Lipid Update

Jorge Plutzky, MD
Director, Preventive Cardiology
Cardiovascular Division
Brigham and Women’s Hospital
Harvard Medical School
Boston, Massachusetts
Overview of Cholesterol Transport

Intestine:
- Dietary Chol
- Fecal neutral sterols
- Chylomicrons
- Sterol transporter

Liver:
- Acetyl CoA
- LDL-R
- SR-BI
- VLDL-C
- IDL-C
- LDL-C

Extrahepatic tissues:
- Chol
- Acetyl CoA

Cholesterol transport pathways include dietary cholesterol uptake, bile acid transport, and the synthesis of VLDL-C, IDL-C, and LDL-C by the liver.
Triglycerides: Energy Resource

Glycerol Backbone

Fatty Acid
Fatty Acid
Fatty Acid

TRI - glyceride

VLDL: Liver
Chylo’s: Gut

LIPASE
(Lipoprotein Lipase)

Fat
Energy
Fatty Acid
CHO/LDL/Triglycerides

VLDL = 20% of all triglycerides

LDL = TC - HDL - VLDL

LDL = TC - HDL - TG/5

Friedewald Equation

Valid through TG ~ < 400 mg/dL
Function and Life Cycle of the LDL Receptor

LDL Binding
LDL-R Defects: Variable function

Transport ER

Recycling

Clustering

Synthesis

Endoplasmic reticulum

LDL Receptor Defects: Span biologic function

Variable rx response
Familial Hypercholesterolemia: A Common Inherited Disorder

FH prevalence is 2x the next most common?

Increased prevalence New England: French Canadians

Familial combined hyperlipidemia has a frequency of 1:200 births; genetic cause is unknown. Sickle cell disease varies greatly by ethnicity. PCKD = polycystic kidney disease.

Tendonous Xanthomas

Extensor Tendons

Achilles Tendon
Dutch Criteria for Familial Hypercholesterolemia (FH)

Diagnoses familial hypercholesterolemia (FH) based on clinical, genetic and family history.

**Entry Criterion**
If yes, 9+ additional criteria required for Definite FH

Patient has elevated cholesterol, family history of FH, and/or family history of premature cardiac death

- Yes

**Family History**
- First-degree relative with premature coronary artery disease and/or vascular disease
  - Male relative <55 years, female relative <60 years
- First-degree relative with known LDL >95th percentile for age and sex
- First-degree relative with tendon xanthomata and/or arcus cornealis
- Children <18 years with known LDL >95th percentile for age and sex

**Clinical History**
- Patient with premature coronary artery disease

**Scoring**
- Unlikely FH diagnosis
- Possible FH diagnosis
- Probable FH diagnosis
- Definite FH diagnosis

https://www.mdcalc.com/dutch-criteria-familial-hypercholesterolemia-fh

Simon Broome

Clinical Dx

FH Dx

Dutch Lipid Clinic Criteria
2013 AHA/ACC Cholesterol Guidelines

Four main statin benefit groups

- LDL $> 190$
  - High-intensity statin

- Increased likelihood genetic hypercholesterolemia: FH

ASCVD
- High-intensity statin
- 10-year risk $> 7.5$
- 10-year risk $< 7.5$

Age 40-75 with diabetes
- Moderate- to high-intensity statin

Age 40-75 without ASCVD or diabetes
- 10-year risk $> 7.5$

JACC 2014;63(25 Pt B):2889-934.
Cholesterol and CHD: Seven Countries Study

4S: Total Mortality/Overall Survival

% ALIVE

Years since randomization

Simvastatin
Placebo

30% risk reduction
P=0.0003

Subjects: 6,605
85% men, 45-73 yr
15% women, 55-73 yr
Baseline lipids:
TC: 221 mg/dL
LDL-C: 150 mg/dL
HDL-C: men, 36 mg/dL
women, 40 mg/dL
Intervention: Lovastatin
20-40 mg/day

C=coronary events defined as fatal/nonfatal myocardial infarction, sudden death, and unstable angina;
MI=fatal/nonfatal myocardial infarction; UA=unstable angina;
RV=revascularizations.

