Practical Lipid Management: Concepts and Controversies

Case Studies

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Cleveland Clinic
Case: Mr. Silver

History, Physical Exam & Laboratory Data

- 57-year-old male
- PMH: HTN, treated with diet, exercise
- Smokes 1-1/2 PPD
- FH: Father, 47 years, died of CHD
- Medications — None
- Physical examination — 5’9”, 210 lb
  — BMI = 30.2, waist 40.5”
  — BP: 145/90

Baseline (fasting levels)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C</td>
<td>252</td>
</tr>
<tr>
<td>LDL-C</td>
<td>156</td>
</tr>
<tr>
<td>HDL-C</td>
<td>38</td>
</tr>
<tr>
<td>TG</td>
<td>290</td>
</tr>
<tr>
<td>Glucose</td>
<td>107</td>
</tr>
<tr>
<td>TSH</td>
<td>1.7</td>
</tr>
</tbody>
</table>

BMI = body mass index; BP = blood pressure; C = cholesterol; TSH = thyroid-stimulating hormone.
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.

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<table>
<thead>
<tr>
<th>Age</th>
<th>Total Cholesterol</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 34 =</td>
<td>-9/-7</td>
<td></td>
</tr>
<tr>
<td>35 – 39 =</td>
<td>-4/-3</td>
<td></td>
</tr>
<tr>
<td>40 – 44 =</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>45 – 49 =</td>
<td>3/3</td>
<td>40 – 49 = 1/1</td>
</tr>
<tr>
<td>50 – 54 =</td>
<td>6/6</td>
<td>&lt;40 = 2/2</td>
</tr>
<tr>
<td>55 – 59 =</td>
<td>8/8</td>
<td></td>
</tr>
<tr>
<td>60 – 64 =</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>65 – 69 =</td>
<td>11/12</td>
<td></td>
</tr>
<tr>
<td>70 – 74 =</td>
<td>12/14</td>
<td></td>
</tr>
<tr>
<td>75 – 79 =</td>
<td>13/16</td>
<td></td>
</tr>
<tr>
<td>80 – 84 =</td>
<td>15/18</td>
<td></td>
</tr>
</tbody>
</table>

**Systolic Blood Pressure**

<table>
<thead>
<tr>
<th>Age</th>
<th>If Untreated</th>
<th>If Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 39 =</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>40 – 49 =</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td>50 – 59 =</td>
<td>3/4</td>
<td>3/4</td>
</tr>
<tr>
<td>60 – 69 =</td>
<td>5/6</td>
<td>5/7</td>
</tr>
<tr>
<td>70 – 79 =</td>
<td>8/10</td>
<td>8/10</td>
</tr>
<tr>
<td>80 – 84 =</td>
<td>12/14</td>
<td>12/14</td>
</tr>
</tbody>
</table>

**Smoker**

<table>
<thead>
<tr>
<th>Age</th>
<th>Age</th>
<th>Age</th>
<th>Age</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 39 =</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>40 – 49 =</td>
<td>5/7</td>
<td>3/4</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>50 – 59 =</td>
<td>8/9</td>
<td>5/7</td>
<td>3/4</td>
<td>1/2</td>
</tr>
<tr>
<td>60 – 69 =</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 – 79 =</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total points:**

<table>
<thead>
<tr>
<th>Age</th>
<th>10-year CHD risk (%) for men:</th>
<th>10-year CHD risk (%) for women:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0</td>
<td>0/0</td>
<td>&lt;1/1</td>
</tr>
<tr>
<td>0</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>1</td>
<td>1/1</td>
<td>1/1</td>
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<tr>
<td>2</td>
<td></td>
<td>1/1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1/1</td>
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<tr>
<td>4</td>
<td></td>
<td>1/1</td>
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<tr>
<td>5</td>
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<td>1/1</td>
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<td>17</td>
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<td>18</td>
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<tr>
<td>27</td>
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<tr>
<td>28</td>
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<td>1/1</td>
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<tr>
<td>29</td>
<td></td>
<td>1/1</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>1/1</td>
</tr>
</tbody>
</table>

Limitations of Framingham Risk Score

• Does not take family history into account

• May underestimate lifetime risk in individuals ≤50 years of age with ≥1 NCEP risk factor

• May not accurately calculate risk in certain ethnic groups because original Framingham population was almost entirely of European origin

• May not accurately incorporate risk due to insulin-resistant conditions such as metabolic syndrome

• Does not include emerging risk factors such as CRP, LP(a), apo B and others
ATP III: The Metabolic Syndrome
Diagnosis established with ≥3 of these risk factors.

