Why Focus on Aggressive Treatment of Dyslipidemia

- Dyslipidemia is common
  - 98,800,000 over 18 with Elevated Cholesterol > 200 mg/dL (~45%)
  - 32% have LDL > 130 mg/dl (71 million adults)
  - 42 million (18.9%) adults with HDL <40 mg/dL
  - 10% of adolescents 12 to 19 have cholesterol > 200 mg/dl

- Inadequate control of dyslipidemia is responsible for 4 million yearly deaths worldwide and 350,000 in the US
  - WHO estimates that dyslipidemia accounts for 39% of the worldwide burden of CVD

- There is a known relationship between dyslipidemia and systemic vascular inflammation and atherogenesis

- Treatment strategies for cholesterol have been shown to substantially reduce CV events

Evolution of the Treatment Approach

- Framingham
- MRFIT
- LRC-CPPT
- Coronary Drug Project
- Helsinki Heart
- CLAS (angio)

- Angiographic Trials (FATS, POSCH, SCOR, STARS, Ornish, MARS)
- Meta-Analyses (Holme, Rossouw)

- 4S, WOSCOPS, CARE, LIPID, AFCAPS/TexCAP, VAHIT, others

- HPS PROVE-IT ASCOT-LLA PROSPER ALLHAT-LLT

- TNT IDEAL CARDS A to Z ALLIANCE

- Written by the 27 lipid experts of the Adult Treatment Panel III
- 1600 primary references reviewed for scientific evidence
- Evidence statements graded as to type and strength of evidence
- Recommendations emanated from evidence statements

NCEP-ATP III: Risk Assessment—CHD Risk Categories

10-year CHD risk (%)

- 0-1 RF
- ≥2 RFs (calculate Framingham risk)
- CHD, Diabetes
- Atherosclerotic disease

- For persons without known CHD, other forms of atherosclerotic disease, or diabetes:
  - Count the number of risk factors.
  - Use Framingham scoring for persons with ≥2 risk factors* to determine the absolute 10-year CHD risk.

### Framingham Heart Study Cumulative Point Scale for Estimating 10-Year CHD Risk (Men/Women)

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Total Cholesterol</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 34</td>
<td>-9/-7</td>
<td>-1/-1</td>
</tr>
<tr>
<td>35 – 39</td>
<td>-4/-3</td>
<td>0/0</td>
</tr>
<tr>
<td>40 – 44</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>45 – 49</td>
<td>3/3</td>
<td>3/4</td>
</tr>
<tr>
<td>50 – 54</td>
<td>6/6</td>
<td>1/2</td>
</tr>
<tr>
<td>55 – 59</td>
<td>8/8</td>
<td>0/1</td>
</tr>
<tr>
<td>60 – 64</td>
<td>10/10</td>
<td>1/1</td>
</tr>
<tr>
<td>65 – 69</td>
<td>11/12</td>
<td>1/2</td>
</tr>
<tr>
<td>70 – 74</td>
<td>12/14</td>
<td>2/3</td>
</tr>
<tr>
<td>75 – 79</td>
<td>13/16</td>
<td>3/4</td>
</tr>
<tr>
<td>80 – 84</td>
<td>14/18</td>
<td>4/5</td>
</tr>
<tr>
<td>85 – 89</td>
<td>15/20</td>
<td>5/6</td>
</tr>
<tr>
<td>90 – 94</td>
<td>16/22</td>
<td>6/7</td>
</tr>
<tr>
<td>95 – 99</td>
<td>17/24</td>
<td>7/8</td>
</tr>
<tr>
<td>≥100</td>
<td>18/26</td>
<td>8/9</td>
</tr>
<tr>
<td>≥105</td>
<td>19/28</td>
<td>≥10</td>
</tr>
</tbody>
</table>

**Total Cholesterol**
- **<160**: 0/0
- **160 – 199**: 4/4
- **200 – 239**: 3/3
- **240 – 279**: 2/2
- **≥280**: 1/1

**HDL-C**
- **>60**: -1/-1
- **50 – 59**: 0/0
- **40 – 49**: 1/1
- **<40**: 2/2

**Systolic Blood Pressure**
- **If Untreated**: 0/0
- **If Treated**: 1/1

<table>
<thead>
<tr>
<th>Smoker</th>
<th>Age</th>
<th>Age</th>
<th>Age</th>
<th>Age</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Yes</td>
<td>8/9</td>
<td>5/7</td>
<td>3/4</td>
<td>1/2</td>
<td>1/1</td>
</tr>
</tbody>
</table>

**Total points**: <9 9 10 11 12 13 14 15 16 ≥17
- **10-year CHD risk (%) for men**

**Total points**: <9 9 10 11 12 13 14 15 16 ≥17
- **10-year CHD risk (%) for women**

#### ATP III: LDL-C Goals of Treatment in Different Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>TLC When LDL-C (mg/dL)</th>
<th>Consider Drug Therapy When LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD/CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130 (100–129: drug optional)</td>
</tr>
<tr>
<td>2+ risk factors (10-year risk &lt;20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10%–20%: ≥130 10-year risk &lt;10%: ≥160</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160–189: drug optional)</td>
</tr>
</tbody>
</table>

**TLC** = therapeutic lifestyle changes

---

NCEP-ATP III: Treatment

- **Therapeutic Lifestyle Changes**
  - Improve diet
  - Weight reduction
  - Physical activity

- **Pharmacologic Treatment**
  - HMG-CoA reductase inhibitors (statins)
  - Bile acid sequestrants
  - Cholesterol absorption inhibitor
  - Fibric acid
  - Nicotinic acid
  - Fish Oil

- **Exclude Secondary Causes**
  - HMG-CoA reductase inhibitors (statins)
  - Bile acid sequestrants
  - Cholesterol absorption inhibitor
  - Fibric acid
  - Nicotinic acid
  - Fish Oil

---

**Therapeutic Lifestyle Changes**

- **Diet**
  - Reduce intake of saturated fats and dietary cholesterol
  - Total fat range should be 25%-30% of total calories
  - Saturated fat <7% of calories
  - Reduce intake of trans fatty acids
  - <200 mg/day of cholesterol
  - Carbohydrates: 50 -60% of total calories
  - Increase intake of
    - Plant stanols/sterols: 2 g/d
    - Viscous (soluble) fiber: 10-25 g/d
    - Omega-3 polyunsaturated fatty acids
    - Soy protein--25–40 g/day when replacing animal food products
  - Regular physical activity: > 30 minutes 5 to 7 times/week
  - Weight loss to maintain BMI <25

---

Consideration of Secondary Causes of Hyperlipidemia

• Other Conditions
  – Diabetes
  – Hypothyroidism
  – Obstructive liver disease/biliary cirrhosis
  – Transplantation
  – Renal disorders
    – Nephrotic syndrome
    – Chronic renal failure
    – Hemodialysis patients

• Drugs
  – Estrogen/progestins
  – Protease inhibitors
  – Anabolic steroids
  – Corticosteroids
  – Isotretinoin (Accutane®)
  – Cyclosporine


Drug Therapy for Lipid Abnormalities

<table>
<thead>
<tr>
<th>Drug</th>
<th>LDL ↓</th>
<th>HDL ↑</th>
<th>TRIG ↓</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>18-55%</td>
<td>5-15%</td>
<td>7-30%</td>
<td>Myopathy, ↑ liver enzymes</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>15-30%</td>
<td>3-5%</td>
<td>May ↑</td>
<td>GI distress, constipation, ↓ drug absorption</td>
<td>Very elevated triglycerides</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>5-25%</td>
<td>15-35%</td>
<td>20-50%</td>
<td>Flushing, GI distress, liver toxicity, ↑ glucose and uric acid</td>
<td>Liver disease, severe gout, peptic ulcer disease</td>
</tr>
<tr>
<td>Fibric Acids</td>
<td>5-20%</td>
<td>10-20%</td>
<td>20-50%</td>
<td>GI distress, gallstones, myopathy</td>
<td>Severe kidney or liver disease</td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitor</td>
<td>15-25%</td>
<td>1-3%</td>
<td>5-14%</td>
<td>GI distress, ↑ liver enzymes with statins</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Fish Oil</td>
<td>May ↑</td>
<td>10%</td>
<td>20-50%</td>
<td>GI distress</td>
<td>Fish Allergy</td>
</tr>
</tbody>
</table>
Overview of Statin Trials: Major Coronary Events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Secondary</th>
<th>High Risk</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>LDL</td>
<td>LDL</td>
<td>LDL</td>
</tr>
<tr>
<td>4S</td>
<td>4444</td>
<td>188</td>
<td>20,536</td>
</tr>
<tr>
<td></td>
<td>-36%</td>
<td>-35%</td>
<td>-29%</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>150</td>
<td>6595</td>
</tr>
<tr>
<td></td>
<td>-25%</td>
<td>-26%</td>
<td>-26%</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>139</td>
<td>6605</td>
</tr>
<tr>
<td></td>
<td>-28%</td>
<td>-25%</td>
<td>-27%</td>
</tr>
<tr>
<td>HPS</td>
<td>20,536</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>WOS</td>
<td>6595</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>AF/TexCAPS</td>
<td>6605</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Reduction
-38* -35% -29% -26% -27% -38* -29% -26% -27%

*P<0.001; †P=0.002. ‡P<0.0001.


