Lipid Management Update 2017

Primary Care Internal Medicine Course

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### Cholesterol and CHD: Seven Countries Study

#### Table: TC mg/dL (mmol/L)

<table>
<thead>
<tr>
<th>Country</th>
<th>CHD Mortality Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europe</td>
<td>100</td>
</tr>
<tr>
<td>United States</td>
<td>125</td>
</tr>
<tr>
<td>Southern Europe, Inland</td>
<td>150</td>
</tr>
<tr>
<td>Southern Europe, Mediterranean</td>
<td>175</td>
</tr>
<tr>
<td>Siberia</td>
<td>200</td>
</tr>
<tr>
<td>Japan</td>
<td>225</td>
</tr>
<tr>
<td>Japan</td>
<td>250</td>
</tr>
<tr>
<td>Japan</td>
<td>275</td>
</tr>
<tr>
<td>Japan</td>
<td>300</td>
</tr>
<tr>
<td>Japan</td>
<td>325</td>
</tr>
<tr>
<td>Japan</td>
<td>350</td>
</tr>
</tbody>
</table>

#### Graph:

- **CHD mortality rates (%)**
- **TC mg/dL (mmol/L)**

The Cholesterol Century

1908: Ignatovski - Egg yolks/milk - atherosclerosis in rabbits
1910: Cholesterol in human atherosclerotic lesions
1920: Antibiotics: Increased interest in atherosclerosis
1933: “Not an inevitable degenerative disease elderly” - Aschoff
1935: The Cholesterol Hypothesis
1994: The Cholesterol Mechanism: Statin Trials
2017: New Era in Therapeutics
Overview of Cholesterol Transport

- Dietary Chol
- Biliary Chol
- Chylomicron remnants
- Fecal neutral sterols
- Sterol transporter

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

Intestine:
- Chol
- Chylomicrons

Extrahepatic tissues:
- HDL-C
- LDL-C
- Acetyl CoA
- Chol

Sterol transporter
CW: History

- 27 yo on vacation
- Mild chest discomfort while playing football on beach
- Took a break, sitting, sudden onset severe CP
- Local EW: EKG inferior ST elevation/IMI
- Rx: IV thrombolytic, heparin, ASA
- Cath: 85% mid-LAD, 90% RCA with thrombus.
- Rx: PCI of LAD c/b spiral dissection - emergent CABG x 4V: (3 SVGs and LIMA)
- Stable since without sx, on statin
- Wants to get pregnant, what to do about statin therapy
Case CW: Familial Hypercholesterolemia

- Autosomal dominant
- **Defect:** LDL receptor (Apo B/ApoE receptor) mutations
- **Strong association with premature CAD**
- > 200 mutations found
- Overlap with familial defective apo B-100
- Increased in certain populations (founder effect):
  - Lebanon, French Canadians, Lithuanian Jews
- Differences between heterozygous and homozygous FH
Lipid-lowering across a spectrum of risk:

<table>
<thead>
<tr>
<th>RISK</th>
<th>4S</th>
<th>LIPID</th>
<th>CARE</th>
<th>WOS</th>
<th>AFCAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Primary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

CHO

<table>
<thead>
<tr>
<th>LDL</th>
<th>1^o Endpt CAD (Benefit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td>+</td>
</tr>
<tr>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>139</td>
<td>+</td>
</tr>
</tbody>
</table>

WOS

| 192 | + |

AFCAPS

| 150 | + |
4S: Total Mortality/Overall Survival

1994

% ALIVE

30% risk reduction
P=0.0003

AFCAPS: LDL-Lowering in PEOPLE With No HX OF CAD and Average Cholesterol Levels

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.