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 population specific* (Waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>≥88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>TG</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>

* South Asian: Male ≥90 cm; Female ≥80 cm

CV Event–Free Survival according to Metabolic Syndrome Status and CRP Levels: *Women’s Health Study*

Noninvasive Screening – Coronary Artery Calcium Score (CACS)

Relationship between CACS and the baseline Framingham risk score in the prediction of coronary death or nonfatal MI*

![Multidetector CT calcium scoring image](image)

*Hazard ratio by bivariate Cox regression analysis. Risk categories are the estimated 10-year risk for coronary death or MI based on the Framingham risk score. The CACS is measured by coronary computed tomography (CCT).

ATP III: Additional CHD Risk Factors

• Emerging risk factors: can help reassess risk and guide intensity of risk-reduction therapy
  – Lipoprotein(a)
  – Impaired fasting glucose
  – Subclinical atherosclerosis
  – LDL Particle number
  – Homocysteine
  – Prothrombotic factors
  – Proinflammatory factors

• Life-habit risk factors: targets for intervention; not used to set lower LDL-C goal
  – Obesity
  – Physical inactivity
  – Atherogenic diet

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 such as strong family history of premature CHD, metabolic syndrome, elevation of other markers of risk or inflammation: e.g. hs-CRP, LP(a), carotid IMT (intimal medial thickness), coronary calcification score, ABI (ankle-brachial index)
- Rheumatoid arthritis, Lupus
Question

What are the LDL and Non-HDL goals for therapy?

1) LDL <70 mg/dL and non-HDL <100 mg/dL
2) LDL <100 mg/dL and non-HDL <130 mg/dL
3) LDL <130 mg/dL and non-HDL <160 mg/dL
The first priority is to lower LDL-C. The first line drug is statin therapy. Secondary goal is non-HDL-C: LDL-C goal + 30 mg/dL.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD/CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 Optional &lt;70</td>
<td>&lt;130 Optional &lt;100</td>
</tr>
<tr>
<td>&gt;2 risk factors (10-year risk 10%-20%)</td>
<td>&lt;130 Optional &lt;100</td>
<td>&lt;160 Optional &lt;130</td>
</tr>
<tr>
<td>&gt;2 risk factors (10-year risk &lt;10%)</td>
<td>&lt;130</td>
<td>&lt;160</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt;160</td>
<td>&lt;190</td>
</tr>
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</table>

If LDL-C targets not achieved with maximum tolerated statin therapy treat to achieve at least 30 to 40% reduction in LDL-C.
What should be the initial therapy?

1) Therapeutic life style changes (TLC) trial for 3 months before considering medications
2) Pravastatin 20 mg/day
3) Simvastatin 40 mg/day plus TLC
4) Ezetimibe
Overview of Statin Trials
Major Coronary Events

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

% Reduction

-38* -25* -25† -27† -31* -38*

*P<0.001; †P=0.002; ‡P<0.0001.

Summary of Lipid Lowering Trials

Primary Prevention Trials

y = 0.0599x - 3.3952
R² = 0.9305
p < 0.0019

Secondary Prevention Trials

y = 0.1629x - 4.6776
R² = 0.9029
p < 0.0001

Angiographic ("Regression") Trials

y = 0.0004x - 0.0267
R² = 0.6116
p = 0.001

LDL Cholesterol (mg/dL)

CHD Events (%)
### 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></td>
<td></td>
</tr>
</tbody>
</table>

24% SE 3 reduction (2P<0.00001)

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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

- 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

- 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

Reasons for Stopping Statins

- Myalgias, elevated CPK
- LFT abnormalities
- GI intolerance/headache
- Memory loss
- Causes Diabetes
- Bad press/misconceptions/drug resistant patient/cost

- How common are these adverse reactions?
- How would you treat these patients?
## 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>

What is the incidence of rhabdomyolysis with statin use

1) <0.1%
2) 0.1 to 0.5%
3) 0.5 to 1%
4) 1 to 2%
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\(^3\)**
- 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%

*Based on clinical trials published between 1990 and 2003.
**Based on FDA reports of rhabdomyolysis from January 1, 1990, to March 31, 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:

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

- 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
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

Without Symptoms:

- Recheck CK and document to see if there is weakness on exam. Recheck other medications carefully. Look for secondary causes
- 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**
  - Hold statin
  - Look for cause
The reported dose related range of liver function abnormalities with statin use is