Residual Cardiovascular Risk in Major Statin Trials

CHD events occur in patients treated with statins

<table>
<thead>
<tr>
<th>Trial</th>
<th>Secondary</th>
<th>High Risk</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>LDL</td>
<td>LDL</td>
<td>LDL</td>
</tr>
<tr>
<td>4S</td>
<td>4444</td>
<td>188</td>
<td>20,536</td>
</tr>
<tr>
<td></td>
<td>-35%</td>
<td>-35%</td>
<td>-29%</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>150</td>
<td>6595</td>
</tr>
<tr>
<td></td>
<td>-25%</td>
<td>-26%</td>
<td>-26%</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>139</td>
<td>6605</td>
</tr>
<tr>
<td></td>
<td>-28%</td>
<td>-25%</td>
<td>-27%</td>
</tr>
<tr>
<td>HPS</td>
<td>20,536</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>WOS</td>
<td>6595</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>AFCAPS/</td>
<td>6605</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>TexCAPS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of Lipid Lowering Trials

**Primary Prevention Trials**

- **S**-Py = 0.1629x - 4.6776
  - \( R^2 = 0.9029 \)
  - \( p < 0.0001 \)

**Secondary Prevention Trials**

- **LIPID-P**
  - \( y = 0.0599x - 3.3952 \)
  - \( R^2 = 0.9305 \)
  - \( p < 0.0019 \)

**Angiographic (“Regression”) Trials**

- **LCAS-P**
  - \( p = 0.0004 \)
  - \( R^2 = 0.6116 \)

Recent Coronary IVUS Progression Trials

**Relationship between LDL-C and Progression Rate**

- Median Change in Percent Atheroma Volume (%)
- Mean Low-Density Lipoprotein Cholesterol (mg/dL)

**Recent Coronary IVUS Progression Trials**

- **CAMELOT**
  - Placebo
- **REVERSAL**
  - Pravastatin
- **ACTIVATE**
  - Atorvastatin
- **ASTEROID**
  - Rosuvastatin
- **A-Plus**
  - Placebo
Aggressive LDL Lowering in CHD

PROVE-IT
4162 pts post ACS for 2 years
*Death, MI, UA, revascularization

CHD death, MI, resuscitation after cardiac arrest, fatal/nonfatal stroke

Treating to New Targets

Mean LDL-C on therapy
95 mg/dL vs. 62 mg/dL

Mean LDL-C on therapy
101 mg/dL vs. 77 mg/dL


HPS: Statin Benefit is Independent of Baseline LDL

20,536 Patients

<table>
<thead>
<tr>
<th>Baseline LDL (mg/dl)</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>Statin better</th>
<th>Statin worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 (n=3,421)</td>
<td>282</td>
<td>358</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100–129 (n=7,068)</td>
<td>668</td>
<td>871</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥130 (n=10,047)</td>
<td>1083</td>
<td>1356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>24% SE 3 reduction (2P&lt;0.00001)</td>
<td></td>
</tr>
</tbody>
</table>

ASCOT-LLA Primary End Point: Nonfatal MI and Fatal CHD

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th># of Events</th>
<th>End of Treatment Mean LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitor 10 mg</td>
<td>5,168</td>
<td>100</td>
<td>90 mg/dL</td>
</tr>
<tr>
<td>Placebo</td>
<td>5,137</td>
<td>154</td>
<td>126 mg/dL</td>
</tr>
</tbody>
</table>

Baseline LDL = 130 mg/dL

36% Relative Risk Reduction
(*P* = .0005)

HR = 0.64
(0.50–0.83)

In a post-hoc analysis, a significant difference at 90 days was observed between treatment groups.


Steno-2: Multifactorial Intervention and CVD in Type 2 DM

![Steno-2 Graph]

Intensive therapy
- Conventional therapy

Patients (%)

<table>
<thead>
<tr>
<th>A1C &lt;6.5%</th>
<th>Cholesterol &lt;175 mg/dL</th>
<th>Triglycerides &lt;150 mg/dL</th>
<th>Systolic BP &lt;130 mm Hg</th>
<th>Diastolic BP &lt;80 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>P=0.01</td>
<td>P=0.01</td>
<td>P=0.01</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>

Benefits of Aggressive LDL-C Lowering in Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Diabetes</th>
<th>Treatment</th>
<th>Control</th>
<th>Aggressive lipid-lowering better</th>
<th>Aggressive lipid-lowering worse</th>
<th>Difference in LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>Diabetes, HTN</td>
<td>9.2</td>
<td>11.9</td>
<td>0.77</td>
<td>0.036</td>
<td>35†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.001</td>
<td>0.0003</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CARDS</td>
<td>Diabetes, no CVD</td>
<td>5.8</td>
<td>9.0</td>
<td>0.63</td>
<td>0.001</td>
<td>46†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.001</td>
<td>0.0003</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HPS</td>
<td>All diabetes</td>
<td>9.4</td>
<td>12.6</td>
<td>0.73</td>
<td>&lt;0.0001</td>
<td>39†</td>
</tr>
<tr>
<td></td>
<td>Diabetes, no CVD</td>
<td>9.3</td>
<td>13.5</td>
<td>0.67</td>
<td>0.0003</td>
<td>39†</td>
</tr>
<tr>
<td>TNT</td>
<td>Diabetes, CHD</td>
<td>13.8</td>
<td>17.9</td>
<td>0.75</td>
<td>0.026</td>
<td>22*</td>
</tr>
</tbody>
</table>

*Atorvastatin 10 vs 80 mg/day
†Statin vs placebo

Relative risk

0.5 0.7 0.9 1 1.7

Modifications to NCEP-ATP III Based on Recent Clinical Evidence

- LDL-C goal <70 mg/dL is therapeutic option for very high-risk patients
  - Extends to patients at very high risk with baseline LDL-C <100 mg/dL
- Factors that favor the optional goal of <70 mg/dL include CVD plus
  - Multiple major risk factors (especially diabetes)
  - Severe and poorly controlled risk factors (especially smoking)
  - Metabolic syndrome
  - Acute coronary syndromes
- For moderately high risk patients, LDL-C <100 mg/dL is an option
- In patients with elevated LDL-C at baseline (≥160 mg/dL)
  - Standard statin doses not sufficient for optimal LDL-C reduction
  - Consider high dose statins and/or combination therapy
Lessons from Recent Clinical Trials

• LDL-C remains the primary goal of therapy
• Statins are the first line therapy
• Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:
  —with overt CVD
  —without CVD who are over the age of 40 years and have one or more other CVD risk factors
• Treat to achieve at least a 30 to 40% reduction in LDL-C
• Optimize statin therapy to highest tolerated dose to achieve goal before adding additional therapies


Residual CVD Risk in Patients Treated With Intensive Statin Therapy

Statistically significant, but clinically inadequate CVD reduction\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>PROVE IT-TIMI 22(^2)</th>
<th>IDEAL(^3)</th>
<th>TNT(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4162</td>
<td>8888</td>
<td>10 001</td>
</tr>
<tr>
<td>LDL-C,(^*) mg/dL</td>
<td>95</td>
<td>104</td>
<td>101 77</td>
</tr>
<tr>
<td>Patients Experiencing Major CVD Events, %</td>
<td>22.4</td>
<td>12.0</td>
<td>8.7</td>
</tr>
</tbody>
</table>

\(^*\)Mean or median LDL-C after treatment

Diabetic Patients Have Particularly High Residual CVD Risk After Statin Treatment

Event Rate (No Diabetes) | Event Rate (Diabetes)
--- | ---
On Statin | On Placebo | On Statin | On Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>On Statin</th>
<th>On Placebo</th>
<th>On Statin</th>
<th>On Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS1* (CHD patients)</td>
<td>19.8%</td>
<td>25.7%</td>
<td>33.4%</td>
<td>37.8%</td>
</tr>
<tr>
<td>CARE2†</td>
<td>19.4%</td>
<td>24.6%</td>
<td>28.7%</td>
<td>36.8%</td>
</tr>
<tr>
<td>LIPID3‡</td>
<td>11.7%</td>
<td>15.2%</td>
<td>19.2%</td>
<td>22.8%</td>
</tr>
<tr>
<td>PROSPER4§</td>
<td>13.1%</td>
<td>16.0%</td>
<td>23.1%</td>
<td>18.4%</td>
</tr>
<tr>
<td>ASCOT-LLA5‡</td>
<td>4.9%</td>
<td>8.7%</td>
<td>9.6%</td>
<td>11.4%</td>
</tr>
<tr>
<td>TNT6║</td>
<td>7.8%</td>
<td>9.7%</td>
<td>13.8%</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

*CHD death, nonfatal MI, stroke, revascularizations
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
║CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg versus 10mg atorvastatin)


Lipids in Subjects with and without Diabetes

NHANES III
N = 2844

Recommended ADA cut points

CHD Risk: HDL-C and Triglycerides as Predictor

Meta-analysis of 17 population-based prospective studies

RR of CHD After 4 yr

Increase in Disease Risk *%

Men

Women

Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk  
(Non–HDL-C = TC-HDL-C)