70% of AFCAPS subjects untreated under ATPbII
The Statin Decade – Benefit across full Spectrum of CAD

Primary prevention

Patients at high risk of CHD (high cholesterol or BP)
- WOSCOPS (pravastatin)
- ASCOT (atorvastatin)

Patients at low risk of CHD or low HDL-C
- AFCAPS/TexCAPS (lovastatin)

Secondary prevention

Majority of CHD patients (broad range of cholesterol levels)
- LIPID (pravastatin)
- CARE (pravastatin)

High-risk CHD patients (high cholesterol)
- 4S (simvastatin)

Continuum of risk

Placebo MI rate/100 subjects/5 yrs

<table>
<thead>
<tr>
<th>NNT</th>
<th>12</th>
<th>30</th>
<th>34</th>
<th>46</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.6</td>
<td>15.9</td>
<td>13.2</td>
<td>11.8</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>3.4</td>
<td>4.6</td>
<td>5.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

NNT = Number Needed to Treat; MI = Myocardial Infarction
2013 AHA/ACC Cholesterol Guidelines

Four main statin benefit groups

- **ASCVD**
  - Age ≤ 75 – High-intensity statin†
  - Age > 75 – Moderate-intensity statin

- **LDL > 190**
  - High-intensity statin

- Age 40-75 with diabetes
  - LDL 70-189
  - 10-year risk ≥7.5% - High-intensity statin
  - 10-year risk <7.5% - Moderate-intensity statin

- Age 40-75 without ASCVD or diabetes
  - 10-year risk ≥7.5%
  - Moderate- to high-intensity statin

Don’t treat to LDL target

JACC 2014;63(25 Pt B):2889-934.
Conceptual Changes In Guidelines

- **Don’t treat to specific targets**: Treating to targets results in under- and overtreatment*; use appropriate-intensity treatment
- LDL-C reduction of 50% are “high-intensity” statins, and “moderate-intensity” lower LDL-C by 30%-49%
- First 2 groups: recommend using high-intensity; second 2 groups use moderate-intensity

* Specific LDL targets of 100 and 70 were part of ATP III 2004 update and ACC/AHA guidelines for CHD patients in 2006

Non-statin therapies to achieve an LDL goal not recommended
LDL-C Lowering and Benefit of Statins

- NCEP 2004
- WOSCOPS - PBO
- AFCAPS - PBO
- AFCAPS - Rx
- WOSCOPS - Rx
- 4S - PBO
- LIPID - PBO
- CARE - PBO
- HPS - PBO
- 4S - Rx
- LIPID - Rx
- CARE - Rx
- HPS - Rx
- PROVE-IT - ATV80
- TNT - ATV80
- PROVE-IT - ATV10
- TNT - ATV10
- PROVE-IT - PRA
- AFCAPS - Rx
- ASCOT - Rx
- ASCOT - PBO
- WOSCOPS - PBO
- WOSCOPS - Rx

Is even lower LDL better
In high risk population:
acute coronary syndrome?
PROVE-IT
PROVE-IT: Changes from Post-ACS Baseline LDL-C

Note: Changes in LDL-C may differ from prior trials:
- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline

<table>
<thead>
<tr>
<th>Time</th>
<th>Pravastatin 40mg</th>
<th>Atorvastatin 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rand.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Days</td>
<td>21% ↓</td>
<td>49% ↓</td>
</tr>
<tr>
<td>4 Mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median LDL-C (Q1, Q3)
- Pravastatin 40mg: 95 (79, 113)
- Atorvastatin 80mg: 62 (50, 79}

P<0.001
All-Cause Death or Major CV Events in All Randomized Subjects

- **Pravastatin 40mg** (26.3%)
- **Atorvastatin 80mg** (22.4%)

16% RR
(P = 0.005)

Cannon CP et al. NEJM 2004
Overview of Cholesterol Transport

NPC1L1: Ezetimibe

Non-statin
**Ezetimibe + Statin:**
~10-20% LDL Reduction With All Tested Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Mean % Change in LDL-C From Untreated Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td></td>
</tr>
<tr>
<td>Mono. + Ezetib</td>
<td>(n=220)</td>
</tr>
<tr>
<td></td>
<td>-25%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>(n=205)</td>
</tr>
<tr>
<td>Mono. + Ezetib</td>
<td>-25%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>(n=263)</td>
</tr>
<tr>
<td>Mono. + Ezetib</td>
<td>-39%*</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>(n=248)</td>
</tr>
<tr>
<td>Mono. + Ezetib</td>
<td>-40%*</td>
</tr>
</tbody>
</table>

All data are pooled across doses.