1) <0.1 to 2%
2) 1 to 4%
3) 3 to 6%
<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose (mg)</th>
<th>Serum Transaminase Elevations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crestor® (rosuvastatin calcium)</strong></td>
<td>5, 10, 20, 40</td>
<td>0.4, 0.0, 0.0, 0.1</td>
</tr>
<tr>
<td><strong>Lipitor® (atorvastatin calcium)</strong></td>
<td>10, 20, 40, 80</td>
<td>0.2, 0.2, 0.6, 2.3</td>
</tr>
<tr>
<td><strong>Pravachol® (pravastatin sodium)</strong></td>
<td>20, 40</td>
<td>≤1.2</td>
</tr>
<tr>
<td><strong>Vytorin™ (ezetimibe/simvastatin)</strong></td>
<td>All Doses 10/80</td>
<td>1.8, 3.6</td>
</tr>
<tr>
<td><strong>Zocor® (simvastatin)</strong></td>
<td>20, 40, 80</td>
<td>~1.0</td>
</tr>
</tbody>
</table>
Statins and ALT/AST Abnormalities

**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 Statins in Someone with elevated 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%)
Statin-Associated Transaminase Elevations

• Progression to liver failure due to statins is exceedingly rare

• 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

### Statin Advisory: Monitoring Parameters, Follow-Up Schedule

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monitoring Schedule</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.

Prevention – Secondary Population LDL

LDLc (w/2FUPs) - Statin Tolerant

Baseline

Follow-Up
Prevention - Secondary Population LDL

LDLc (w/2FUPs) - Statin Intolerant

LDLc (mg/dL) Median (IQR)

Baseline

Follow - Up

## Statin Intolerance

Comparison of Lipoprotein percent Changes between different strategy groups  
\( a: p<0.05 \) compared to intermittent dosing; \( b: p<0.05 \) compared to daily dosing

<table>
<thead>
<tr>
<th>Lipoprotein change (%) LS Mean ± SE</th>
<th>Statin Discontinued n=442</th>
<th>Intermittent Statin Dosing n=142</th>
<th>Daily statin dosing n=1014</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>-8.8 ± 1.5&lt;sub&gt;ab&lt;/sub&gt;</td>
<td>-17.2 ± 2.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-21.2 ± 0.9</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-8.3 ± 2.2&lt;sub&gt;ab&lt;/sub&gt;</td>
<td>-21.3 ± 4.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-27.7 ± 1.4</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.2 ± 1.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.2 ± 2.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>TG</td>
<td>-15.1 ± 2.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-13.7 ± 5.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-21.1 ± 1.7</td>
</tr>
</tbody>
</table>

Comparison of Lipoprotein percent Changes between different rosuvastatin 2.5 to 5 mg strategy groups  
\( a: p<0.05 \) compared to intermittent dosing; \( b: p<0.05 \) compared to statin-discontinued group

<table>
<thead>
<tr>
<th>Lipoprotein change (%) LS Mean ± SE</th>
<th>Statin discontinued n=442</th>
<th>Once per week n=29</th>
<th>Twice per week n=28</th>
<th>Thrice per week n=31</th>
<th>More than trice per week n=9</th>
<th>daily n=158</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>-4.5±1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-9.2±4.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-3.1±4.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-13.8±5.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-20.3±8.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-19.7±2.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.9±2.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-12.0±6.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-10.5±6.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-16.8±7.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-25.4±12.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-27.6±3.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL-C</td>
<td>2.8±1.3</td>
<td>-2.1±3.7</td>
<td>4.0±3.4</td>
<td>2.0±3.8</td>
<td>0.1±6.9</td>
<td>0.3±1.6</td>
</tr>
<tr>
<td>TG</td>
<td>-4.4±2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-7.0±8.6</td>
<td>-10.0±7.8</td>
<td>-15.5±8.8</td>
<td>-24.0±16.1</td>
<td>-15.6±3.7</td>
</tr>
</tbody>
</table>
Statin Intolerance

Mampuya w et al. Abstract AHA 2011
Statin Intolerance

- Search for other causes
- Trial of different statin or stop and rechallenge at lower dose
- 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
Case: 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 no bruits
- Left femoral bruit
- No edema
### Case: Mr. Smith

**Laboratory Data**

<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>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>
</tbody>
</table>

- CBC normal
- Creatinine: 1.32 Complete metabolic panel otherwise normal
- Albumin/creatinine ratio of 56 mcg/mg
- Ankle brachial index (ABI) of 0.81 on left (normal >0.90)
- EKG: normal sinus rhythm, LVH by voltage criteria
- ABI was 0.84 on the left and 1.12 on the right