2693 Men
3101 Women

Why Look Beyond LDL Lowering with Statin Therapy

- Cardiovascular events occur in individuals with low LDL-C
  - Still occur in treatment groups after LDL lowering with statins
  - In statin/placebo clinical trials, when patients with diabetes are treated with statins, their CVD event rates were higher than the CVD event rates of those patients without diabetes on placebo.
  - IVUS: LDL <70 mg/dL, 20% with progression associated with DM, increased BP, less increase in HDL, less decrease in Apo-B
- Impact of other atherogenic particles including low or abnormally functioning HDL, VLDL remnants, triglycerides, small dense LDL
  - Non-HDL-C associated with increase risk
  - Independent risk of low HDL, elevated triglycerides
  - Apo B and apo B/Apo A1 ratio better predictor of risk
- Epidemic of obesity metabolic syndrome and diabetes – high-risk patients seen more frequently

Triglyceride Level Remains CVD Risk Factor in Patients Treated With Statins

CARE and LIPID

N = 13,173

<table>
<thead>
<tr>
<th>Triglyceride Level, mg/dL</th>
<th>Placebo</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99-126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>127-158</td>
<td></td>
<td></td>
</tr>
<tr>
<td>159-207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;207</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVD Event Rate

- Slope = .018
- P = .02


*CVD death, nonfatal MI, CABG, PTCA
Major Cardiovascular Events According to On-treatment HDL-C: Treating to New Targets

At 5 Years, a 39% Lower Risk of Major Events in Those With Highest HDL-C vs Those With Lowest HDL-C Levels

![Graph showing the 5-year risk of major CV events (% in patients with LDL-C <70 mg/dL) across different quintiles of HDL cholesterol levels.](image)

- Q1 (<37): Hazard ratio (95% CI) versus Q5: 0.86 (0.57–1.25)
- Q2: 0.67 (0.36–0.98)
- Q3: 0.55 (0.35–0.86)
- Q4: 0.61 (0.38–0.97)


Benefit of Combination HDL Raising and LDL Lowering with Statins

![Graph showing the change in atheroma volume (mm³) across different levels of LDL-C and % change in HDL-C.](image)

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>% Change HDL-C</th>
<th>Change Atheroma Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;87.5</td>
<td>&gt;7.5</td>
<td>-10.0</td>
</tr>
<tr>
<td>87.5-&lt;90.5</td>
<td></td>
<td>-5.0</td>
</tr>
<tr>
<td>90.5-&lt;92.5</td>
<td>&lt;7.5</td>
<td>-1.0</td>
</tr>
<tr>
<td>&gt;92.5</td>
<td>&lt;7.5</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;97.5</td>
<td>&gt;7.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

P<0.001 for trend

Management of Dyslipidemia beyond LDL

- Lifestyle changes and secondary causes
- Pharmacologic therapy
  - Fibrate
  - Niacin
  - Omega-3 fatty acids
  - PPAR-\(\gamma\) or -\(\alpha\) agonists
- Combination therapy
- Secondary causes of Hypertriglyceridemia
  - Nephrotic syndrome
  - Diabetes mellitus
  - Hypothyroidism
  - Medications (Estrogens, Tamoxifen, Beta-blocker, Cyclosporin, asparaginase, accutane)

### Fibrate Trials

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Drug</th>
<th>Duration</th>
<th>(\Delta)LDL</th>
<th>(\Delta)TG</th>
<th>(\Delta)HDL</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS</td>
<td>4081</td>
<td>Gemfibrozil</td>
<td>5.4 y</td>
<td>-10%</td>
<td>-43%</td>
<td>+&gt;10%</td>
<td>34% ↓ fatal/nonfatal CHD ((P&lt;0.02))</td>
</tr>
<tr>
<td>BIP</td>
<td>3122</td>
<td>Bezafibrate</td>
<td>6.2 y</td>
<td>-6.5%</td>
<td>-21%</td>
<td>+18%</td>
<td>9.4% ↓ nonfatal events (P=0.26)</td>
</tr>
<tr>
<td>VA-HIT</td>
<td>2531</td>
<td>Gemfibrozil</td>
<td>5.1 y</td>
<td>0%</td>
<td>-31%</td>
<td>+6%</td>
<td>22% ↓ fatal/nonfatal CHD (P=0.006)</td>
</tr>
<tr>
<td>FIELD</td>
<td>9795</td>
<td>Fenofibrate</td>
<td>5 y</td>
<td>-6%</td>
<td>-22%</td>
<td>+1%</td>
<td>11% ↓ CHD ((P=.16))</td>
</tr>
</tbody>
</table>

Outcomes in Fibrate Trials: Diabetic or Metabolic Syndrome Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Drug</th>
<th>RRR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS*</td>
<td>292</td>
<td>13.0%</td>
<td>3.9%</td>
<td>71%</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>FIELD2†</td>
<td>7664</td>
<td>10.8%</td>
<td>9.5%</td>
<td>19%</td>
<td>.004</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP3‡</td>
<td>1470</td>
<td>18.4%</td>
<td>14.1%</td>
<td>25%</td>
<td>.03</td>
</tr>
<tr>
<td>VA-HIT4§</td>
<td>769</td>
<td>29.4%</td>
<td>21.2%</td>
<td>32%</td>
<td>.004</td>
</tr>
</tbody>
</table>

RRR, relative risk reduction

* Patients with TG >204 mg/dL and an LDL/HDL >5 (may or may not have had DM or the MS)
† Patients with diabetes and no prior CVD
‡ Patients with the metabolic syndrome
§ Patients with diabetes

References:

Efficacy of Niacin: Combined Data from Pivotal Studies with Niacin ER

<table>
<thead>
<tr>
<th>Change from Baseline (%)</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>Lp(a)</th>
<th>TG</th>
<th>BL</th>
<th>500</th>
<th>1000</th>
<th>1500</th>
<th>2000</th>
<th>2500*</th>
<th>3000*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>-5</td>
<td>-12</td>
<td>-16</td>
<td>-22</td>
<td>-29</td>
<td>-30</td>
<td>-32</td>
<td>-39</td>
<td>-44</td>
<td></td>
</tr>
<tr>
<td>Greater than recommended daily doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cleveland Clinic
Coronary Drug Project: Macrovascular Outcomes*

- **15% Reduction**
  - Placebo (n = 2789)
  - Niacin (n = 1119)

- **26% Reduction**
  - Placebo (n = 2789)
  - Niacin (n = 1119)

- **24% Reduction**
  - Placebo (n = 2789)
  - Niacin (n = 1119)

- **47% Reduction**
  - Placebo (n = 2789)
  - Niacin (n = 1119)

*Total follow-up experience (mean, 6.2 yrs) †5-year incidence
TIA, transient ischemic attack

CDP: Reduction in Recurrence of MI* By Baseline Fasting Plasma Glucose

- **30% Reduction**
  - Placebo
  - Niacin

- **24% Reduction**
  - Placebo
  - Niacin

- **25% Reduction**
  - Placebo
  - Niacin

- **57% Reduction**
  - Placebo
  - Niacin

*6-year follow-up
Interactive P-value = NS
The ACCORD Trial: Lipid Study
Statin + Fenofibrate

N=5518
Mean Age: 62 yr
Mean f/u: 4.7 yr

Annual rate of primary outcome was not significantly different:
- 2.2% in fenofibrate group vs. 2.4 in placebo group
- Death: 1.5% vs 1.6%


ACCORD Lipid: Primary Outcome By Treatment Group and Baseline Subgroups

Primary outcome: 12.4% vs. 17.3% compared with
10.1 % in both groups in all patients

**ARBTER 3: 24 Months**

- Statin (n = 61)
- 12 months Statin + Niacin ER (n = 125)
- 24 months Statin + Niacin ER (n = 57)

* * P<.001 versus statin monotherapy


---

**ARBTER 6-HALTS: Treatment effects on carotid intima-media thickness**

- Change from baseline in mean carotid IMT (mm)
- Niacin
- Ezetimibe

Ongoing “Events” Trials of Combined LDL-C Lowering and HDL-C Raising

AIM HIGH: Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes

- ER niacin plus simvastatin vs simvastatin alone at comparable levels of on-treatment LDL-C
- n = 3,300 /Completion Q3, 2010

HPS2-THRIVE: A Randomized Trial of the Long-Term Clinical Effects of Raising HDL Cholesterol With Extended Release Niacin/Laropiprant

- Participants have established CVD and receive LDL lowering therapy (40 mg of simvastatin or 10/40 mg ezetimibe/simvastatin)
- Laropiprant - selective prostaglandin D2 receptor-1 (DP1) antagonist - reduces frequency and intensity of niacin-induced flushing
- n = 20,000 /Completion Q4, 2011

NCEP-ATP III and 2004 Modifications

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Level</th>
<th>LDL-C Goal (mg/dL)</th>
<th>TLC When LDL-C (mg/dL)</th>
<th>Consider Drug Therapy When LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD/CHD risk equivalents (10-year risk &gt;20%)</td>
<td>Very high risk</td>
<td>Optional &lt;70</td>
<td>≥100</td>
<td>≥100 (&lt;100: drug optional)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>&lt;100</td>
<td>≥130</td>
<td>≥130 (100–129: drug optional)</td>
</tr>
<tr>
<td>2+ risk factors (10-year risk &lt;20%)</td>
<td>High intermediate (10 year risk 10 to 20%)</td>
<td>Optional &lt;100</td>
<td>≥130</td>
<td>(100-129: drug optional)</td>
</tr>
<tr>
<td></td>
<td>Intermediate (10 year risk &lt;10%)</td>
<td>&lt;130</td>
<td>≥160</td>
<td></td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>Low</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥180 (160–189: drug optional)</td>
</tr>
</tbody>
</table>

