Management of Dyslipidemia
2015

Principles of Prevention in Primary Care Practice

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## Statin Era: CV Risk Reduction 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>CHO</td>
<td>High</td>
<td>Mod.</td>
<td>Av.</td>
<td>High</td>
<td>Av.</td>
</tr>
<tr>
<td>LDL</td>
<td>188</td>
<td>150</td>
<td>139</td>
<td>192</td>
<td>150</td>
</tr>
<tr>
<td>1° Endpt CAD (Benefit)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- **Secondary prevention**
- **Primary prevention**
4S: Total Mortality/Overall Survival

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.

70% of AFCAPS subjects untreated under ATPII

MI=fatal/nonfatal myocardial infarction; UA=unstable angina; RV=revascularizations.

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
    - 4S (simvastatin)
      - High-risk CHD patients (high cholesterol)
    - LIPID (pravastatin) CARE (pravastatin)
      - Majority of CHD patients (broad range of cholesterol levels)
    - HPS (simvastatin)
      - Patients at high risk of CHD (high cholesterol or BP)
    - WOSCOPS (pravastatin) ASCOT (atorvastatin)
      - Patients at low risk of CHD or low HDL-C
“Residual risk”: Major CV Events Statin Arm, Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>WOSCOP</th>
<th>AFCAPS/TexCAPS</th>
<th>HPS</th>
<th>ASPEN</th>
<th>CARDS</th>
<th>4S</th>
<th>LIPID</th>
<th>CARE</th>
<th>TNT Total</th>
<th>TNT Met S</th>
<th>TNT Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔLDL-C</td>
<td>-26%</td>
<td>-27%</td>
<td>-29%</td>
<td>-29%</td>
<td>-40%</td>
<td>-36%</td>
<td>-25%</td>
<td>-28%</td>
<td>-21%</td>
<td>-24%</td>
<td>-20%</td>
</tr>
</tbody>
</table>
Is Lower Better (LDL)?

65 yo post-MI
Atorva 80 mg
LDL 105
New Cholesterol Guidelines

New Approaches to Cholesterol Management
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 or 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
Major Recommendations for Statin Therapy for ASCVD Prevention

- For secondary prevention or LDL > 190 mg/dL, give high-intensity statin *unless* age > 75 years old or intolerant; then use moderate-intensity statin
- For diabetes (type 1 or 2, age 40-75) use moderate-intensity statin *unless* 10-year risk > 7.5%; then use high-intensity statin
- For primary prevention age 40-75 years, use moderate- to high-intensity statin if 10-year risk is > 7.5%
Conceptual Changes In Guidelines

• **Don’t treat to specific targets**

  Rationale for not including lower LDL targets?
  Not same drug titrated to different LDL targets.
  No RCT data for non-statin drugs.

• **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*
CHD Events Are Reduced Proportional to LDL-C Lowering w/ Statins

$y = 0.1629x \cdot 4.6776$

$R^2 = 0.9029$

$P < 0.0001$

New Questions, New Issues

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></th>
<th>Pravastatin 40mg</th>
<th>Atorvastatin 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24h</td>
<td>95 (79, 113)</td>
<td>62 (50, 79)</td>
</tr>
<tr>
<td>Rand.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Mos.</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>8 Mos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Mos.</td>
<td></td>
<td></td>
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<tr>
<td>Final</td>
<td></td>
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</tbody>
</table>

Median LDL-C (Q1, Q3)

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
Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D.,
Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S.,
Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D.,
Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D.,
Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D.,
KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D.,
Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H.,
Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D.,
for the IMPROVE-IT Investigators*
### 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>
</tbody>
</table>

**Δ in mg/dL**

- LDL-C: -16.7
- TC: -19.3
- TG: -16.7
- HDL: +0.6
- hsCRP: -0.5

**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

‘Guideline’ change?

7-year event rates
New Questions, New Issues

Other ways to address risk in the post-statin era?

