<td>1,840</td>
</tr>
<tr>
<td>Salmon Atlantic farmed</td>
<td>2,150</td>
</tr>
<tr>
<td>Salmon Chinook</td>
<td>1,740</td>
</tr>
<tr>
<td>Salmon Coho wild</td>
<td>1,060</td>
</tr>
<tr>
<td>Salmon Coho farmed</td>
<td>1,280</td>
</tr>
<tr>
<td>Herring Atlantic</td>
<td>2,000</td>
</tr>
<tr>
<td>Herring Pacific</td>
<td>2,130</td>
</tr>
<tr>
<td>Mackerel Pacific and jack</td>
<td>1,850</td>
</tr>
<tr>
<td>Mackerel Atlantic</td>
<td>1,200</td>
</tr>
<tr>
<td>Mackerel king</td>
<td>400</td>
</tr>
<tr>
<td>Halibut Atlantic and Pacific</td>
<td>470</td>
</tr>
<tr>
<td>Halibut Greenland</td>
<td>1,180</td>
</tr>
<tr>
<td>Tuna bluefin</td>
<td>1,500</td>
</tr>
<tr>
<td>Tuna yellowfin</td>
<td>280</td>
</tr>
<tr>
<td>Tuna skipjack</td>
<td>300</td>
</tr>
<tr>
<td>Bluefish</td>
<td>990</td>
</tr>
<tr>
<td>Pollock Alaskan</td>
<td>120***</td>
</tr>
<tr>
<td>Cod Atlantic</td>
<td>160</td>
</tr>
<tr>
<td>Cod Pacific</td>
<td>280</td>
</tr>
<tr>
<td>Sablefish (black cod)**</td>
<td>1,790</td>
</tr>
<tr>
<td>Bass sea</td>
<td>760</td>
</tr>
<tr>
<td>Bass freshwater</td>
<td>760</td>
</tr>
<tr>
<td>Whitefish</td>
<td>1,610</td>
</tr>
<tr>
<td>Trout rainbow wild</td>
<td>990</td>
</tr>
<tr>
<td>Trout rainbow farmed</td>
<td>1,150</td>
</tr>
</tbody>
</table>

DHA = docosahexaenoic acid (22:6 n-3); EPA = eicosapentaenoic acid (20:5 n-3). *Cooked fish (dry heat) often has less omega-3 fatty acid content than raw fish: 100 g of fish would be approximately 4 ozs, which would be a bit larger than a deck of playing cards or cassette tape. The amount of omega-3 fatty acids varies considerably in the same type of fish, depending on the environment and location. **Sablefish or "black cod" is not part of the codfish family. ***Alaskan Pollock is the fish used in many fast-food restaurants, where it is usually battered and fried.
EPA+DHA and Lipid Levels in Patients with TG >500 mg/dL

<table>
<thead>
<tr>
<th>Baseline (mg/dL)</th>
<th>TG</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
<th>TC</th>
<th>VLDL-C</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>816</td>
<td>22</td>
<td>27</td>
<td>296</td>
<td>175</td>
<td>89</td>
</tr>
</tbody>
</table>

Change in Median Levels

Placebo
- TG: -45.0%
- HDL-C: -13.8%
- Non-HDL-C: -3.6%
- TC: -1.7%
- VLDL-C: -0.9%
- LDL-C: -4.8%

EPA+DHA (4 g/day)
- TG: 6.7%
- HDL-C: 9.1%
- Non-HDL-C: 0.0%
- TC: 45.0%
- VLDL-C: 42.0%
- LDL-C: 45.0%

P values:
- TG: P<0.0001
- HDL-C: P=0.0002
- Non-HDL-C: P=0.0015
- TC: P=0.0059
- VLDL-C: P<0.0001
- LDL-C: P<0.0001

Pooled analysis (N=82).
Statin + (EPA+DHA): COMBOS Primary and Secondary Efficacy Results

Median Change from Baseline (%)

- Non-HDL-C
- TG
- VLDL-C
- LDL-C
- HDL-C
- Apo B

Additional changes to baseline simvastatin therapy

- EPA+DHA 4 g/d + simvastatin 40 mg/d (n=123)
- Placebo + simvastatin 40 mg/d (n=133)

*P<0.0001 between groups. †P=0.0232 between groups. ‡P=0.0522 between groups.

COMBOS=Combination of Prescription Omega-3 with Simvastatin.

MARINE Study: EPA Median Placebo-adjusted Change from Baseline for Efficacy Endpoints

**ITT Population**

- **TG**: Median Placebo-adjusted Change (%)
  - Non-HDL-C: –17.7 *
  - VLDL-C: –28.6 §
  - Lp-PLA₂: –13.6 §
  - Apo B: –8.5 †
  - TC: –16.3 *
  - LDL-C: –2.3 NS
  - HDL-C: –3.6 NS
  - VLDL-TG: –25.8 †

- **EPA**
  - 4 g/day

*P<0.0001. †P<0.01. § P<0.001. NS = P≥0.05.

P-values reflect differences between EPA vs placebo.

ANCHOR Study: EPA-based Changes in Lipid Endpoints

12-week trial in high-risk statin-treated patients (N=702) with residually ↑TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL). ANCHOR=Effect of AMR101 (Ethyl Icosapentenate) on Triglyceride (Tg) Levels in Patients on Statins With High Tg Levels (≥200 and <500 mg/dL). Ballantyne CM et al. Am J Cardiol. 2012;110:984-92.