Intensity of therapy should be selected to achieve a 30 to 40% LDL reduction

TLC = therapeutic lifestyle changes

NCEP ATP III Current Guidelines Provide Direction on How to Treat Patients With Dyslipidemia

- The first priority of treatment is to lower LDL-C
  - The first line of drug therapy to manage LDL-C is statins

- If TG are $\geq 500$ mg/dL, lowering TG is primary target, options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy; than treat LDL-C to goal

- If LDL-C at goal but TG $\geq 200$ mg/dL
  - Non-HDL-C (TC-HDL-C) is a second target of therapy
  - Combining a fibrate or nicotinic acid with an LDL-C-lowering drug can be considered
  - Non-HDL-C goal = LDL-C goal + 30 mg/dL

- TG $\geq 150$ mg/dL is defined as borderline high and should be addressed

- A specific goal for HDL-C is not specified
  - HDL-C $<40$ mg/dL is defined as low
  - Treatment of low HDL-C should be considered for high-risk patients

---

ADA Consensus Statements for Patients With Diabetes Mellitus or Cardiometabolic Risks

| Suggested Treatment Goal in Patients With Cardiometabolic Risk (CMR) and Lipoprotein Abnormalities | Goals |
|---|---|---|
| | LDL-C $^1$ (mg/dL) | Non-HDL-C $^1$ (mg/dL) | apo B $^1$ (mg/dL) |
| Highest-risk patients: | | | |
| 1) Known CVD or | <70 | <100 | <80 |
| 2) Diabetes plus one or more additional CVD risk factor(s) | | | |
| | | | |
| High-risk patients: | | | |
| 1) No diabetes or known CVD but 2 or more major CVD risk factors or | <100 | <130 | <90 |
| 2) Diabetes but no other CVD risk factors | | | |

In addition to LDL-C goal, for patients with diabetes, the ADA suggests:
- Lowering TG to $<150$ mg/dL and
- Raising HDL-C to $>40$ mg/dL in men and $>50$ mg/dL in women

Combination therapy of LDL-cholesterol lowering drugs (statins) with fibrates or niacin may be necessary to achieve lipid targets
2008 AAP Recommendations

- Emphasis on overweight, high TG and low HDL:
  - Lifestyle management, weight management
- Screen
  - FHx of CVD or dyslipidemia (parents or grandparents <55)
  - FHx not known and other RF’s (overweight, obese, HPB, smoking, DM)
  - 1<sup>st</sup> between 2 and 10 years with fasting lipid profile
  - Retest 3 to 5 years if normal range
- For individuals over 8 years of age, pharmacologic therapy considered
  - Fiber up to 20 gm/day
  - Plant stanols/sterols
  - Statins as first line treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LDL Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other RF’s</td>
<td>&gt;190</td>
</tr>
<tr>
<td>FHx or other RF’s</td>
<td>&gt;160</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt;130</td>
</tr>
</tbody>
</table>

* Risk factors defined as obese, overweight, hypertension, cigarette smoking

Pediatric Lipid Clinic

<table>
<thead>
<tr>
<th>Value (mg/dL)</th>
<th>Baseline Visit</th>
<th>After 2nd Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>LDL</td>
<td>236</td>
<td>129</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>97</td>
<td>77</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>309</td>
<td>197</td>
</tr>
</tbody>
</table>
Conclusions

• Strong relationship between lipid abnormalities and CVD risk

• Identification of the high risk patient and early aggressive treatment
  – LDL-C target goals are set by the 10-year CHD risk
  – Non-HDL-C is a secondary target for therapy

• Life habit risk factors (smoking, physical inactivity, obesity)
  – Targets for CVD prevention and should be included in evaluation
  – Metabolic syndrome is a target for extensive TLC

• More aggressive LDL-C reduction provides greater CHD event reduction in high-risk patients and a greater rationale for lower-target LDL-C levels and more intensive LDL-C lowering therapy
  – Modifications to NCEP and AHA/ACC/ADA guidelines suggest goal of <70 mg/dL in the highest-risk, <100 mg/dL in high intermediate risk and initiation of medical therapy at lower LDL-C thresholds
  – Statins are primary treatment in all high risk patients
  – More aggressive goals will require use of higher dose statins + combo Rx

Conclusions (cont’d)

• Combination therapies have intuitive interest and appeal
  – Limits to what can be achieved with statins
  – Atherogenic properties of other lipoproteins
  – ENHANCE and ILLUSTRATE raise awareness that the way we treat lipids remains important
  – Limited data on benefits of therapies added to statins
  – Await clinical trials
    – Aim High, HPS2
    – IMPROVE-IT

• Novel risk markers and measures of pre-clinical atherosclerosis
  – Additive with Framingham assessment
  – May help guide treatment decisions, particularly in intermediate-risk patients
  – May broaden the population for drug therapy

• Other high risk groups such as RA, SLE, high risk children should be targeted for earlier statin therapy
Every Life Deserves World Class Care

Hyperlipidemia Case Presentations

Michael B. Rocco, M.D.
Medical Director, Stress Testing and Cardiac Rehab
Sections of Preventive Cardiology and Clinical Cardiology
Cardiovascular Medicine
Heart and Vascular Medicine
Mr. Smith

History and Physical Exam

- 49-year-old African-American male recently diagnosed with type 2 diabetes
- Past medical history of hypertension on medications
- Admits to sedentary lifestyle and no time for exercise. When he tries to walk briskly uphill, he develops a cramp in the left calf.
- Denies any other history of previous cardiovascular symptoms or previous cardiovascular testing
- Smokes 1ppd, drinks alcohol occasionally
- No complaint of ED
- Family Hx: Father RCA stent age 54, died age 62 of MI; Mother and aunt have diabetes
- Medications
  - Metformin 500 mg bid
  - Amlodipine 10 mg qd

- 5’10”, 225 lb
- BMI=32.3; waist 40”
- BP: 142/90 mm Hg
- Normal S1, S2, no murmurs, rubs or gallops
- Chest clear
- No JVD
- Carotids normal without bruit
- Left femoral bruit
- No edema

Mr. Smith

Laboratory Data

Baseline (fasting levels)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C</td>
<td>232 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td>(calculated)</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>36 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>278 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>156 mg/dL</td>
</tr>
<tr>
<td>HbA1C</td>
<td>7.6% (nl: 4–6)</td>
</tr>
<tr>
<td>TSH</td>
<td>1.2 mU/L</td>
</tr>
<tr>
<td>CBC</td>
<td>normal</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.32, Complete metabolic panel otherwise normal</td>
</tr>
<tr>
<td>Albumin/creatinine ratio</td>
<td>56 mcg/mg</td>
</tr>
<tr>
<td>Glucose</td>
<td>156 mg/dL</td>
</tr>
<tr>
<td>HbA1C</td>
<td>7.6% (nl: 4–6)</td>
</tr>
<tr>
<td>TSH</td>
<td>1.2 mU/L</td>
</tr>
<tr>
<td>EKG</td>
<td>normal sinus rhythm, LVH by voltage criteria</td>
</tr>
<tr>
<td>ABI</td>
<td>0.84 on the left and 1.12 on the right</td>
</tr>
</tbody>
</table>

C=cholesterol; TG=triglycerides; HbA1C=hemoglobin A1C; TSH=thyroid-stimulating hormone.
Question

Mr. Smith’s CVD Risk (annual CVD event rate) is
1) Low (< 1%)
2) Intermediate (1 to 1.5%)
3) High intermediate (1.5 to 2%)
4) High (≥ 2%)

High risk features include:

- Multiple CV risk factors
- Clinical symptoms ABI’s consistent with PAD
- LVH on EKG
- Microalbuminuria
- Metabolic pattern
- Family history

Question

Initial management proven to reduce cardiovascular events should consist of all of the following EXCEPT:
1) Aggressive management of lipids
2) Reduction of A1C to <6.0%
3) Aspirin
4) Change amlodipine to an ACE inhibitor
5) Exercise program and weight reduction
6) Discontinue cigarette smoking
**Question**

What would be his target for therapy

1) LDL <70 mg/dL and non-HDL <100/Apo-B <80 mg/dL
2) LDL <100 mg/dL and non-HDL <130/Apo-B <90 mg/dL
3) LDL <130 mg/dL and non-HDL <160/Apo-B <100 mg/dL

**Question**

How would you initially treat this patient’s lipids?