AFCAPS: LDL-Lowering in PEOPLE With No HX OF CAD and Average Cholesterol Levels

70% of AFCAPS subjects untreated under ATPII
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**

- Continuum of risk
  - Placebo MI rate/100 subjects/5 yrs
    - 12: 22.6
    - 30: 15.9
    - 34: 13.2
    - 46: 11.8
    - 50: 7.9
    - 4: 4.5

- NNT
  - High-risk CHD patients (high cholesterol)
    - 4S (simvastatin)
  - Majority of CHD patients (broad range of cholesterol levels)
    - LIPID (pravastatin)
    - CARE (pravastatin)
  - Patients at high risk of CHD (high cholesterol or BP)
    - HPS (simvastatin)
  - Patients at low risk of CHD or low HDL-C
    - WOSCOPS (pravastatin)
    - ASCOT (atorvastatin)
BB

- 64 yo HTN, T2D, hypercholesterolemia, CAD
- 2015: PCI/stenting of LAD after presenting NSTEMI
- Meds:
  - Metoprolol XL 50, lisinopril 20, ASA, clopidogrel, atorvastatin 80 mg
- No complaints
- LDL 90, HDL 38, TG 180

LDL: Good Enough?
### 2013 AHA/ACC Cholesterol Guidelines

#### Four main statin benefit groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCVD</strong></td>
<td>- Age ≤ 75 – High-intensity statin†</td>
</tr>
<tr>
<td></td>
<td>- Age &gt; 75 – Moderate-intensity statin</td>
</tr>
<tr>
<td><strong>LDL ≥ 190</strong></td>
<td>- High-intensity statin</td>
</tr>
<tr>
<td><strong>Age 40-75 with diabetes</strong></td>
<td>- 10-year risk ≥ 7.5% - High-intensity statin</td>
</tr>
<tr>
<td>LDL 70-189</td>
<td>- 10-year risk &lt; 7.5% - Moderate-intensity statin</td>
</tr>
<tr>
<td><strong>Age 40-75 without ASCVD or diabetes</strong></td>
<td>- Moderate- to high-intensity statin</td>
</tr>
<tr>
<td>10-year risk ≥ 7.5%</td>
<td></td>
</tr>
</tbody>
</table>

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Cholesterol Treatment to Reduce Atherosclerotic Risk
Attempt to Identify 4 Statin Groups

1. Does the patient have a history of heart disease or stroke? Are they using secondary prevention?

2. Is LDL > 190 mg/dL?

3. Does patient have diabetes, 40-75 years old, with LDL of 70-189 mg/dL?

4. Does patient have global 10-year risk score ≥ 7.5% for primary prevention of risk assessment?
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
High-, Moderate-, and Low-Intensity Statin Therapy

High-Intensity Statin Therapy
Lowers LDL-C, on average, by approximately ≥ 50%

- Atorvastatin (40)-80 mg
- Rosuvastatin 20 (40) mg

Moderate-Intensity Statin Therapy
Lowers LDL-C, on average, by approximately 30% to < 50%

- Atorvastatin 10 (20) mg
- Rosuvastatin (5) 10 mg
- Simvastatin 20-40 mg‡
- Pravastatin 40 (80) mg
- Lovastatin 40 mg
- Fluvastatin XL 80 mg
- Fluvastatin 40 mg bid
- Pitavastatin 2-4 mg
Conceptual Changes In Guidelines

- Don’t treat to specific targets* 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
New Cholesterol Guidelines

Scientific Statement

New Approaches to Cholesterol Management
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
LDL-C Lowering and Benefit of Statins

Is even lower LDL better

In high risk population:

acute coronary syndrome?
**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>Pravastatin 40mg</th>
<th>Atorvastatin 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>21% ↓</td>
<td>49% ↓</td>
</tr>
</tbody>
</table>

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

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>-25%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-25%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-36%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-51%</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

Study Design

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

### Table

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

**Median Time avg 69.5 vs. 53.7 mg/dL**

### Diagram

- **Mean LDL-C (mg/dL)**

**Number at risk:**

<table>
<thead>
<tr>
<th></th>
<th>EZ/Simva</th>
<th>Simva</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>1078</td>
<td>1068</td>
</tr>
<tr>
<td>84</td>
<td>3484</td>
<td>3387</td>
</tr>
<tr>
<td>72</td>
<td>4508</td>
<td>4395</td>
</tr>
<tr>
<td>60</td>
<td>5354</td>
<td>5267</td>
</tr>
<tr>
<td>48</td>
<td>6256</td>
<td>6192</td>
</tr>
<tr>
<td>36</td>
<td>6583</td>
<td>6607</td>
</tr>
<tr>
<td>24</td>
<td>6864</td>
<td>6939</td>
</tr>
<tr>
<td>12</td>
<td>7264</td>
<td>7289</td>
</tr>
<tr>
<td>6</td>
<td>7701</td>
<td>7843</td>
</tr>
<tr>
<td>1</td>
<td>8306</td>
<td>8921</td>
</tr>
<tr>
<td>QE</td>
<td>8899</td>
<td>9009</td>
</tr>
</tbody>
</table>