*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%)
Mortality in People with Diabetes

Causes of Death

65 to 75% of Mortality in diabetics is due to CVD

Type 2 Diabetes and Coronary Heart Disease

Seven-Year Incidence of Fatal/Nonfatal MI

- **No diabetes**
  - No DM, No MI: 3.5% (n=1304)
  - No DM, MI: 18.8% (n=69)

- **Diabetes**
  - DM, No MI: 20.2% (n=890)
  - DM, MI: 45% (n=169)

*P* < 0.001

Influence of Multiple Risk Factors on CV Mortality in Men With and Without Diabetes

Multiple Risk Factor Intervention Trial (MRFIT)

In a diabetic patient without CVD even the presence of a single risk factor confers a very high risk (80% lifetime risk of CVD).

Risk factors: cholesterol >200 mg/dL, smoking, and SBP >120 mm Hg. SBP=systolic blood pressure.

Goals in Management of CVD in Diabetics

• Prevent future adverse cardiovascular events
  – Correctly risk stratify patient
  – Identify and treat risk factors

• Improve symptomatic state
  – Enhance quality of life

• Identify extent of ischemia
  – Influence revascularization for morbidity and mortality benefits

• Identify subclinical disease
  – Intensify risk factor management
  – Earlier assessment for ischemia
Question

Initial management proven to reduce cardiovascular events should consist of all of the following EXCEPT:

1) 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
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 A$_{1c}$</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.

STENO-2: Reduction in Cardiovascular Disease Through a Multifactorial Intervention in Patients Who Have Type 2 Diabetes and Microalbuminuria

Intensive Treatment Goals: hemoglobin A\textsubscript{1c}, $<6.5\%$; cholesterol, $<175$ mg/dL; triglycerides, $<150$ mg/dL; systolic blood pressure, $<130$ mm Hg; diastolic blood pressure, $<80$ mm Hg.

STENO-2: Risk-Factor Targets Attained at 7.8 Years With an Intensive Treatment Program

- Average in intensive vs conventional group:
  - HbA1c: 7.9 vs 9.0
  - LDL-C: 83 vs 126 mg/dL
  - Systolic BP: 131 vs 146 mmHg

STENO-2: Lipid-lowering Therapy Accounted for More Than 70% of Cardiovascular Risk Reduction

Analysis of STENO-2 data based on the risk engine from the United Kingdom Prospective Diabetes Study (UKPDS)

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
**ADA/ACC 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<sup>1</sup> (mg/dL) | Non-HDL-C<sup>1</sup> (mg/dL) | apo B<sup>1</sup> (mg/dL) |
| **Highest-risk patients:** | | | |
| 1) Known CVD or 2) Diabetes plus one or more additional CVD risk factor(s) | <70 | <100 | <80 |
| **High-risk patients:** | | | |
| 1) No diabetes or known CVD but 2 or more major CVD risk factors or 2) Diabetes but no other CVD risk factors | <100 | <130 | <90 |

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

*Diabetes Care. 2008;31 811-822.*
How would you initially treat this patient’s lipids?

1) Atorvastatin 40 mg/d
2) Simvastatin 20 mg/d plus Fenofirate 148 mg/d
3) Extended release niacin 2000 mg/d
4) Simvastatin 10 mg/d
5) Ezetimibe 10 mg/d
6) Addition of Pioglitazone
7) Omega 3 Fish oil 4000 mg/d
## Benefits of Aggressive LDL-C Lowering in Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary event rate (%)</th>
<th>Aggressive lipid-lowering</th>
<th>Difference in LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>better</td>
</tr>
<tr>
<td><strong>ASCOT-LLA</strong></td>
<td>Diabetes, HTN</td>
<td>9.2</td>
<td>11.9</td>
</tr>
<tr>
<td><strong>CARDS</strong></td>
<td>Diabetes, no CVD</td>
<td>5.8</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>HPS</strong></td>
<td>All diabetes</td>
<td>9.4</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Diabetes, no CVD</td>
<td>9.3</td>
<td>13.5</td>
</tr>
<tr>
<td><strong>TNT</strong></td>
<td>Diabetes, CHD</td>
<td>13.8</td>
<td>17.9</td>
</tr>
</tbody>
</table>