*P<0.0001. †P<0.01. NS = P≥0.05.
P-values reflect differences between EPA vs placebo.

TG ≥200 and <500 mg/dL

Baseline values (mg/dL)

<table>
<thead>
<tr>
<th>Lipid Endpoint</th>
<th>EPA 4 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-21.5 *</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-13.6 *</td>
</tr>
<tr>
<td>Apo B</td>
<td>-9.3 *</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-6.2 †</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-4.5 ‡</td>
</tr>
</tbody>
</table>
## Selected OM-3 CVD Outcome Studies

<table>
<thead>
<tr>
<th>OM-3 Type/dose</th>
<th>GISSI-P(^1-2)</th>
<th>ORIGIN(^3)</th>
<th>JELIS(^4)</th>
<th>REDUCE-IT(^5) (Ongoing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type/dose</td>
<td>EPA/DHA 1 g/day</td>
<td>EPA/DHA 1 g/day</td>
<td>EPA 1.8 g/day</td>
<td>EPA 4 g/day</td>
</tr>
<tr>
<td>Population</td>
<td>Italian</td>
<td>International</td>
<td>Japanese</td>
<td>International</td>
</tr>
<tr>
<td>N</td>
<td>11,324</td>
<td>12,536</td>
<td>18,645</td>
<td>~8,000</td>
</tr>
<tr>
<td>Gender</td>
<td>85% male</td>
<td>65% male</td>
<td>31% male</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>Risk Profile</td>
<td>Recent MI (≤3 mos; median 16 days)</td>
<td>High CV risk, and IFG, IGT, or T2DM</td>
<td>80% 1(^o) prev; TC ≥6.5 mM; excl MI ≤6 mos prior</td>
<td>TG &gt;150 mg/dL +CHD or ↑CHD risk</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3.5 years</td>
<td>6.2 years (median)</td>
<td>4.6 years (mean)</td>
<td>4–6 years (planned)</td>
</tr>
<tr>
<td>Statin Use</td>
<td>Minimal</td>
<td>53–55%</td>
<td>100% (sim or prav)</td>
<td>All on statins (LDL-C ≤goal)</td>
</tr>
<tr>
<td>Primary End Point</td>
<td>Tot. mort, NF CVD</td>
<td>CV death</td>
<td>MACE</td>
<td>MACE</td>
</tr>
<tr>
<td>Result</td>
<td>RRR 10% (P=0.05) / 15% (P=0.023)</td>
<td>HR=0.98 P=0.72</td>
<td>RRR 19% (no minimum TG level) P=0.011</td>
<td>NA (Power 15% RRR)</td>
</tr>
</tbody>
</table>

**Low-dose OM-3 doesn’t ↓CVD in statin-era. Mid-dose OM-3 does ↓CVD --STRENGTH trial just started w/ EPA/DHA (FFA) in TG 200–500 mg/dL--**

excl=excluded; GISSI= Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; MACE=major adverse cardiac event; mos=months; ORIGIN=Outcome Reduction with an Initial Glargine Intervention; pbo=placebo; prev=prevention; REDUCE-IT=Reduction of Cardiovascular Events with EPA-Intervention Trial; RR=relative risk; RRR=relative risk reduction.

Introduction / Outline

- Omega-3 fatty acids
- DGAT inhibitors
- Apo CIII inhibitors
Reduced VLDL-TG Production

Increased VLDL Conversion

Adipose Tissue

CHYL

VLDL

FA

DGAT

PA(P)

TG

VLDL

VLDL-TG

Production

LPL

Apo B

Beta-oxidation

Acetyl Co-A

Lipogenesis
Introduction / Outline

- Omega-3 fatty acids
- DGAT inhibitors
- Apo CIII inhibitors
VERY LOW-DENSITY LIPOPROTEIN

apo B-100
Unesterified Cholesterol
apo C-III
Triglyceride
apo E
Phospholipid
apo C-II
Cholesterol Ester

DIAMETER: 400 - 700 Å
ApoCIII

• Apolipoprotein C-III (ApoC-III) is a small protein that resides on various lipoproteins
• Inhibits lipoprotein/hepatic lipases
• Impairs hepatic uptake of triglyceride (TG)-rich lipoproteins (such as lipoprotein remnants)
• Generally promotes hypertriglyceridemia.
• May contribute to insulin resistance
• May contribute to atherosclerosis.
FIGURE 44-12 Simplified figure of deoxyribonucleic acid (DNA) sequencing which constitutes a gene. DNA is a nuclear genetic helix molecule that encodes the “blueprint” information for constructing cellular components. A nucleotide is composed of a sugar (pentose), phosphate backbone, and a nitrogen-containing heterocyclic base (purine or pyrimidine). Sequences of nucleotides forming nucleic acids are illustrated by DNA. Genes are strands of DNA that contain coding sequences which determine what and when functional proteins are translated, and thus determine what and when inherited traits are expressed.
FIGURE 44-13 Antisense disruption of protein translation. One strand of the dual-stranded DNA represents the “sense” genetic code sequence, while the other paired strand represents “antisense” genetic coding. During transcription, the antisense DNA strand serves as a template for the formation of single-stranded messenger ribonucleic acids (mRNA), which is termed “sense.” Sense mRNA migrate from the nucleus into the cytosol where ribosomes “translate” the genetic information for protein production. Antisense agents block target sense mRNA, impairing its associated protein translation and production.

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