Better risk predictors?
Apolipoprotein B

- THE risk molecule?
- One apo B molecule/particle
- Measure of particle number:
  - Most atherogenic parameter?
- Highly correlated with non-HDL cholesterol
  - 0.95 when TG < 300 mg/dl
  - 0.80 when TG higher
LDL Levels vs Apo B (particle number, non-HDL)

= 99 mg/dL

4 ApoB

12

Smaller, denser LDL

More atherogenic?
Higher Plasma Apo B Lipoprotein Levels Promote Atherosclerosis

Rationale for therapeutic Apo B lowering:
- Broader targeting of risk molecules
- Decreased retention, inflammatory response to retention


Williams KJ et al. A.ATVB. 2005;25:1536-1540
CHD Risk Based on Lipids and Apolipoproteins

(n = 91,307)

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
<th>Apo A1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean usual level, mg/dL</td>
<td>125</td>
<td>85</td>
<td>37</td>
<td>126</td>
</tr>
<tr>
<td>2</td>
<td>145</td>
<td>99</td>
<td>44</td>
<td>139</td>
</tr>
<tr>
<td>3</td>
<td>159</td>
<td>108</td>
<td>49</td>
<td>148</td>
</tr>
<tr>
<td>4</td>
<td>173</td>
<td>118</td>
<td>55</td>
<td>158</td>
</tr>
<tr>
<td>5</td>
<td>198</td>
<td>137</td>
<td>66</td>
<td>178</td>
</tr>
</tbody>
</table>

Non-HDL Target:
30 points above the LDL target

Therapeutic intervention?
Intensify statin
Add 2\textsuperscript{nd} LDL agent
Add fibrate

Non-HDL-C = Total cholesterol \ - \ HDL-C
Elevated non-HDL (30 points above target LDL):

- LDL < 70, non-HDL < 100
- LDL < 100, non-HDL < 130

More potent statin
Second agent on LDL: ezetimibe, BAS, niacin
Treat triglycerides: fibrate, fish oil
Lifestyle
Evidence now exists for lower LDL levels in patients with significant CV risk. OK to use targets.

Estimate risk:
AHA/ACC Risk calculator, Reynolds Risk Score, F-ham

LDL Options:
  Higher dose, more potent statin
  Ezetimibe – additional 15 - 20%
  Bile Acid Resins: Colesevelam
  Not if hyperTG
  Modest glucose-lowering effect
New Questions, New Issues

Statin Intolerance
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? 10%?
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>
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<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>
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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

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

A new (often non-generic) statin at the lowest conceivable dose (half, QOD) + pep talk…
New Questions, New Issues

Is a statin going to give my patient diabetes?
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.
Case

64 yo man, T2D, 3V CAD, CABG 2009
Meds: atorva 80, ASA, lisinopril/HCTZ, metoprolol
Lipid profile:
  LDL 68, HDL 34, TG 380
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? 10%?
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**Liver and Muscle Effects**

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Statin Discontinuation after Adverse Reaction

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

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


5 Yr Risk of Major CV Events (%)

On-Treatment, LDL-C < 70

HDL

TG

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


Secondary Causes of Hypertriglycerideridemia

- 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

*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, %

<table>
<thead>
<tr>
<th></th>
<th>Combined End Point</th>
<th>Nonfatal</th>
<th>MI</th>
<th>CHD Death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DM</td>
<td>18</td>
<td>22</td>
<td>21</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>DM</td>
<td>32</td>
<td>40</td>
<td></td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.004</td>
<td>.17</td>
<td>.09</td>
<td>.88</td>
<td>.67</td>
</tr>
<tr>
<td>P</td>
<td>.26</td>
<td>.02</td>
<td></td>
<td>.046</td>
<td>.</td>
</tr>
</tbody>
</table>
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

- **CHD Events**: Placebo 5.9, Fenofibrate 5.2 (11% Reduction, P = .16)
- **Nonfatal MI**: Placebo 4.2, Fenofibrate 3.2 (24% Reduction, P = .01)
- **CHD Death**: Placebo 1.9, Fenofibrate 2.2 (19% Increase, P = .22)
- **Total CVD Events**: Placebo 13.9, Fenofibrate 12.5 (11% Reduction, P = .035)
- **Coronary Revasc**: Placebo 7.4, Fenofibrate 5.9 (21% Reduction, P = .003)

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

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

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

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

ACCORD - Lipid

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.

Simvastatin 20 - 40 mg* + Fenofibrate 54 - 160 mg**

*According to patients’ LDL-C levels and CVD history

5,518 patients

Simvastatin 20 - 40 mg* + Placebo

Mean 4.7 year follow-up

* 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  19811160  412  249  137
Placebo  2753  2634  2528  2442  19791161  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>% of event (no. in group)</td>
<td></td>
<td></td>
<td></td>
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</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?