*Atorvastatin 10 vs 80 mg/day
\(^\dagger\)Statin vs placebo

---

Lipid Management in Diabetes: Meta-analyses

• BMJ 338: 2009
  – 10 Trials: >16,000 with DM compared to >54,000 without DM receiving standard statin therapy for 4.1 years
  – LDL of 140, age 63
  – Similar 30% CHD, 19% CVA, 12% mortality in both groups

• Lancet 371: 2008
  – 14 Trials: 6,956 DM with CVD compared to 11,703 without CVD
  – LDL of 132, age 64
  – Similar 22% CHD, 21% CVA, 9% mortality in both groups

• Lancet 376: 2010
  – 5 trials: 39,612 individuals with 5.1 years f/u
  – Further 15% reduction in CV risk for 0.51 mmol/L LDL reduction
  – Similar to proportional reductions of statin vs. control trials
  – Independent of baseline LDL-C
Question

Does statin therapy increase the risk of developing diabetes

1) True
2) False
Statins and Diabetes Risk

• 2012: FDA warns of small increase in blood sugar levels and type 2 diabetes with statins
• However, increase in blood sugar did not diminish the effect of statins on reducing heart disease risk.

• Conflicting results in randomized trials:
  • PROSPER: 32% increase risk of diabetes in elderly
  • JUPITER: 27% increase risk of investigator reported diabetes in rosuvastatin treated patients
  • WOSCOPS: pravastain might reduce frequency of diabetes
  • PROVE-IT: substudy: worse glycemic control with high dose atorvastatin

Sattar et al. Lancet. 2010; 375: 735-42
Statins and Diabetes Risk

• Sattar: meta-analysis of 13 statin trials in 91,140 patients
  – 4278 developed diabetes: 4.89% vs. 4.5% (.39% difference; 174 cases)
  • 9% increased risk of incident diabetes
  • ~1 additional case per 1000 patient-years
  – Highest in older patients but not influenced by statin type, BMI or change in LDL-C

• Preiss: meta-analysis of 5 trials in 32772 patients. High vs moderate dose ev
  – 2749 developed diabetes: 8.8% vs. 8.4% (.4% difference; 149 cases)
  • 12% increased risk of diabetes: 16% reduction in CVD
  • 2 additional cases per 1000 patient years
  – Not influenced by age, BMI, fasting glucose

• Risk is low in both absolute terms and when compared to reduction in CV risk

Sattar et al. Lancet. 2010; 375: 735-42
Preiss et al. JAMA. 2011; 305: 2556-64
Statins and Diabetes Risk: Clinical Implications

- Sattar and Data from Cholesterol Treatment Trialists (CTT) of 71,370 non-diabetics
  - 5.4 less cardiac events (not including stroke or revascularization) for 255 patients treated for 4 years for each 1 mmol/L reduction in LDL-C
  - One extra case of diabetes treating 255 patients for 4 years.

- Preiss:
  - One additional case of diabetes for every 498 patients over 1 year
  - One fewer CVD event for every 155 patients over 1 year

- Questions:
  - Statin type: Hydrophilic vs. lipophilic
  - Statin dose related or aggressiveness of LDL-C lowering
  - Differential effects in different populations; elderly, metabolic syndrome, asian
  - Diabetes or increased in blood sugar
  - Association vs. causality

- The small increase risk of diabetes is outweighed by the reduction in CV risk in those for whom statin therapy is recommended

- Despite the increased in diabetes, the reduction in CVD risk is maintained across groups.
Diabetic Patients Have Particularly High Residual CVD Risk After Statin Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Event Rate (No Diabetes)</th>
<th>Event Rate (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Statin</td>
<td>On Placebo</td>
</tr>
<tr>
<td>HPS(^1*) (CHD patients)</td>
<td>19.8%</td>
<td>25.7%</td>
</tr>
<tr>
<td>CARE(^2\dagger)</td>
<td>19.4%</td>
<td>24.6%</td>
</tr>
<tr>
<td>LIPID(^3\dagger)</td>
<td>11.7%</td>
<td>15.2%</td>
</tr>
<tr>
<td>PROSPER(^4\dagger)</td>
<td>13.1%</td>
<td>16.0%</td>
</tr>
<tr>
<td>ASCOT-LLA(^5\dagger)</td>
<td>4.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>TNT(^6\dagger)</td>
<td>7.8%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

\(^{*}\)CHD death, nonfatal MI, stroke, revascularizations  
\(^{\dagger}\)CHD death, nonfatal MI, CABG, PTCA  
\(^{\ddagger}\)CHD death and nonfatal MI  
\(^{\S}\)CHD death, nonfatal MI, stroke  
\(^{\|}\)CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg versus 10mg atorvastatin)