**Time since randomization (months)**
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?

7-year event rates
No evidence for a lower LDL-C limit in CV event reduction


**TNT**
Rate of major CV events

- **Achieved LDL-C (mg/dL)**
  - **<64**
  - **64–<77**
  - **77–<106**
  - **≥106**

- **P for trend across LDL-C <0.0001**

- **% of patients with major CV events**

  - Lower LDL-C Better
  - Higher LDL-C Better

**JUPITER**
Risk of primary endpoint

- **Placebo**
- **Not <50 vs placebo**
- **<50 vs placebo**
- **<50 vs not <50**

- **Risk of primary endpoint**
  - **<50 vs placebo**
  - **<50 vs not <50**

- **Lower LDL-C Better**
- **Higher LDL-C Better**

**PROVE-IT**
Risk of primary endpoint

- **>80–100**
- **>60–80**
- **>40–60**
- **≤40**

- **Risk of primary endpoint**
  - **>80–100**
  - **>60–80**
  - **>40–60**
  - **≤40**

- **Lower LDL-C Better**
- **Higher LDL-C Better**

Evidence exists for lower LDL levels in patients with significant CV risk even on max intensity statin.

OK to use LDL targets. (‘17 Update)

Options:

- Higher dose, more potent statin
- Ezetimibe (‘17 update): +15 - 20% LDL decrease
- Bile Acid Resins: Colesevelam (Welchol)
  - Not if TG > 300 mg/dL
  - Modest glucose-lowering effect
  - No proven CV event reduction
• 58 yo familial hypercholesterolemia,
• Family hx premature CAD
• CABG 54 yo, PCI 56 yo
• Meds:
  – Rosuva 40 mg, ezetimibe 10
• LDL 114 (baseline 220), HDL 44, TG 110
• Options?
Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.
Lifelong Low Cholesterol Via PCSK9 Mutations Are Associated With Protection Against CAD But No Other Abnormalities
Function and Life Cycle of the LDL Receptor
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Effect of Human Mutations in PCSK9 on Plasma LDL-C

Alirocumab Administered 2 weekly (Q2W) SC: Change in Calculated LDL-C from Baseline to Week 12

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

McKenney et al JACC 2012;59:2344-53
OSLER-1 & OSLER-2: LDL-C Levels over Time

FOURIER: Evolocumab effects on LDL-C Over Time.

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Evolocumab</td>
<td></td>
</tr>
<tr>
<td>Absolute difference (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Percentage difference</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
</tr>
</tbody>
</table>

FOURIER:
Evolocumab decreases recurrent CV events in patients with known CAD
FOURIER: Study Design

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

RANDOMIZED DOUBLE BLIND

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Sabatine MS et al. N Engl J Med 2017
## 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: Primary Endpoint

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

Cumulative Incidence (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6.0</td>
<td>9.1</td>
</tr>
<tr>
<td>12</td>
<td>5.3</td>
<td>10.7</td>
</tr>
<tr>
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<td>10.7</td>
<td>14.6</td>
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<tr>
<td>24</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
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</tr>
<tr>
<td>36</td>
<td></td>
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No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13,780</td>
<td>13,784</td>
</tr>
<tr>
<td>6</td>
<td>13,278</td>
<td>13,351</td>
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<tr>
<td>12</td>
<td>12,825</td>
<td>12,939</td>
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<tr>
<td>18</td>
<td>11,871</td>
<td>12,070</td>
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<tr>
<td>24</td>
<td>7610</td>
<td>7771</td>
</tr>
<tr>
<td>30</td>
<td>3690</td>
<td>3746</td>
</tr>
<tr>
<td>36</td>
<td>686</td>
<td>689</td>
</tr>
</tbody>
</table>
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 8,337 in the evolocumab group and 8,339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.
FIGURE 2A Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

Patients with stable clinical ASCVD without comorbidities, on statin for secondary prevention

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

YES

NO

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin. Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

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

YES

NO

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe first

Consider adding or replacing with PCSK9 inhibitor second

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

NO

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

**Patients with clinical ASCVD with comorbidities,* on statin for secondary prevention**

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

  - **NO**
    - 1. Address statin adherence.
    - 2. Intensify lifestyle (may consider phytosterols).
    - 3. Increase to high-intensity statin if not already taking.
    - 4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡
      - Consider referral to lipid specialist if statin intolerant.
    - 5. Control other risk factors.