*P < 0.01 for ZETIA + statin vs statin alone.
Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32
## LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
<td></td>
</tr>
</tbody>
</table>

**Median Time avg**

69.5 vs. 53.7 mg/dL
**Primary Endpoint — ITT**

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (• 30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT= 50

No concern on cancer  
‘Guideline’ change?
PCSK9 Loss of Function Mutations: Decreased Plasma LDL-C and CHD

81% of PCSK9^Y142X and PCSK9^C679X subjects had mean plasma LDL-C below 50th percentile

<table>
<thead>
<tr>
<th>Mutant Gene Product</th>
<th>Pattern of Inheritance (chromosome)</th>
<th>Prevalence</th>
<th>Mutation Effect</th>
<th>Aver LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL receptor</td>
<td>Auto Dom (19p13.2)</td>
<td>HTZs: 1/500 HMZs: 1/10^6</td>
<td>Loss of function</td>
<td>HTZs: 350 HMZs: 700</td>
</tr>
<tr>
<td>Apolipoprotein B-100</td>
<td>Auto Dom (2p24)</td>
<td>HTZs: 1/1000* HMZs: 1/10^6*</td>
<td>Loss of function</td>
<td>HTZs: 270 HMZs: 320</td>
</tr>
<tr>
<td>ARH adaptor</td>
<td>Auto Rec (1p36-p35)</td>
<td>Very rare</td>
<td>Loss of function</td>
<td>HMZs: 470</td>
</tr>
<tr>
<td>PCSK9 protease</td>
<td>Auto Rec (1p34.1-p32 )</td>
<td>Very rare</td>
<td>Gain of function</td>
<td>HTZs: 225</td>
</tr>
</tbody>
</table>
Effect of Human PCSK9 mutations on Plasma LDL-C

The Role of PCSK9 in the Regulation of LDL Receptor Expression
27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks
## FOURIER: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>62.5±9.1</td>
<td>62.5±8.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>10,397 (75.4)</td>
<td>10,398 (75.5)</td>
</tr>
<tr>
<td>White race — no. (%)†</td>
<td>11,748 (85.2)</td>
<td>11,710 (85.0)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>85.0±17.3</td>
<td>85.5±17.4</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>2,287 (16.6)</td>
<td>2,284 (16.6)</td>
</tr>
<tr>
<td>Europe</td>
<td>8,666 (62.9)</td>
<td>8,669 (62.9)</td>
</tr>
<tr>
<td>Latin America</td>
<td>913 (6.6)</td>
<td>910 (6.6)</td>
</tr>
<tr>
<td>Asia Pacific and South Africa</td>
<td>1,918 (13.9)</td>
<td>1,917 (13.9)</td>
</tr>
<tr>
<td>Type of atherosclerosis‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction — no. (%)</td>
<td>11,145 (80.9)</td>
<td>11,206 (81.3)</td>
</tr>
<tr>
<td>Median time from most recent previous myocardial infarction (IQR) — yr</td>
<td>3.4 (1.0–7.4)</td>
<td>3.3 (0.9–7.7)</td>
</tr>
<tr>
<td>Nonhemorrhagic stroke</td>
<td>2686 (19.5)</td>
<td>2651 (19.2)</td>
</tr>
<tr>
<td>Median time from most recent previous stroke (IQR) — yr</td>
<td>3.2 (1.1–7.1)</td>
<td>3.3 (1.1–7.3)</td>
</tr>
<tr>
<td>Peripheral artery disease — no. (%)</td>
<td>1,858 (13.5)</td>
<td>1,784 (12.9)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension — no./total no. (%)</td>
<td>11,045/13,784 (80.1)</td>
<td>11,039/13,779 (80.1)</td>
</tr>
<tr>
<td>Diabetes mellitus — no. (%)</td>
<td>5,054 (36.7)</td>
<td>5,027 (36.5)</td>
</tr>
<tr>
<td>Current cigarette use — no./total no. (%)</td>
<td>3854/13,783 (28.0)</td>
<td>3923/13,779 (28.5)</td>
</tr>
</tbody>
</table>
FOURIER: Evolocumab effects on LDL-C Over Time.

No. at Risk
Placebo 13,779 13,251 13,151 12,954 12,596 12,311 10,812 6926 3352 790
Evolocumab 13,784 13,288 13,144 12,964 12,645 12,359 10,902 6958 3323 768

Absolute difference (mg/dl) 54 58 57 56 55 54 52 53 50
Percentage difference 57 61 61 59 58 57 55 56 54
P value <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001

FOURIER:
Evolocumab decreases recurrent CV events in patients with known CAD
FOURIER: Primary Endpoint

- Hazard ratio, 0.85 (95% CI, 0.79–0.92)
- P<0.001

Cumulative Incidence (%)