LDL Particle Number Distribution in T2DM Patients with Low LDL-C

LDL-C 71-99 mg/dL (n=1,484)

LDL-C ≤70 mg/dL (n=871)

AHA Scientific Sessions, 2005
Major Cardiovascular Events on Statins: by HDL-C and Triglycerides

### TNT

<table>
<thead>
<tr>
<th>Quintile of HDL Cholesterol Level (mg/dL)</th>
<th>No. of events</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (&lt;37)</td>
<td>57</td>
<td>473</td>
</tr>
<tr>
<td>Q2 (37 to &lt;42)</td>
<td>50</td>
<td>525</td>
</tr>
<tr>
<td>Q3 (42 to &lt;47)</td>
<td>34</td>
<td>550</td>
</tr>
<tr>
<td>Q4 (47 to &lt;55)</td>
<td>34</td>
<td>569</td>
</tr>
<tr>
<td>Q5 (≥55)</td>
<td>36</td>
<td>544</td>
</tr>
</tbody>
</table>

5-Year Risk of Major CV Events (%) in Patients With LDL-C <70 mg/dL

Hazard ratio (95% CI) versus Q1
- Q2: 0.85 (0.57–1.25)
- Q3: 0.57 (0.36–0.88)
- Q4: 0.55 (0.35–0.86)
- Q5: 0.61 (0.38–0.97)

### CARE and LIPID

- Slope = 0.029, P < 0.001
- Slope = 0.018, P = 0.02

CVD Event Rate*

- Placebo
- Pravastatin

N = 13,173

*CHD death, nonfatal MI, CABG, PTCA

Triglyceride mg/dL

Mechanisms Relating Insulin Resistance and Dyslipidemia

Fat Cells

Liver

\[ \text{Insulin Resistance (IR)} \]

\[ \text{FFA} \]

\[ \text{VLDL-TG} \]

\[ \text{Apo B} \]

\[ \text{Apo C-III} \]

\[ \text{CETP} \]

\[ \text{VLDL} \]

\[ \text{HDL} \]

\[ \text{LDL} \]

\[ \text{SD LDL} \]

\[ \text{(lipoprotein or hepatic lipase)} \]

Kidney

\[ \text{Apo A-1} \]
Lipids in Diabetic and Nondiabetic Subjects

NHANES III
N = 2844

<table>
<thead>
<tr>
<th></th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td></td>
<td>HDL-C</td>
</tr>
<tr>
<td>VLDL</td>
<td></td>
<td>Apo A-1</td>
</tr>
<tr>
<td>LDL-P and Small Dense LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IVUS: Benefit of Combination HDL Raising and LDL Lowering with Statins

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>% Change HDL-C</th>
<th>Change Atheroma Volume (mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;87.5</td>
<td>&gt;7.5</td>
<td>-10.0</td>
</tr>
<tr>
<td>&lt;87.5</td>
<td>&lt;7.5</td>
<td>-7.5</td>
</tr>
<tr>
<td>&gt;87.5</td>
<td>&gt;7.5</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;87.5</td>
<td>&lt;7.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

P<0.001 for trend

Cardiovascular events occur in individuals with treated LDL-C
  - Still occur in treatment groups after LDL lowering with statins
  - Patients with diabetes on statins, have CVD event rates 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
    • Progression in DM more strongly related to TG/HDL ratio

Impact of other atherogenic particles including low or abnormally functioning HDL, VLDL remnants, triglycerides, small dense LDL
  - Independent risk of low HDL, elevated triglycerides
  - Non-HDL-C, Apo B, LDL-C particle number Apo B/Apo A1 ratio better predictor of risk
  - On Rx non-HDL and Apo B better predictor of recurrent events

Epidemic of obesity, diabetes, metabolic syndrome and associated high risk combined dyslipidemic
Management of Dyslipidemia beyond LDL

• Lifestyle changes and secondary causes

• Pharmacologic therapy
  – Fibrate
  – Niacin
  – Ezetimibe
  – Resins
  – Omega-3 fatty acids
  – PPAR-γ or -α agonists

• Secondary causes of Hypertriglyceridemia
  – Nephrotic syndrome
  – Diabetes mellitus
  – Hypothyroidism
  – Medications (Estrogens, Tamoxifen, Beta-blocker, Cyclosporin, asparaginase, accutane)
The following statements are true except:

1) Possible concerns with niacin use include risk of gout and worsening glucose control