1) Fibrates
2) Statins
3) Niacin
4) Resins
5) Cholesterol absorption inhibitors
6) Omega 3 Fish oil
### Mr. Smith

**Follow-up Visit 1**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Months*</th>
<th>Rosuvastatin 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C</td>
<td>232</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>140</td>
<td>80</td>
<td>Goal: &lt;70 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>36</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>278</td>
<td>229</td>
<td>Goal: &lt;150 mg/dL</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>196</td>
<td>126</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>136</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>7.6</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>WNL</td>
<td>WNL</td>
<td></td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>230</td>
<td>221</td>
<td></td>
</tr>
</tbody>
</table>

### Question

Reasonable further options for management include all except:

1) Continue present statin dose and work at weight reduction and glucose control
2) Add niacin
3) Add a fibrate
4) Increase the statin dose
5) Add fish oil
## Mr. Smith
### Follow-up Visit 2

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Months</th>
<th>8 Months</th>
<th>Niacin ER 1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C</td>
<td>232</td>
<td>164</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>140</td>
<td>80</td>
<td>70</td>
<td>Goal: &lt;70 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>36</td>
<td>38</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>278</td>
<td>229</td>
<td>165</td>
<td>Goal: &lt;150 mg/dL</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>196</td>
<td>126</td>
<td>103</td>
<td>Goal: &lt;100 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>136</td>
<td>110</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>7.6</td>
<td>6.8</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>WNL</td>
<td>WNL</td>
<td>WNL</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>230 lb</td>
<td>221 lb</td>
<td>215 lb</td>
<td></td>
</tr>
</tbody>
</table>

## Mrs. Hart
### History and Physical Exam

- 70 yo female with DM, HTN, Hyperlipidemia
- CAD: history of BMS to Circ in 2004 and DES to RCA in 2008
- She has been tried on Simvastatin, Lovastatin and Lipitor in the past with complaints of muscle aches.
- Welchol stopped in the past due to GI distress
- She is sent to lipid clinic for further management
- Medications
  - ASA, clopidogrel, metoprolol, lisinopril
  - OTC fish oil, red yeast rice, no-flush niacin
- TC 280 mg/dL
- HDL 30 mg/dL
- TG 300 mg/dL
- LDL 190 mg/dL
- Non-HDL 250 mg/dL
Mrs. Jones
History and Labs

• 54 yo obese female with HTN, Hyperlipidemia, impaired fasting glucose

• Presented with unstable angina and underwent BMS to circumflex

• Started on atorvastatin 80 mg/day

• Other medications:
  • ASA, clopidogrel for 30 days, ramipril
  • OTC: tylenol for headaches, fish oil

• Baseline CMP was normal except for fasting glucose of 116 mg/dL
  • LDL: 158 mg/dL
  • HDL: 39 mg/dL
  • TG: 235 mg/dL
  • ALT: 46 U/L (ULN 50)
  • AST: 32 U/L (ULN 40)

Followup Labs: 3 months

• TC: 157 mg/dl
• HDL: 42 mg/dL
• TG: 186 mg/dL
• LDL: 78 mg/dL
• Non-HDL 250 mg/dL
• ALT: 92 U/L
• AST: 42 U/L

Reasons for Stopping Statins

• Myalgias
• LFT abnormalities
• GI intolerance/headache
• Memory loss
• Bad press/misconceptions/drug resistant patient
  — e.g. renal failure
• Cost
**Statin Advisory: Monitoring Parameters, Follow-Up Schedule**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, dyspepsia</td>
<td>Evaluate baseline symptoms, 6–8 wk after initiating therapy, then at each follow-up visit</td>
</tr>
<tr>
<td>Muscle soreness, tenderness, or pain</td>
<td>Evaluate baseline muscle symptoms and CK levels; muscle symptoms 6–12 wk after initiating therapy and at each follow-up visit; CK measurement when muscle soreness, tenderness, or pain present</td>
</tr>
<tr>
<td>ALT, AST</td>
<td>Evaluate baseline ALT/AST, 12 wk after initiating therapy, then annually or as indicated</td>
</tr>
</tbody>
</table>

ALT=alanine transferase; AST=aspartate transferase.

**Terminology to Describe Muscle Injury**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>muscle ache or weakness <em>without</em> creatine kinase (CK) elevation¹</td>
</tr>
<tr>
<td>Myopathy</td>
<td>muscle symptoms <em>with</em> increased CK levels &gt;10 x ULN²</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>muscle symptoms with marked CK elevation (typically &gt;10 x ULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)¹</td>
</tr>
</tbody>
</table>

Incidence of Myopathy and Rhabdomyolysis With Statins

- Dose-related myopathy occurs in approximately 0.1% to 0.5% of patients on statin monotherapy\(^1\).
- The incidence of statin-associated rhabdomyolysis across large, randomized, controlled statin trials is <0.1%\(^2\)*.
- The reported incidence of fatal rhabdomyolysis with statins is extremely rare:
  - 0.15 death per 1 million prescriptions\(^3\)**
  - 0.44 per 10,000 person years with statin
  - 2.82 per 10,000 person years with fibrates
  - 5.98 per 10,000 person years with statin + fibrates
    - Gemfibrozil 7:10,614 with Fenofibrate 1:3.434
- A review of 5 large-scale controlled clinical trials of statin safety reported the following\(^2\):
  - Rate of myopathy ranged from 0.1% to 0.6%
  - Rate of rhabdomyolysis ranged from 0.03% to 0.05%
- Myalgias reported in prescribing info: 1.2 to 3.2%
  - Up to 11% in registries

*Based on clinical trials published between 1990 and 2003.
**Based on FDA reports of rhabdomyolysis from 1-1990, to 3-2002.

Statin Advisory: Risk Factors for Statin-Associated Myopathy

- Myopathy more likely to occur at higher doses
- Attention should be paid to factors that may increase risk for myopathy

Concomitant meds or consumption of:
- Fibrates: gemfibrozil
- Nicotinic acid (rarely)
- Cyclosporine
- Azole antifungals
  - Itraconazole, ketoconazole
- Macrolide antibiotics
  - Erythromycin, clarithromycin
- HIV protease inhibitors
- Nefazodone (antidepressant)
- Verapamil
- Amiodarone
- Large quantities of grapefruit juice (>1 qt/d)
- Alcohol abuse

Other considerations:
- Advanced age (especially >80 yr; women > men)
- Genetics
- Small body frame, frailty
- Multisystem disease
  - (eg, chronic renal insufficiency, especially in DM)
- Multiple medications
- Perioperative periods
- Obstructive liver disease
- Hypothyroid
- Transplant patients

Statin Intolerance

• Search for other causes

• Trial of different statin or stop and rechallenge at lower dose
  - Will try multiple statins

• Trial of low dose, reduced frequency of potent statin

• Trial of Co Enzyme Q10 for myalgias

• Non-statin drug therapies
  - Niacin with ezetimibe
  - Niacin with Resin

• Emphasis on TLC
  - Nutrition consultation
    - Plant stanols and sterols
    - Soluble fiber: dietary, supplemental
  - Exercise Rx

Red Rice Yeast

• Product of yeast on red rice

• Monacolins

• Potent HMG-Coa Reductase inhibitor

• Mevinolin (AKA Lovastain (Mevacor))
No Flush Niacin

- No Flush
  - Most expensive ($21/month)
  - Contains no free nicotinic acid
  - Ineffective treatment
- Sustained-release
  - Less expensive ($10/month)
  - Full amount of free nicotinic acid
  - Hepatotoxicity frequent with some brands
- Immediate release
  - Least expensive ($8/month)
  - Full amount of free nicotinic acid
  - Used safely for 50 years
  - Effective treatment

Ann Inter Med 2003;138:996-1002

Statins and the Incidence of Clinically Significant Transaminase Elevations

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose (mg)</th>
<th>Serum Transaminase Elevations* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crestor® (rosuvastatin calcium)</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>0.1</td>
</tr>
<tr>
<td>Lipitor ® (atorvastatin calcium)</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>2.3</td>
</tr>
<tr>
<td>Pravachol® (pravastatin sodium)</td>
<td>20</td>
<td>≤1.2</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>1.2</td>
</tr>
<tr>
<td>Vytorin™ (ezetimibe/simvastatin)</td>
<td>All Doses</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>10/80</td>
<td>3.6</td>
</tr>
<tr>
<td>Zocor® (simvastatin)</td>
<td>20</td>
<td>~1.0</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

- The data in the above analysis were derived from prescribing information and not from comparative trials

*Clinically significant elevations in transaminase levels were defined as the following: Rosuvastatin and atorvastatin: >3 x ULN occurring on 2 or more occasions; simvastatin and ezetimibe/simvastatin: persistent elevations >3 x ULN; pravastatin: >3 x ULN in pts with normal baseline liver function, and >4 x ULN in pts with baseline transaminase levels above ULN but <1.5 x ULN. Based on prescribing information for the individual statins.
Statin-Associated Transaminase Elevations

- Progression to liver failure due to statins is exceedingly rare
  - Acute liver failure (0.02-0.07 per million)
  - Hepatitis – never been reported
  - Cholestasis – never been reported

- Transaminitis – 0.5% to 1.3%
  - Reversal of transaminase elevation is frequently noted with a reduction in statin dose
  - Elevations do not often recur with either readministration or selection of another statin

- Statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C
- Treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver condition


ALT/AST < 3X ULN

- Review meds/ETOH
- Look for other causes
- Repeat labs in 6-12 weeks on same or lower dose

ALT/AST > 3X ULN

- Repeat in 1 to 2 weeks, if persistently high, stop statin
- Recheck in 2 to 4 weeks
- May consider rechallenge with lower dose or different statin
Should you start statin in someone with high ALT/AST?