No. at Risk
- Placebo: 13,780, 13,278, 12,825, 11,871, 7610, 3690, 686
- Evolocumab: 13,784, 13,351, 12,939, 12,070, 7771, 3746, 689

Months

- Placebo: 6.0, 5.3, 9.1
- Evolocumab: 10.7, 14.6

- Evolocumab is significantly lower than Placebo.
FOURIER: Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evolocumab (N = 13,769)</th>
<th>Placebo (N = 13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events — no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10,664 (77.4)</td>
<td>10,644 (77.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>3410 (24.8)</td>
<td>3404 (24.7)</td>
</tr>
<tr>
<td>Thought to be related to the study agent and leading to discontinuation of study regimen</td>
<td>226 (1.6)</td>
<td>201 (1.5)</td>
</tr>
<tr>
<td>Injection-site reaction*</td>
<td>296 (2.1)</td>
<td>219 (1.6)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>420 (3.1)</td>
<td>393 (2.9)</td>
</tr>
<tr>
<td>Muscle-related event</td>
<td>682 (5.0)</td>
<td>656 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>8 (0.1)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Cataract</td>
<td>228 (1.7)</td>
<td>242 (1.8)</td>
</tr>
<tr>
<td>Adjudicated case of new-onset diabetes†</td>
<td>677 (8.1)</td>
<td>644 (7.7)</td>
</tr>
<tr>
<td>Neurocognitive event</td>
<td>217 (1.6)</td>
<td>202 (1.5)</td>
</tr>
<tr>
<td>Laboratory results — no. of patients/total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase level &gt;3 times the upper limit of the normal range</td>
<td>240/13,543 (1.8)</td>
<td>242/13,523 (1.8)</td>
</tr>
<tr>
<td>Creatine kinase level &gt;5 times the upper limit of the normal range</td>
<td>95/13,543 (0.7)</td>
<td>99/13,523 (0.7)</td>
</tr>
</tbody>
</table>

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.
Patient Disposition

Randomized 18,924 patients

Alirocumab (N=9462)
Placebo (N=9462)

Follow-up*: median 2.8 (Q1–Q3 2.3–3.4) years
8242 (44%) patients with potential follow-up ≥3 years

1955 patients experienced a primary endpoint
726 patients died

- Premature treatment discontinuation
  - Alirocumab: 1343 (14.2%)
  - Placebo: 1496 (15.8%)
- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
  - Alirocumab: 730 (7.7%)
  - Placebo: Not applicable
- Patients lost to follow-up (vital status)
  - Alirocumab: 14
  - Placebo: 9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively
ODYSSEY OUTCOME Trial, Alirocumab (Praluent)

LDL-C: ITT and On-Treatment Analyses

Mean LDL-C (mg/dL)

Placebo
ITT On-treatment*

Alirocumab
ITT†
On-treatment*

Months Since Randomization

0 4 8 12 16 20 24 28 32 36 40 44 48

93.3 96.4 103.1

39.8 48.0 66.4

37.6 42.3 53.3
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at Risk</td>
<td>9462</td>
<td>8962</td>
</tr>
<tr>
<td>0.5 years</td>
<td>8805</td>
<td>8846</td>
</tr>
<tr>
<td>1.0 years</td>
<td>8201</td>
<td>8345</td>
</tr>
<tr>
<td>2.0 years</td>
<td>3471</td>
<td>3574</td>
</tr>
<tr>
<td>3.0 years</td>
<td>629</td>
<td>653</td>
</tr>
</tbody>
</table>

ARR* 1.6%

HR 0.85
(95% CI 0.78, 0.93)
P=0.0003
All-Cause Death

ARR† 0.6%
HR 0.85
(95% CI 0.73, 0.98)
P=0.026*

*Nominal P-value
†Based on cumulative incidence

Number at Risk
Placebo 9462 9219 8888 3898 737
Alirocumab 9462 9217 8919 3946 746
Primary Efficacy in Main Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>Incidence (%)</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>7164</td>
<td>8.3</td>
<td>9.5</td>
<td>0.86 (0.74, 1.01)</td>
</tr>
<tr>
<td>80 - &lt;100</td>
<td>6128</td>
<td>9.2</td>
<td>9.5</td>
<td>0.96 (0.82, 1.14)</td>
</tr>
<tr>
<td>≥100</td>
<td>5629</td>
<td>11.5</td>
<td>14.9</td>
<td>0.76 (0.65, 0.87)</td>
</tr>
</tbody>
</table>