2) Controlled clinical trials have demonstrated a statistically significant CVD event benefit in all diabetics when niacin/fibrate is added to statins

3) Combination therapy has been shown to favorable effect some surrogate markers for cardiovascular disease outcomes

4) Fibrates should be used with caution with statins due to increased risk of myopathy

5) TZD’s favorably benefit the lipid profile
# Fibrate Trials

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Drug</th>
<th>Duration</th>
<th>ΔLDL</th>
<th>ΔTG</th>
<th>ΔHDL</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>

The ACCORD Trial
Lipid Study

5518 patients followed for 4.7 years

Mean Total Cholesterol

Mean LDL-C

Mean HDL-C

Median Triglycerides

No of participants
Fenofibrate  Placebo
Fenofibrate  Placebo

The ACCORD Trial
Lipid Study

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%

Comparison of ACCORD subgroup results with those from prior fibrate studies

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (P-value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: Subgroup</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>-71% (0.005)</td>
</tr>
<tr>
<td>Circ 1992;85:37-45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP (Bezafibrate)</td>
<td>-7% (0.24)</td>
<td>TG &gt; 200 mg/dl</td>
<td>-40% (0.02)</td>
</tr>
<tr>
<td>Circ 2000;102:21-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIELD (Fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG &gt; 204 mg/dl and HDL-C &lt; 42 mg/dl</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>DMCare 2009;32:493-8.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-8% (0.32)</td>
<td>TG &gt; 204 mg/dl and HDL-C ≤ 34 mg/dl</td>
<td>-31%</td>
</tr>
</tbody>
</table>

Circ 1992;85:37-45
Circ 2000;102:21-7
DMCare 2009;32:493-8.
ADVENT: Niacin ER Effects on HbA₁C in Patients With Type 2 Diabetes

N = 148, 47% were receiving concomitant statin therapy
*Versus placebo at 16 weeks

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

*6-year follow-up

Interactive P-value = NS

30% Reduction

24% Reduction

25% Reduction

57% Reduction

Nonfatal MI Event Rate, %

Baseline Fasting Plasma Glucose, mg/dL

Placebo
Niacin

ARBITER 3: 24 Months

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

Change in CIMT, mm

* P<.001 versus statin monotherapy

Incremental Benefit of Niacin Added to Statin Therapy

- AIM-HIGH was designed to test whether the addition of niacin to statin (+ ezetimibe) would provide an additional 25% reduction in CV events in patients with stable, non-acute, established CV disease with well controlled LDL-C

- On May 26, 2011 the NHLBI announced that the AIM-HIGH Study was stopped for Futility (lack of efficacy) based on interim results
  - The interim analysis concluded that the trial would not be able to show a significant difference in CV outcome event rates between the two study arms

- The levels of ischemic stroke were low overall, though more were observed in the niacin plus simvastatin arm

- HPS-2 THRIVE is ongoing
ADA Lipid Goals and Recommendations: 2011

- Lifestyle modifications

- Primary LDL-C goal < 100 mg/dL; LDL-C < 70 mg/dL is an option
  - In individuals without overt CVD, the primary goal is an LDL cholesterol <100 mg/dl, <70 mg/dL is option if one or more RF’s
  - In individuals with overt CVD, a lower LDL cholesterol goal of 70 mg/dl, using a high dose of a statin, is a reasonable option.

- Statin therapy added to lifestyle changes, regardless of baseline LDL-C, if
  - Overt CVD
  - Without CVD but age > 40 yr + 1 or more other CVD risk factors

- Without overt CVD and age < 40 yr:
  - Consider statin if LDL-C > 100 mg/dL or multiple risk factors, despite lifestyle therapy

- In drug-treated patients, a reduction in LDL-C of ~30–40% from baseline

- TG’s < 150 mg/dL, HDL-C > 40 mg/dL (men), > 50 mg/dL (women): desirable
  - Combination therapy to achieve lipid goals may be needed but outcome studies needed

*Diabetes Care. 20011;34 (suppl1):S11-S61.*
# ADA Lipid Goals and Recommendations: 2011

<table>
<thead>
<tr>
<th></th>
<th>First Priority</th>
<th>Second Priority</th>
</tr>
</thead>
</table>
| **LDL-C Lowering** | Therapeutic Lifestyle changes  
<100 mg/dL  
<70 mg/dL optional  
Statins | Additional adjunctive lipid therapies                                       |
| **HDL-C Raising**  | Therapeutic Lifestyle changes  
>40 mg/dL-men  
>50 mg/dL-women  
Statins | Additional adjunctive lipid therapies                                       |
| **TG Lowering**   | Glycemic control  
Statins  
Therapeutic lifestyle changes  
- Weight loss  
- Increased physical activity  
-Smoking cessation | Additional adjunctive lipid therapies                                       |