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

    - **NO**
      - CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
        1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
        2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
        3. Patient preferences (see Table 5)

    - Optional non-statin medications to consider
      - Consider either ezetimibe§ or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed¶

    - **NO**
      - 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.
FIGURE 2B  Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

Patients with clinical ASCVD with comorbidities,*
on statin for secondary prevention

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

NO

YES

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

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

YES

NO

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Optional non-statin medications to consider

Consider either ezetimibe§ or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed¶

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

NO

Decision for no additional medication

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
- 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
PCSK9 Inhibitor Therapy

- LDL particle
- LDL Receptor
- Endocytosis
- Clathrin-coated vesicle
- LDL-R
- PCSK9
- Golgi Apparatus
- PCSK9 Apparatus
- Endoplasmic reticulum
- Nucleus
- SREBP
- Lysosome
- Hepatocyte
Two approved: Praluent, Repatha

Expensive (~$15,000/yr). Payors?

Use:

Hx CVD, High CVD risk
- TRUE statin intolerance
- Unacceptable LDL level
- lipoprotein (a)?
- “co-morbidities”
• 64 yo HTN, T2D, hypercholesterolemia, CAD
• 2015: PCI/stenting of LAD after presenting NSTEMI
• Meds:
  – Metop 50, lisinopril 20, ASA, clopidigrel, atorva 80 mg
• No complaints

• LDL 90, HDL 38, TG 180

• Change in lipid therapy?

Trial rosuvastatin 20 mg
Add ezetimibe 10 mg
Consider PCSK9i
A genetic basis for risk as a function of lifetime exposure?

Increased genetic FH screening at birth?

JACC 2016;67(22):2578-2589.
BB

- 64 yo HTN, T2D, hypercholesterolemia, CAD
- 2015: PCI/stenting of LAD after presenting NSTEMI
- Meds:
  - Metop 50, lisinopril 20, ASA, clopidigrel, atorva 80 mg
- c/o diffuse muscle aches – thinks it’s the statin
- LDL 90, HDL 38, TG 180
- Confirmed when he checked with the internet
- Further supported by his neighbor
  - (whose cousin is radiologist – who is
    VERY smart and familiar with CV issues)
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
4S: Total Mortality/Overall Survival

More people quit the placebo than quit the Statin.

# PROVE-IT: Atorva 80 vs Prava 40 mg in ACS

**Liver and Muscle Effects**

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin 80mg</th>
<th>Pravastatin 40mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 3 UL</td>
<td>3.3%</td>
<td>1.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>CK &gt; 3x ULN</td>
<td>1.5%</td>
<td>1.1%</td>
<td>0.24</td>
</tr>
<tr>
<td>DC for Myalgias</td>
<td>3.3%</td>
<td>2.7%</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Statin Discontinuation after 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

GAUSS3 Design: Two Double-Blind Phases

Phase A
- 511 patients with a history of intolerance to multiple statins due to muscle-related adverse effects
- 10 weeks: Atorvastatin 20 mg
- 10 weeks: Atorvastatin 20 mg

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
- 24 weeks: Monthly SC evolocumab 420 mg
- 24 weeks: Daily oral ezetimibe 10 mg
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>
</tbody>
</table>

| Did not complete Phase A                                         | 20/511 |

A Genome-wide Association Study (GWAS) Identifies Novel Loci Associated with Clinically Defined Statin-Associated Muscle Symptoms in a Double-Blind Cross-Over Re-challenge Trial

Erik Stroes, Ricardo Dent, et al. AHA late breaker 2016
What do we do about the patient with ‘statin intolerance’?