*P-values for interaction
2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

Endorsed by the National Lipid Association
More aggressive LDL lowering:
   LDLs < 70 high risk patients
Use of ezetimibe endorsed
PCSK9 inhibitors endorsed
- Diabetes
- <3 months)ASCVD event
- ASCVD event on a statin
- Poorly controlled other major CVD RF (incl cigs)
- Elevated LP (a)
- CKD
- Symptomatic CHF
- Maintenance hemodialysis
- > 65 yo
- Prior MI or non-hemorrhagic stroke
- Symptomatic PAD, Hx non-MI related cor revascularization
- Residual CAD (> 40% stenosis in > 2 large ca)
- HDL-C men <40 mg/dL, women <50 mg/dL
- hs-CRP >2 mg
- Metabolic syndrome

---

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†

YES

Decision for no additional medication

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
4S: Total Mortality/Overall Survival

Statin intolerance?

More people quit the placebo than quit the statin

30% risk reduction
P=0.0003
GAUSS3 Design: Two Double-Blind Phases

**Phase A**

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Atorvastatin 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Atorvastatin 20 mg</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

511 patients with a history of intolerance to multiple statins due to muscle-related adverse effects

**Phase B**

Participants entered Phase B only if they had muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during statin treatment

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Monthly SC evolocumab 420 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Daily oral ezetimibe 10 mg</td>
</tr>
</tbody>
</table>
### GAUSS3 Phase A

**statin-placebo blinded challenge**

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N = 491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
</tbody>
</table>
Statin Discontinuation without Adverse Reaction

Patients who were treated with a statin over the subsequent 12 mo (n = 30,412)

Patients who were treated with the same statin (n = 8,741)
- Patients who were taking a statin 12 mo after the original discontinuation: 8,554
- Patients who were taking the same statin 12 mo after the original discontinuation: 5,529
- Patients who were taking the original statin at the same or a higher dose: 3,658
- Patients who were not taking a statin 12 mo after the original discontinuation: 187

Patients who were treated with a different statin (n = 21,671)
- Patients who were taking a statin 12 mo after the original discontinuation: 21,253
- Patients who were not taking a statin 12 mo after the original discontinuation: 418

98.0% of patients who restarted statins were on a statin at 12 months

Statin Intolerance

Increased LFTs → Up to 3x ULN
Increased CKs → Up to 10x ULN
Myalgias → With or without CK changes

Clinical trials: ~5 % subjects
Clinical experience: Higher? 15-20%?

Serious adverse event: Rare
Rhabdomyolysis 1.5 cases per 1000,000 exposures
What do we do about the patient with ‘statin intolerance’?

• It may not be the statin.  
  Try education.
• It may be dose related. Start lowest possible.  
  Half lowest dose? QOD? M W F?
• It may be statin specific. Try different one.  
  Rosuva? Pitavastatin?
What about triglycerides?
TG ≥150 mg/dL Predicts Higher CHD\textsuperscript{a} Risk in Statin Takers with LDL-C <70 mg/dL

PROVE IT-TIMI 22 Trial\textsuperscript{b} (N=4162)

\begin{itemize}
  \item \textbf{LDL-C <70 mg/dL}
    \begin{itemize}
      \item TG <150 mg/dL: 11.7%, HR: 0.72, P=0.017
      \item TG ≥150 mg/dL: 16.5%, HR: 0.84, P=0.192
    \end{itemize}
  \end{itemize}

\textsuperscript{a}Death, MI, and recurrent ACS. \textsuperscript{b}ACS patients on atorvastatin 80 mg or pravastatin 40 mg. \textsuperscript{c}Adjusted for age, gender, low HDL-C, smoking, hypertension (HTN), obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment. CHD=coronary heart disease; HR=hazard ratio; PROVE IT-TIMI=Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis In Myocardial Infarction. Miller M et al. J Am Coll Cardiol. 2008;51:724-30.
**Most Hypertriglyceridemia Is Secondary Often Pro-Atherogenic**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinically Aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Genetic susceptibility ~10-15%*</td>
</tr>
<tr>
<td>Positive energy balance</td>
<td>↑Saturated fat, ↑glycemic index content, alcohol</td>
</tr>
<tr>
<td>↑ Carbohydrate intake</td>
<td>↑Simple sugars (fructose, sucrose, etc.)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Especially ↑ visceral (abdominal) obesity</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>More so if poorly controlled</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Only if not adequately controlled therapy</td>
</tr>
<tr>
<td>Other conditions</td>
<td>Nephrotic syndrome, pregnancy, polycystic ovarian syndrome</td>
</tr>
<tr>
<td>Medications</td>
<td>Antiretroviral regimens (for HIV)</td>
</tr>
<tr>
<td></td>
<td>Some phenothiazines and 2nd-generation antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretics, bile acid sequestrants, beta-blockers</td>
</tr>
<tr>
<td></td>
<td>Oral estrogen, tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids and isotretinoin</td>
</tr>
<tr>
<td>Recreational drugs</td>
<td>Marijuana (↑ApoC-III), tobacco</td>
</tr>
</tbody>
</table>

* Depends on classification/cut point, population studied.