• Kiyici et al.,
  – 44 patients with biopsy proven NASH
  – Atorvastatin 10mg for 6 months
  – Decrease in cholesterol, AST, ALT, AP, and GGT

• Chalasani et al., (moderate AST/ALT elevation)
  – Effect of statins over 6 months (mild/moderate, severe)
    – High AST/ALT placed on statin (4.7%, 0.6%)
    – High AST/ALT not placed on statin (6.4%, 0.4%)
    – Normal AST/ALT placed on statin (1.9%, 0.2%)

Prevention – Secondary Population LDL

[Graph showing LDLc (w/2FUPs) - Statin Tolerant with median IQR values over time]
Prevention - Secondary Population LDL

LDLc (w/2FUPs) - Statin Intolerant

Baseline

Follow-Up

Every Life Deserves World Class Care
Case Presentations
Anticoagulation Issues

Michael B. Rocco, M.D.
Jonathan Schaffer, M.D.

Preoperative Knee Replacement

- 64yo WM, BMI 32
- Persistent atrial fibrillation for 4 years
- Hypertension controlled on current therapy
- Diabetes, HbA1c of 7.1, Creatinine 1.2
- No previous history of VTE
- Drug eluting stent placed in proximal LAD 3 months ago at another institution. Presented with unstable angina and cath demonstrated 95% LAD stenosis
- No history of MI, LV function normal on Echo
- Meds: ASA 81mg qday, warfarin 5mg qday, clopidogrel 75mg qday, metoprolol succinate 100 mg qday, lisinopril 20 mg qday, metformin 1000 mg bid, simvastatin 40 mg qday.
- Ortho wants to schedule for knee replacement using spinal and femoral nerve catheter ASAP
- Denies recurrent chest pain, DOE, PND orthopnea, palpitations, hypoglycemic episodes
- EKG: atrial fibrillation rate 82, LVH
Preoperative Knee Replacement

- CV risk for non-cardiac surgery
- Need for stress testing
  - Will it alter treatment decisions
- Atrial fibrillation rate control
- Withdrawal of antiplatelet therapy
  - Clopidogrel
  - ASA
- Withdrawal of warfarin
  - Need for bridging with heparin
- VTE prophylaxis
- Peri-operative medications
- Diabetes management
- Type of anesthesia

Proposed Approach to the Management of Patients with Previous PCI Who Require Noncardiac Surgery

- PCI, percutaneous coronary intervention
AHA/ACC/SCAI/ACS/ADA 2007 Science Advisory
Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents

- Premature discontinuation greatly increases the risk for stent thrombosis and associated clinical events.
- Patients’ ability to comply with prolonged dual therapy and need for subsequent invasive procedures should be considered when choosing stent type.
- In patients likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of a bare metal stent or balloon angioplasty with provisional stent implantation.
- Patients should receive 12 months of dual antiplatelet therapy after DES.
- Patients and other health care providers should consult with the patient’s cardiologist before stopping dual therapy.
- Elective surgery associated with a significant risk of bleeding should be postponed until an appropriate course of dual antiplatelet therapy (1 month for BMS, 12 months for DES).
- For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late stent thrombosis.


---

Preoperative Revision of Hip for Loosening

- 74yo WF, BMI 22
- Hip has loosened and she has impending fracture requiring surgery sooner than later
- No evidence of infection
  - Normal CRP, Sed rate, WBC and aspiration
- Prosthetic St. Judes mechanical mitral valve 15 years ago implanted elsewhere for mitral regurgitation. Pre-op cath revealed no obstructive CAD
- Recent Echo: moderate left atrial enlargement, ejection fraction 45%
- Hypertension controlled on therapy
- Venous stasis disease with intact skin
- Meds: ASA 81mg qday, warfarin 3mg qday, lisinopril 10mg qday, carvedilol 12.5 bid, simvastatin 40mg qday
- Ortho wants to schedule for hip revision using spinal anesthesia next week
- Denies chest pain, edema, PND, orthopnea, palpitations. Has unchanged mild SOB with 2 flights of stairs

---
Preoperative Knee Replacement

- CV risk for non-cardiac surgery
- Withdrawal of antiplatelet therapy
  - ASA
- Withdrawal of warfarin
  - Need for bridging with heparin
- Peri-operative medications
- VTE prophylaxis
- Type of anesthesia

Clinical Risk Factors for Perioperative Cardiovascular Complications

- History of ischemic heart disease
- History of compensated or prior heart failure;
- History of cerebrovascular disease;
- Diabetes mellitus; and
- Renal insufficiency (defined in the Revised Cardiac Risk Index as a preoperative serum creatinine of >2 mg/dL)
Bridging Rx in Patients with Mechanical Valves

Recommended: Class I

- Low risk of thrombosis (bileaflet mechanical AVR with no risk factors): stop warfarin 48 to 72 hours prior for INR <1.5 and restart within 24 hours. Heparin is usually unnecessary I
- High risk of thrombosis (mechanical MVR or mechanical AVR with any risk factor): UFH when INR falls <2.0 (typically 48 hours pre surgery), stopped 4 to 6 hours before surgery restarted as early after surgery as bleeding allows, and continue until INR in therapeutic with warfarin. I

Reasonable: Class II

- Reasonable to give FFP with mechanical valves who require emergent procedures. FFP preferable to vitamin K. IIa
- High risk of thrombosis: therapeutic doses of subcutaneous UFH (15,000 U q12 hours) or LMWH (100 U/kg q12 hours) may be considered during period of subtherapeutic INR IIb

Not Recommended: Class III

- Patients with mechanical valves who require interruption of warfarin, high dose vitamin K should not be given routinely since this may create a hypercoagulable condition.

Recommendations for Perioperative Beta-Blocker Therapy

<table>
<thead>
<tr>
<th>Surgery</th>
<th>No Clinical Risk Factors</th>
<th>CAD or High Risk (1 or more clinical risk factors)</th>
<th>Patients Currently Taking Beta Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Class Iib, Level of Evidence: B</td>
<td>Class Iia, Level of Evidence: B</td>
<td>Class 1, Level of Evidence: C</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>...</td>
<td>Class Iia, Level of Evidence: B</td>
<td>Class 1, Level of Evidence: C</td>
</tr>
<tr>
<td>Low risk</td>
<td>...</td>
<td>...</td>
<td>Class 1, Level of Evidence: C</td>
</tr>
</tbody>
</table>
## ACC/AHA Guidelines for Non-cardiac Surgery

### Table 13. Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Deep Vein Thrombosis, %</th>
<th>Pulmonary Embolism, %</th>
<th>Successful Prevention Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>2</td>
<td>0.4</td>
<td>Less than 0.01; no specific prophylaxis; may use &quot;aggressive&quot; mobilization</td>
</tr>
<tr>
<td>Moderate</td>
<td>10 to 20</td>
<td>2 to 4</td>
<td>1 to 2; 0.1 to 0.4; LDUH (every 12 h), LMWH (less than or equal to 3400 U daily), GCS, or IPC</td>
</tr>
<tr>
<td>High</td>
<td>20 to 80</td>
<td>8 to 8</td>
<td>2 to 4; 0.4 to 1.0; LDUH (every 8 h), LMWH (more than 3400 U daily), or IPC</td>
</tr>
<tr>
<td>Highest</td>
<td>40 to 80</td>
<td>10 to 20</td>
<td>4 to 10; 0.2 to 5.0; LMWH (more than 3400 U daily), fondaparinux, or LMWH (RF 2 to 3), or IPC/GCS plus LDUH/LMWH</td>
</tr>
</tbody>
</table>

IPA = iliofemoral; GCS = graduated compression stockings; IPC = intermittent compression devices; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; RF = relative risk; VTE = venous thromboembolism.
### Cardiac Risk Stratification for Noncardiac Surgical Procedures

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>Procedure Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular (reported cardiac risk often &gt; 5%)</td>
<td>Aortic and other major vascular surgery</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular surgery</td>
</tr>
<tr>
<td>Intermediate (reported cardiac risk generally 1%-5%)</td>
<td>Intraperitoneal and intrathoracic surgery</td>
</tr>
<tr>
<td></td>
<td>Carotid endarterectomy</td>
</tr>
<tr>
<td></td>
<td>Head and neck surgery, Orthopedic surgery, Prostate surgery</td>
</tr>
<tr>
<td>Low (reported cardiac risk generally &lt;1%)</td>
<td>Endoscopic procedures</td>
</tr>
<tr>
<td></td>
<td>Superficial procedure /Breast surgery</td>
</tr>
<tr>
<td></td>
<td>Cataract surgery</td>
</tr>
<tr>
<td></td>
<td>Ambulatory surgery</td>
</tr>
</tbody>
</table>

### Cardiac Evaluation and Care Algorithm for Noncardiac Surgery (1)

1. **Step 1**
   - Need for emergency noncardiac surgery? Yes (Class I, LOE C)
   - Operating room
   - Perioperative surveillance and postoperative risk stratification and risk factor management
   - Perioperative surveillance and postoperative risk stratification and risk factor management
   - Perioperative surveillance and postoperative risk stratification and risk factor management

2. **Step 2**
   - Active cardiac conditions* Yes (Class I, LOE B)
   - Evaluate and treat per ACC/AHA guidelines
   - Consider operating room
   - Evaluate and treat per ACC/AHA guidelines
   - Consider operating room

3. **Step 3**
   - Low risk surgery No (Class I, LOE B)
   - Proceed with planned surgery
   - Proceed with planned surgery
   - Proceed with planned surgery

4. **Step 4**
   - Functional capacity greater than or equal to 4 METs without symptoms Yes (Class IIa, LOE B)
   - Proceed with planned surgery
   - Proceed with planned surgery
   - Proceed with planned surgery
Cardiac Evaluation and Care Algorithm for Noncardiac Surgery (2)

**Step 5**
- No or unknown
- 3 or more clinical risk factors?
- 1-2 clinical risk factors?
- No clinical risk factors?

- **Vascular Surgery**
  - Class IIa, LOE B
  - Consider testing if it will change management
  - Proceed with planned surgery

- **Intermediate risk surgery**
  - Proceed with planned surgery with HR control (Class IIa, LOE B)
  - or consider noninvasive testing (Class IIb LOE B) if it will change with management

Recommendations for Beta-Blocker Medical Therapy

**Recommended: Class I**
- Continue in patients undergoing surgery who are receiving beta blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs.