• It may not be the statin.
• It may be dose related.
• It may be statin specific
64 yo HTN, T2D, hypercholesterolemia, CAD

- A new statin
- Lowest conceivable dose
  - (half starting dose, QOD or Mon Wed Fri)
- Pep talk
- Unproven, sometimes effective:
  - CoQ10 supplementation
  - Vitamin D correction
- Persistent sx:
  - Ezetimibe
  - PCSK9i rx
New Questions, New Issues

Is a statin going to give my patient diabetes?
No major RF T2D

Incident CVD

Incident T2D

1 or + RF T2D

Ridker, Lancet 2013
Small risk for increased incidence of T2D all statins.
Increased risk if T2D risk factors?
Any increase in diabetes offset by decreased CV events.
Use appropriately.
What about triglycerides?

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

LDL 68, HDL 34, TG 380
HDL & TG predict CV events, statin treated low LDL: TNT + PROVE-IT


On-Treatment, LDL-C < 70

HDL

5 Yr Risk of Major CV Events (%)

<table>
<thead>
<tr>
<th>Q1 (&lt;38)</th>
<th>Q2 (38&lt;42)</th>
<th>Q3 (42&lt;46)</th>
<th>Q4 (46&lt;50)</th>
<th>Q5 (&gt;50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+64%

TG

30-day risk of death, MI or recurrent ACS (%)

<table>
<thead>
<tr>
<th>≥2.3 mM/L (n=603)</th>
<th>&lt; 2.3 mM/L (n=2796)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.3</td>
<td>13.5</td>
</tr>
</tbody>
</table>

+56%

Secondary Causes of Hypertriglyceridemia

- Nephrotic syndrome (Urine analysis)
- Thyroid abnormalities (TSH)
- Drugs (Thiazides, HRT, beta blockers, HIV rx)
- Diet (Excess carbs)
- Diabetes:
  - Inadequate control
  - Undiagnosed
- Alcohol
- Obesity
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

25% diabetes 50% insulin resistant

%+
-30* -22† -21 -27‡
LDL HDL Nonfatal MI/CHD death CHD death Stroke All-cause mortality

*P<0.01; †P=0.006; ‡P=0.05
P=placebo group; Rx=treated group.
HB Rubins et al NEJM 1999
VA-HIT
CVD Risk Reduction in Diabetics Compared With Nondiabetics

Cumulative Event Rate Change, %

Combined End Point
Nonfatal
MI

Combined

Nonfatal

MI

CHD
Death

Stroke

Non DM

DM

P=0.004
P=0.17
P=0.09

P=0.004
P=0.02
P=0.046

P=0.67

P=0.88

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.

FIELD: Fenofibrate

Primary and Secondary End Points

Lancet. 2005;366:1849

11% Reduction

P = .16

24% Reduction

P = .01

19% Increase

P = .22

11% Reduction

P = .035

21% Reduction

P = .003

CHD Events* Nonfatal MI Total CVD Events† Coronary Revasc

*Primary: Nonfatal MI and CHD death
†Secondary: CHD events, stroke, CVD death, revasc
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.

* 20 mg for primary prevention patients, 40 mg for secondary prevention patients
** 160 mg if baseline GFR ≥50 ml/min/1.73 m²; 54 mg if baseline GFR between 30 and 50 ml/min/1.73 m²


# 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
Fenofibrate 2765 2644 2565 2485 1981160 412 249 137
Placebo 2753 2634 2528 2442 1979161 395 245 131

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><strong>% of event (no. in group)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
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
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 (> 400-500 mg/dL)
Alternatives, add on: fish oil
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: Results niacin

Primary Outcome

Niacin?:

Lipoprotein (a) elevations (emerging risk factor)
(In addition to a statin)

Guidelines only “guide”:
- Value in patient groups for treatment decision
- Lower likely better: LDL targets ok, especially in known CVD
- Ezetimibe is an option.
- Statin Intolerance: Caution....

Triglycerides matter: more evidence needed
- R/O secondary causes
- Eating/activity important
- Fibrates if elevated TG/low HDL, significant CV risk

Eating/Lifestyle matters – more implementation

PCSK9 inhibitors as needed for elev LDL, true statin intolerance

New opportunities for CV risk reduction in T2D:
- SGLT2 inhibitors - empafloglozin
- GLP1 agonists - liraaglutide

After 100+ years of study, progress continues.