HIV=human immunodeficiency virus

Lifestyle and Diet Can Have Big Impacts on Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Diet / Lifestyle Change</th>
<th>Lipid Profile Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (5–10%)</td>
<td>~50% Reduction in TG with Lifestyle Interventions</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
</tr>
<tr>
<td>↑Fruits, vegetables &amp; low-fat dairy; ↓ added sugar</td>
<td></td>
</tr>
<tr>
<td>↓Total carb; ↓Fat (to 33–50% of calories)</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td>Brisk 30-min walk, 3x/wk</td>
<td></td>
</tr>
</tbody>
</table>

Lipid Consequences of Hypertriglycerideridemia

Atherogenic Dyslipidemia
- ↑ TG / VLDL-C
- ↑ SD LDL / ↑ LDL-P
- ↓ HDL-C + Apo A-I

Fatty liver + ↑ VLDL synthesis Promote ↑ TG

Apo=apolipoprotein; CETP=CE transfer protein; FFA=free fatty acid; HDL=high-density lipoprotein; HDL-C=HDL cholesterol; HDL-P=HDL particle; LDL=low-density lipoprotein; LDL-P=LDL particle; SD=small dense; VLDL=very-low-density lipoprotein; VLDL-C=VLDL cholesterol.
VA-HIT:
Fibrate Decreases CVD Events in CHD Patients With Low HDL-C

Subjects: 2,531 men
Age: ≤74 (avg 64) yr
Baseline LDL-C: 111 mg/dL
Baseline HDL-C: 32 mg/dL
Baseline TG: 161 mg/dL
Duration: 7 yr
Intervention: Gemfibrozil 600 mg bid

*P < 0.01; †P = 0.006; ‡P = 0.05
P = placebo group; Rx = treated group.
HB Rubins et al NEJM 1999

25% diabetes
50% insulin resistant
VA-HIT

CVD Risk Reduction in Diabetics Compared With Nondiabetics


Cumulative Event Rate Change, %

- **Combined End Point**: 18% (P = .004) for DM vs 32% (P = .004) for No DM
- **Nonfatal MI**: 22% (P = .17) for DM vs 21% (P = .09) for No DM
- **CHD Death**: 41% (P = .02) for DM
- **Stroke**: 10% (P = .67) for DM

P = .26

FIELD: Design

9795 patients, age 50-75 years, type 2 diabetes diagnosed after age 35 years, no clear indication for cholesterol-lowering therapy at baseline (total cholesterol 116-251 mg/dL, plus either total cholesterol to HDL ratio ≥4.0 or triglyceride >88.6 mg/dL)

Fenofibrate (200 mg daily) n=4895

Placebo N=4900

Endpoints:
- Primary – Composite of CHD death or nonfatal MI at 5 year follow-up
- Secondary – Composite of total CV events, CV mortality, total mortality, stroke, coronary revascularization and all revascularization at 5 year follow-up

The primary composite endpoint of CHD death or nonfatal MI was not significantly lower in the fenofibrate group compared to the placebo group.


**Composite CHD death or nonfatal MI at 5 years (% of treatment arm)**

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>5.2%</td>
<td>5.9%</td>
</tr>
<tr>
<td>P</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>
FIELD: Fenofibrate

Primary and Secondary End Points

Lancet. 2005;366:1849

11% Reduction

24% Reduction

19% Increase

11% Reduction

21% Reduction

*Primary: Nonfatal MI and CHD death

†Secondary: CHD events, stroke, CVD death, revasc

Lancet. 2005;366:1849
Statin Drop In’s in FIELD

No Prior CVD: 78%  
Prior CVD: 22%

Primary Prevention Drop-In Rates
- Placebo: 16%
- Fenofibrate: 7%

Secondary Prevention Drop-In Rates
- Placebo: 23%
- Fenofibrate: 14%

Objective:
To test whether, in the context of good glycemic and LDL-C control, a strategy targeting triglycerides and HDL-C levels provides any additional macrovascular and/or microvascular benefits
## Baseline characteristics: Lipids