**Reasonable: Class II**
- Beta blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing. IIa
- Beta blockers titrated to heart rate and blood pressure are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of > 1 clinical risk factor. IIa
- Beta blockers titrated to heart rate and blood pressure are probably recommended for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of > 1 clinical risk factor;* who are undergoing intermediate-risk surgery. IIa
- The usefulness of beta blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease.* IIb
- The usefulness of beta blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors who are not currently taking beta blockers. IIb

**Not Recommended: Class III**
- Beta blockers should not be given to patients undergoing surgery who have absolute contraindications to beta blockade.
- Routine administration of high-dose beta blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta blockers who are undergoing noncardiac surgery.
Recommendations for Non-Invasive Stress Testing Before Noncardiac Surgery

Recommended: Class I

• Patients with active cardiac conditions in whom noncardiac surgery is planned should be evaluated and treated per ACC/AHA guidelines before noncardiac surgery. I

Reasonable: Class II

• Noninvasive stress testing of patients with 3 or more clinical risk factors and poor functional capacity (< 4 METs) who require vascular surgery is reasonable if it will change management. IIa

• Noninvasive stress testing may be considered for patients with at least 1 to 2 clinical risk factors and poor functional capacity (less than 4 METs) who require intermediate-risk or vascular surgery if it will change management. IIb

Not Recommended: Class III

• With no clinical risk factors undergoing intermediate-risk noncardiac surgery.

• Undergoing low-risk noncardiac surgery.

Recommendations for Preoperative Noninvasive Evaluation of LV Function

Preoperative evaluation of LV function is reasonable: Class II

• For patients with dyspnea of unknown origin to undergo preoperative evaluation of LV function. IIa

• For patients with current or prior HF with worsening dyspnea or other change in clinical status to undergo preoperative evaluation of LV function if not performed within 12 months. IIa

• Reassessment of LV function in clinically stable patients with previously documented cardiomyopathy is not well established. IIb

Preoperative evaluation of LV function not recommended: Class III

• Routine perioperative evaluation of LV function in patients is not recommended.
Recommendations for Preoperative Resting 12-Lead ECG

Preoperative resting 12-lead ECG is recommended for patients with: Class I
- At least 1 clinical risk factor* who are undergoing vascular surgical procedures.
- Known CHD, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgical procedures.

Preoperative resting 12-lead ECG is reasonable for patients with: Class II
- Preoperative resting 12-lead ECG is reasonable in persons with no clinical risk factors who are undergoing vascular surgical procedures. IIa
- Preoperative resting 12-lead ECG may be reasonable in patients with at least 1 clinical risk factor who are undergoing intermediate-risk operative procedures. IIb

Preoperative resting 12-lead is not indicated: Class III
- Preoperative and postoperative resting 12-lead ECGs are not indicated in asymptomatic persons undergoing low-risk surgical procedures.

* Clinical risk factors include history of ischemic heart disease, history of compensated or prior HF, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency.

Perioperative Control of Blood Glucose Concentration

- It is reasonable that blood glucose concentration be controlled during the perioperative period in patients with diabetes mellitus or acute hyperglycemia who are at high risk for myocardial ischemia or who are undergoing vascular and major surgical procedures with planned ICU admission.

- The usefulness of strict control of blood glucose concentration during the perioperative period is uncertain in patients with diabetes mellitus or acute hyperglycemia who are undergoing noncardiac surgical procedures without planned ICU admission.
Intraoperative and Postoperative Use of ST-Segment Monitoring

- Intraoperative and postoperative ST-segment monitoring can be useful to monitor patients with known CAD or those undergoing vascular surgery, with computerized ST segment analysis, when available, used to detect myocardial ischemia during the perioperative period.
- Intraoperative and postoperative ST-segment monitoring may be considered in patients with single or multiple risk factors for CAD who are undergoing noncardiac surgery.

Surveillance for Perioperative MI

- Postoperative troponin measurement is recommended in patients with ECG changes or chest pain typical of acute coronary syndrome.
- The use of postoperative troponin measurement is not well established in patients who are clinically stable and have undergone vascular and intermediate-risk surgery.
- Postoperative troponin measurement is not recommended in asymptomatic stable patients who have undergone low-risk surgery.

Pre-operative Revascularization

**Recommended: Class I**
- Stable angina with left main disease.
- Stable angina with 3-vessel disease (survival benefit greater if LVEF <0.50)
- Stable angina with 2-vessel disease and proximal LAD disease and either LVEF <0.50 or ischemia on non-invasive testing
- Unstable angina or NSTEMI
- Acute STEMI

**Reasonable: Class II**
- Patients in whom PCI is appropriate for mitigation of symptoms and who need elective surgery in the subsequent 12 months, POBA or BMS followed by 4 to 6 weeks of dual-antiplatelet therapy. IIa
- In patients with DES who must undergo urgent therapy that mandates stopping thienopyridine RX, continue aspirin if at all possible IIa
- Not well established in high-risk ischemic patients (e.g. abnormal dobutamine stress with at least 5 segments of WMA) IIb
- Not well established for low-risk (e.g. abnormal dobutamine stress (1 to 4 segments) IIb

**Not Recommended: Class III**
- As routine in patients with stable CAD
- Surgery within 4 to 6 weeks of BMS or 12 months of DES
- Surgery within 4 weeks of balloon angioplasty
ATP III: The Metabolic Syndrome

General Features of the Metabolic Syndrome

- Abdominal obesity
- Atherogenic dyslipidemia
  - Elevated triglycerides
  - Small LDL particles
  - Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (± glucose intolerance)
- Prothrombotic state
- Proinflammatory state

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity* (Waist circumference†)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>TG</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL (&gt;100)</td>
</tr>
</tbody>
</table>


Defining the High Risk Patient

- Known CHD: Prior infarction, documented CAD angiographically, positive stress test, typical angina
- Other clinically significant vascular disease such as carotid artery disease, prior stroke, aortic aneurysm, PVD
- Diabetes
- > 20% ten year risk of myocardial infarction (MI) or CHD related mortality: e.g. Framingham risk score (FRS)
- Intermediate risk by clinical criteria (10 to 20% ten year risk) with other risk factors;
  - strong family history of premature CHD
  - metabolic syndrome
  - elevation of other markers of risk or inflammation: hs-CRP
  - LP(a)
  - carotid IMT, coronary calcification score, ABI (ankle-brachial index)
- Chronic inflammatory illness
**Stepwise Selection of Risk Factors* in 2693 White Patients with Type 2 Diabetes: Time to First Event: UKPDS**

**Coronary Artery Disease (n=280)**

<table>
<thead>
<tr>
<th>Position in Model</th>
<th>Variable</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Low-Density Lipoprotein</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Second</td>
<td>High-Density Lipoprotein</td>
<td>0.0001</td>
</tr>
<tr>
<td>Third</td>
<td>Hemoglobin A₁c</td>
<td>0.0022</td>
</tr>
<tr>
<td>Fourth</td>
<td>Systolic Blood Pressure</td>
<td>0.0065</td>
</tr>
<tr>
<td>Fifth</td>
<td>Smoking</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex.