Lifestyle!
Consider fibrate if significant risk:
- CVD, high TG, low HDL, LDL at goal
- Pancreatitis level TG
Other rx: 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—Design

• Purpose: “[A] rigorous test of the HDL hypothesis…”

• Subjects: N=3414 men/women (85%/15%) w/ prior CVD event and HDL-C 35 (<42/53) LDL-C 74 (algorithm), TG 163 (100-400) [median (range)]

• Randomized Therapy
  – Extended-release niacin (1500-2000 mg hs) vs
  – “Placebo” (immediate-release niacin 100-150 mg hs)

• Open-label titration/addition (keep LDL-C in 40-80 mg/dL)
  – Simvastatin 5-80 mg/d
  – Ezetimibe 10 mg/d + extended release niacin (1500-2000 mg)
AIM-HIGH—Results

HDL-C at Baseline and Follow-up

![Graph showing HDL-C levels over time for combination therapy and monotherapy. The graph indicates statistically significant differences, with P < 0.001. The combination therapy line shows a steady increase from baseline, with a higher peak in Year 2 compared to monotherapy.](#)
AIM-HIGH—Results

Primary Outcome

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

HR 1.02, 95% CI 0.87, 1.21
Log-rank P value = 0.79

16.4% 16.2%

What is an optimal LDL?
What Is Desirable Cholesterol?

Cholesterol Levels Among Different Human Populations

Population-based approaches?

Over the counter interventions on cholesterol?

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

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
ApoB & LDL-C Response
Mean % Change from Baseline, Day 57

LDL-C

Placebo 50 mg 100 mg 150 mg

Apo B

Placebo 50 mg 100 mg 150 mg

* P < 0.0001 vs. Placebo
† P < 0.01 vs. Placebo

FH nonFH nonFH, no Atorva

Stein et al NEJM 2012; 366:1108-18
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.
Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events:
OSLER-1 & OSLER-2

- Evolocumab in patients with high CVD risk
- 4465 participants from 1 of 12 Phase 2 or 3 studies ("parent trials")
- Randomly assigned, 2:1 ratio to either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard rx or standard rx.
- Primary outcome: incidence of adverse events.
- Secondary end point: % change in the LDL-C.

Sabatine MS et al, NEJM 372:1500, 2015
OSLER-1 & OSLER-2:
LDL-C Levels over Time

Sabatine MS et al, NEJM 372:1500, 2015
OSLER-1 & OSLER-2: Cumulative Incidence of CVD Events

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P=0.003

Sabatine MS et al, NEJM 372:1500, 2015
Normal arterial wall

**Time**

Prevention

**Atherosclerosis**

LDL, Triglycerides, HDL
Lifetime Risk of Developing CHD Is High

Risk for First CHD Event for 40-Year-Old Men And Women

# Atherosclerosis Begins Early in Life: Incidence in Male Trauma Victims

<table>
<thead>
<tr>
<th>Study Group</th>
<th>N</th>
<th>Mean Age (yr)</th>
<th>Atherosclerosis Incidence (%)</th>
<th>Cross-Sectional Area Narrowing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enos et al(^1) (Korean War)</td>
<td>300</td>
<td>22.1</td>
<td>77.3</td>
<td>—</td>
</tr>
<tr>
<td>Virmani et al(^2) (Korean War)</td>
<td>94</td>
<td>20.5</td>
<td>56.0</td>
<td>19.0</td>
</tr>
<tr>
<td>McNamara et al(^3) (Vietnam War)</td>
<td>105</td>
<td>22.1</td>
<td>45.0</td>
<td>—</td>
</tr>
<tr>
<td>Joseph et al(^4) (University of Louisville)</td>
<td>95</td>
<td>25.6</td>
<td>75.8</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Lesions present: 1 of 6 teenagers

30 yo female

Ultrasound probe

Plaque
“Atherosclerosis is a pediatric disease.”

Strong et al
JAMA, 281, 727-35,’ 99
Dyslipidemia Rx

Guidelines only “guide”:
- Value in patient groups for treatment
- Lower likely better; can use LDL cutpoints

Statin Intolerance: Caution....
- vit D? lowest dose

Triglycerides matter – more evidence needed
- secondary causes
- Fibrates if elevated TG/low HDL, significant risk

Eating/Lifestyle matters – more implementation

After 100+ years of study, progress continues.

And “truth” continues to evolve....