<table>
<thead>
<tr>
<th>Baseline lipids</th>
<th>Simvastatin + Fenofibrate (n=2,765)</th>
<th>Simvastatin + Placebo (n=2,753)</th>
<th>Overall (n=5,518)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total cholesterol</td>
<td>175 (4.5)</td>
<td>176 (4.5)</td>
<td>175 (4.5)</td>
</tr>
<tr>
<td>Mean LDL-C</td>
<td>100 (2.6)</td>
<td>101 (2.6)</td>
<td>101 (2.6)</td>
</tr>
<tr>
<td>Mean HDL-C</td>
<td>38 (1.0)</td>
<td>38 (1.0)</td>
<td>38 (1.0)</td>
</tr>
<tr>
<td>Median triglycerides</td>
<td>164 (1.9)</td>
<td>160 (1.8)</td>
<td>162 (1.8)</td>
</tr>
</tbody>
</table>

Data presented as mg/dL (mmol/L)

ACCORD Lipid: Changes in HDL-C and triglycerides during the study

Increase in HDL-C was significantly greater in the combination arm

Reduction in triglycerides was significantly greater in the combination arm

Change in mean HDL-C

Change in mean triglycerides

ACCORD Lipid primary macrovascular outcome
(CV death + nonfatal MI + nonfatal stroke)

No. At Risk

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2765</td>
<td>2753</td>
</tr>
<tr>
<td>1</td>
<td>2644</td>
<td>2634</td>
</tr>
<tr>
<td>2</td>
<td>2565</td>
<td>2528</td>
</tr>
<tr>
<td>3</td>
<td>2485</td>
<td>2442</td>
</tr>
<tr>
<td>4</td>
<td>1981</td>
<td>1979</td>
</tr>
<tr>
<td>5</td>
<td>1160</td>
<td>1161</td>
</tr>
<tr>
<td>6</td>
<td>412</td>
<td>395</td>
</tr>
<tr>
<td>7</td>
<td>249</td>
<td>245</td>
</tr>
<tr>
<td>8</td>
<td>137</td>
<td>131</td>
</tr>
</tbody>
</table>

$ p=0.32 $

## ACCORD Lipid

### 31% reduction in events in patients with atherogenic dyslipidemia

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Simvastatin + Fenofibrate</th>
<th>Simvastatin + Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.5 (2765)</td>
<td>11.3 (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride – HDL-C combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG ≥204 mg/dL + HDL-C ≤34 mg/dL</td>
<td>12.4 (485)</td>
<td>17.3 (456)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>All others</td>
<td>10.1 (2264)</td>
<td>10.1 (2284)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 20 patients with type 2 diabetes and atherogenic dyslipidemia needed to be treated for 5 years to prevent one CV event

**ACCORD Lipid**
Comparison of subgroup results with those from prior landmark trials with fibrates

<table>
<thead>
<tr>
<th>Trial (drug)</th>
<th>Primary endpoint: entire cohort (p value)</th>
<th>Lipid subgroup criterion</th>
<th>Primary endpoint: subgroup (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (gemfibrozil)</td>
<td>-34% (0.02)</td>
<td>TG &gt; 200 mg/dL LDL-C/HDL-C &gt; 5.0</td>
<td>Post-hoc -71% (0.005)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 200 mg/dL</td>
<td>Post-hoc -39.5% (0.02)</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG ≥ 204 mg/dL HDL-C &lt; 42 mg/dL</td>
<td>Post-hoc -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%</td>
</tr>
</tbody>
</table>
JELIS: Larger Decrease in MACE in those with TG >150 mg/dL & HDL-C <40 mg/dL*

HR: 0.47
95% CI: 0.23–0.98
P=0.043

Cumulative incidence of major coronary events (%)

Control group

EPA 1.8 gm/day group

-53%

HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

No. of patients

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>475</td>
<td>444</td>
<td>432</td>
<td>414</td>
<td>400</td>
<td>392</td>
<td></td>
</tr>
<tr>
<td>EPA</td>
<td>482</td>
<td>455</td>
<td>443</td>
<td>427</td>
<td>413</td>
<td>403</td>
<td></td>
</tr>
</tbody>
</table>