---

**Predictors of Progression When LDL-C <70 mg/dL**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PAV</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Change in SBP</td>
<td></td>
</tr>
<tr>
<td>Change in HDL-C</td>
<td></td>
</tr>
<tr>
<td>Change in APOB</td>
<td></td>
</tr>
<tr>
<td>Baseline LDL-C</td>
<td></td>
</tr>
<tr>
<td>Concomitant Statin Use</td>
<td></td>
</tr>
<tr>
<td>Change in LDL-C</td>
<td></td>
</tr>
</tbody>
</table>

Bayturan, Nicholls et al J Amer Coll Cardiol 2010 (In Press)
### Niacin Meta-analysis: MACE and CVA

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto OR</th>
<th>55% CI</th>
<th>Peto OR</th>
<th>50% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER-6-HALTS</td>
<td>2/187</td>
<td>1/176</td>
<td>0.25</td>
<td>(0.06, 0.86)</td>
<td>0.27</td>
<td>(0.08, 0.8)</td>
</tr>
<tr>
<td>Gouton-JR et al</td>
<td>3/178</td>
<td>1/176</td>
<td>0.25</td>
<td>(0.06, 0.86)</td>
<td>0.27</td>
<td>(0.08, 0.8)</td>
</tr>
<tr>
<td>APEX2</td>
<td>2/172</td>
<td>2/172</td>
<td>0.14</td>
<td>(0.06, 0.86)</td>
<td>0.14</td>
<td>(0.06, 0.86)</td>
</tr>
<tr>
<td>HALT</td>
<td>1/98</td>
<td>2/98</td>
<td>0.04</td>
<td>(0.01, 1.2)</td>
<td>0.04</td>
<td>(0.01, 1.2)</td>
</tr>
<tr>
<td>UCPS_CPCR</td>
<td>5/100</td>
<td>7/100</td>
<td>0.14</td>
<td>(0.01, 0.9)</td>
<td>0.01</td>
<td>(0.01, 0.9)</td>
</tr>
<tr>
<td>STOCOLM</td>
<td>7/278</td>
<td>5/278</td>
<td>0.25</td>
<td>(0.01, 1.2)</td>
<td>0.01</td>
<td>(0.01, 0.9)</td>
</tr>
<tr>
<td>CAP</td>
<td>2/111</td>
<td>2/111</td>
<td>0.04</td>
<td>(0.01, 0.9)</td>
<td>0.04</td>
<td>(0.01, 0.9)</td>
</tr>
<tr>
<td>Total Test</td>
<td></td>
<td></td>
<td>0.05</td>
<td>(0.02, 0.9)</td>
<td>0.05</td>
<td>(0.02, 0.9)</td>
</tr>
</tbody>
</table>

### ARBITER 6-HALTS: Treatment effects on lipids

**N = 208 on statin therapy**

#### HDL-C

- Percent change from baseline
- Months: 0, 2, 4, 6, 8, 10, 12, 14
- P < 0.001

#### LDL-C

- Percent change from baseline
- Months: 0, 2, 4, 6, 8, 10, 12, 14
- P = 0.01

#### Total-C

- Percent change from baseline
- Months: 0, 2, 4, 6, 8, 10, 12, 14
- P = 0.01

#### Triglycerides

- Percent change from baseline
- Months: 0, 2, 4, 6, 8, 10, 12, 14
- P = 0.001

*Arterial Biology for the Investigation of the Treatment Effects for Reducing Cholesterol 6–HDL and LDL Treatment Strategies*

ILLUSTRATE Trial: *Primary Endpoint*

Percent change in atheroma volume from baseline

- The percent change in atheroma volume did not differ between treatment groups.


### LDL & CRP: PROVE-IT

<table>
<thead>
<tr>
<th>Events/100 person years</th>
<th>On therapy</th>
<th>Events/100 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL &lt; 70 mg/dL</td>
<td>LDL &gt; median</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>CRP &gt; median</td>
<td></td>
</tr>
<tr>
<td>LDL &gt; 70 mg/dL</td>
<td>LDL &gt; median</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>CRP &lt; median</td>
<td>3.1</td>
</tr>
<tr>
<td>CRP &lt; 2 mg/L</td>
<td>LDL &lt; median</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>CRP &gt; median</td>
<td></td>
</tr>
<tr>
<td>CRP &gt; 2 mg/L</td>
<td>LDL &lt; median</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>CRP &lt; median</td>
<td></td>
</tr>
</tbody>
</table>

- The lowest risk was noted in (post-hoc analysis) those with LDL < 70 mg/dL and CRP < 1 mg/L. (1.9 events/100 person years) This accounted for only 15.9% of the population.

JUPITER Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

![Graph showing cumulative incidence of events over follow-up years for Placebo and Rosuvastatin]

- **Placebo**: 251/8901
- **Rosuvastatin**: 142/8901

**Number Needed to Treat (NNTT)** = 25
**ARR**: 0.77 vs 1.36%/yr
**LDL**: 108 mg/dL; 50%
**CRP**: 4.2 mg/L; 37%
**HDL**: 49 mg/dL; 4%
**TGS**: 119 mg/dL; 37%


Jupiter: Importance of Achieving Dual LDL-C and hsCRP Reduction

![Graph showing cumulative incidence of MI, stroke, admission for UA, arterial revascularization, or CV death over follow-up years for Placebo and Rosuvastatin]

- **Placebo**: LDL-C ≥70 mg/dL or hsCRP ≥2 mg/L
- **Rosuvastatin (LDL-C <70 mg/dL and hsCRP <2 mg/L)**

Safety of Fibrates

- **GI**
  - Gallstones
  - Elevated transaminase
  - Increased need for CCK and/or Appendectomy

- **Thromboembolic events (FIELDS)**

- **Myopathy**
  - As monotherapy as well as combo therapy
  - Both gemfibrozil and fenofibrate but more with gemfibrozil
  - 5.5 fold increased risk of myopathy when combined with statins
  - Risk of rhabdo increases with diabetic, CRI, hypothyroidism and in elderly patient

- **Renal Effects**
  - Plasma half-life of fenofibric acid is prolonged
  - Can increase creatinine (less common with gemfibrozil) – 12% in FIELD study. Reversible
  - Fibrates dose lowered in renal patients
  - Fenofibrate – Lower dose with GFR 15-59 and avoid all together if GFR <15
  - Gemfibrozil – better in CRI or transplants patients. However, lower dose to 50% if GFR 15-59 and avoid if GFR drops below 15
Renal Effects: Fibrates

- Plasma half-life of fenofibric acid is prolonged
- Can increase creatinine (less common with gemfibrozil) – 12% in FIELD study. Reversible
- Fibrates dose lowered in renal patients
- Fenofibrate – Lower dose with GFR 15-59 and avoid all together if GFR <15
- Gemfibrozil – better in CRI or transplants patients. However, lower dose to 50% if GFR 15-59 and avoid if GFR drops below 15

Creatinine and GFR Changes From Baseline to Final Visit

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Creatinine % Change</th>
<th>Change in GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>371</td>
<td>0.8</td>
<td>-0.3</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td>637</td>
<td>-1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>10 mg</td>
<td>2909</td>
<td>-1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>20 mg</td>
<td>1432</td>
<td>-1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>40 mg</td>
<td>2107</td>
<td>-1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>1394</td>
<td>-1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>20 mg</td>
<td>1562</td>
<td>-1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>40 mg</td>
<td>221</td>
<td>-2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>80 mg</td>
<td>535</td>
<td>-3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>161</td>
<td>-0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>20 mg</td>
<td>1217</td>
<td>-1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>40 mg</td>
<td>506</td>
<td>-1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>80 mg</td>
<td>500</td>
<td>-1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>159</td>
<td>-1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>20 mg</td>
<td>342</td>
<td>-2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>40 mg</td>
<td>745</td>
<td>-0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Median duration of therapy = 8 weeks.
Glomerular filtration rate (GFR) in mL/min/1.73 m².
Combined All Controlled and Controlled RTLD Pool.
Data on file (DA-CRS-07). AstraZeneca Pharmaceuticals LP. Wilmington, DE.
CK Elevation With Symptoms

- Document severity of symptom
- Evaluate for other causes
- Stop statin if muscle weakness, pain or dark urine
- \(<3X\) ULN, then consider lowering the dose, recheck
- \(>3X\) ULN then stop statin, recheck CK in 5-7 days, if stable repeat in 4-6 weeks
- \(>10X\) ULN, stop statin check for rhabdo

New CK Elevation Without Symptoms

- Recheck CK and document to see if there is weakness on exam. Recheck medication carefully.
- If CK less than 3X ULN, continue statin and recheck in 6 weeks
- CK 3-10X ULN, then either reduce or stop statin
- CK >10X ULN, stop statin and work-up for myositis
Asymptomatic baseline CK elevation

- **CK <3X ULN**
  - May start statin, recheck in 2 months

- **CK 3-10X ULN**
  - Look for cause (hypothyroidism etc)
  - Low dose statin, repeat CK 4-6 weeks

- **CK >10X elevated**
  - Look for cause

### Common OTC Fish Oil

<table>
<thead>
<tr>
<th>Soft Gel or Capsule Name</th>
<th>Amount of EPA and DHA in One Soft Gel or Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkley &amp; Jensen Natural Extra Strength Fish Oil, 1200 mg with Omega-3 Fatty Acids</td>
<td>216 mg EPA and 144 mg of DHA per soft gel 11 tablets QD</td>
</tr>
<tr>
<td>Carlson Super Omega-3 Fish Oil Concentrate 500 mg EPA &amp; DHA</td>
<td>300 mg of EPA and 200 mg of DHA per soft gel 8 tablets QD</td>
</tr>
<tr>
<td>Pharmacy Natural Fish Oil 1000 mg (Distributed by GNC)</td>
<td>180 mg EPA and 120 mg of DHA per soft gel 13 tablets QD</td>
</tr>
<tr>
<td>Origin Natural Fish Oil Omega-3 1200 mg (Distributed by Target Corporation)</td>
<td>216 mg EPA and 144 mg DHA per soft gel 11 tablets QD</td>
</tr>
<tr>
<td>Sundown Cholesterol Free Fish Oil 1000 mg</td>
<td>180 mg EPA and 120 mg DHA per soft gel 13 tablets QD</td>
</tr>
<tr>
<td>Weil – Andrew Weil, MD Omega-3 Complex</td>
<td>333 mg of EPA and 167 mg DHA per soft gel 8 tablets QD</td>
</tr>
</tbody>
</table>