# FDA-Approved Prescription Omega-3 FAs

<table>
<thead>
<tr>
<th></th>
<th>EPA+DHA EE&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>EPA only EE&lt;sup&gt;3&lt;/sup&gt;</th>
<th>EPA+DHA FFA&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>Lovaza, Omtryg</td>
<td>Vascepa</td>
<td>Epanova</td>
</tr>
<tr>
<td>Generic available?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EPA/DHA</td>
<td>55/45</td>
<td>100/0</td>
<td>73/27</td>
</tr>
<tr>
<td>Regimen, capsules</td>
<td>2 BID w/ meals or 4 QD w/ meals&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2 BID w/ meals</td>
<td>2 or 4 QD, meal independent</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>taste perversion, eructation, dyspepsia</td>
<td>arthralgia</td>
<td>abdominal pain or discomfort, eructation, diarrhea, nausea</td>
</tr>
</tbody>
</table>

Expensive to manufacture; variable insurance reimbursement; may incur greater out-of-pocket costs.

---

1Lovaza prescribing information, generics available. 2Omtryg prescribing information 3Vascepa prescribing information. 4Epanova prescribing information. EE: Ethyl Ester; FFA: Free Fatty Acid.
What about triglycerides?

64 yo man, T2D, 3V CAD, CABG 2009
Meds: atorva 80, ASA, lisinopril 10, HCTZ 25, metoprolol
Lipid profile:

   LDL 68, HDL 34, TG 380
Think meds: stop HCTZ, substitute as needed

Lifestyle matters:

  Slightly more active. Decrease simple carbs

Consider fibrate (fenofibrate) if significant risk:
- CVD, high TG, low HDL, LDL at goal
- Pancreatitis level TG (> ~500 mg/dL)

Alternatives: fish oil, weight loss
CHO/LDL/Triglycerides

LDL = TC - HDL - VLDL

LDL = TC - HDL - TG/5
Friedewald Equation

Valid through TG ~ < 400 mg/dL

Non-HDL = TC - HDL
Cholesterol, Trig, Non-HDL

Non-HDL Target:
30 points > LDL target
Therapeutic intervention?
Intensify statin
Add 2\textsuperscript{nd} LDL agent
Add fibrate

Non-HDL-C = Total cholesterol – HDL-C
What about HDL?
HDL Cholesterol Levels and CHD Risk
Framingham Study

Kannel WB. *Am J Cardiol* 1983;52:9B–12B
1989;118(5 Pt 1):1012–1021
AIM-HIGH: Niacin  Primary Outcome

1ª Endpoint: CHD Death, nonfatal MI, ischemic stroke, high-risk ACS, hospitalization for coronary or cerebrovascular revascularization

Niacin:
No evidence for benefit.
Poorly tolerated.

Key Points:

LDL lowering with statins: unequivocal data demonstrating safe, effective reduction in CV events.

Clear indications for statin use:
- ASCVD, CV risk > 7.5%/10 yrs, Diabetes, LDL > 190 mg/dL

Target LDLs likely matter, stay tuned for guideline updates.
- Ezetimibe lowers LDL ~20%, well tolerated, has CV benefit data, is underused.
- PCSK9 inhibitors: use as needed (LDL still too high, true statin intolerance).

Caution before declaring patient statin intolerant:
- Use different statin, lowest doses, education. Rhabdo very rare.

Triglycerides matter:
- R/O secondary causes
- Lifestyle important
- Consider fibrates if elevated TG/low HDL, significant CV risk

Best Next Steps:
- Help a patient overcome statin intolerance.
- Get a patient approved for PCSK9 inhibitor use.
- Help a patient with elevated triglycerides lose 5-10 lbs.
Lipoprotein (a)

- First identified 1963
- Lipoprotein macromolecule
- Evolutionarily conserved:
  - Likely conveyed some advantage
  - Arose in two separate gene duplications
- Constituents:
  - an LDL-like molecule, containing apo B
  - apolipoprotein a structure
Lipoprotein (a)

First identified in 1963, lipoprotein (a) is a lipoprotein macromolecule. It contains:
- An LDL-like molecule, containing apo B
- Apolipoprotein a structure

The diagram shows LDL particles with cholesterol, triglycerides, cholesterol esters, phospholipids, and Apolipoprotein (a).
Lipoprotein (a) Genotype, Level and CHD Risk

Clarke R et al, NEJM 361:2518, 2009
Lp (a): Current Therapeutic Options

- **Niacin**
  - Lowers Lpa ~30%
  - No effect on outcomes
  - Poorly tolerated

- **Statins:**
  - No LP (a) effect
  - Lower LDL component
  - Lower apoB component

- **PCSK9 Inhibitors**
  - 30% decrease
  - Not a likely basis for approval

- Increased/earlier platelet rx?
- Stay tuned…

- Limit other risk factors