*Diabetes Care. 2011;34 (suppl1):S11-S61.*
Lipid Management in Patients with Diabetes

Obtain Fasting Lipid Profile

- LDL-C >100
  - Lifestyle + Statin Rx
  - Goal: LDL <100 mg/dL
- Triglycerides >500
  - Lifestyle
  - Fibrates, niacin, fish oil
- CVD or ≥ 1 RF *
  - Intensify statin Rx **
  - Goal: LDL <70 mg/dL
- No CVD or RF
  - Statin Rx if LDL >100 mg/dL
  - Goal: LDL-C <100 mg/dL

* If CVD or 40 yo with ≥1 RF consider statin therapy regardless of baseline LDL

** If not at LDL goal on maximally tolerated statin consider addition of ezetimibe, colesevelam, niacin
Lipid Management in Patients with Diabetes

Measure Non-HDL-C, Apolipoprotein B, LDL particle number

CVD or ≥ 1 RF
- Non-HDL-C <100 mg/dL
- Apolipoprotein B <80 mg/dL
  - Intensify statin Rx or add fibrate or niacin

No CVD or RF
- Non-HDL-C <130 mg/dL
  - Yes
  - Apolipoprotein B <90 mg/dL
    - Intensify statin Rx or add fibrate or niacin

Continue current therapy

If LDL at goal: further Non-HDL or Apo B lowering with aggressive lifestyle intervention, glucose management, increase statin, niacin, fibrates, fish oil
NHANES 1999-2006
Proportion of Diabetics Achieving RF Goals

* Age adjusted

Case: Matthew R

History, Physical Exam & Laboratory Data

- 11-year-old white male
- Otherwise healthy
- Admits to sedentary lifestyle
- Pediatrician obtained screening lipid panel due to Family History:
  - Father with HL and history of MI and stent age 47
- Medications
  - none
- Physical examination
  - 59.5˝, 104 lb
  - BMI = 20.8 (93th %)
  - BP: 110/70
  - No xanthomas

Baseline* (fasting levels)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C</td>
<td>251</td>
</tr>
<tr>
<td>LDL-C</td>
<td>189</td>
</tr>
<tr>
<td>HDL-C</td>
<td>41</td>
</tr>
<tr>
<td>TG</td>
<td>106</td>
</tr>
<tr>
<td>Glucose</td>
<td>89</td>
</tr>
<tr>
<td>TSH</td>
<td>1.2</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>200</td>
</tr>
<tr>
<td>LP(a)</td>
<td>75</td>
</tr>
</tbody>
</table>

*Represent results of second lipid panel.

C = cholesterol; TG = triglycerides; HbA$_{1c}$ = hemoglobin A$_{1c}$;
nl = normal; TSH = thyroid-stimulating hormone.
Lipid Management in Children

• What are acceptable lipid levels in children?
• How aggressively to treat?
• Is lowering cholesterol with drugs safe?
• How early to start?

• Questions:
  – Screening
  – When to initiate medications
  – Defining high risk groups
# Lipid Levels for Children and Adolescents

<table>
<thead>
<tr>
<th>Category</th>
<th>Acceptable (mg/dL)</th>
<th>Borderline (mg/dL)</th>
<th>High (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Chol</td>
<td>&lt;170</td>
<td>170-199</td>
<td>≥200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;110</td>
<td>110-129</td>
<td>≥130</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>&lt;123</td>
<td>123-143</td>
<td>≥144</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>&lt;90</td>
<td>90-109</td>
<td>≥110</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9 years</td>
<td>&lt;75</td>
<td>75-99</td>
<td>≥100</td>
</tr>
<tr>
<td>10-19 years</td>
<td>&lt;90</td>
<td>90-129</td>
<td>≥130</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;45</td>
<td>35-45</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>&gt;120</td>
<td>110-120</td>
<td>&lt;110</td>
</tr>
</tbody>
</table>
Cholesterol in Youth

- Cholesterol lowest intrauterine and at birth
- Concentrations similar to young adults by 2 years of age
- Decrease 10 to 20% during pubertal development
- Strongest relation to adult levels at 5 to 10 years and 17 to 19 years

- Hyperlipidemia common
  - Child and Adolescent Trial for CV Health: 13.3% 4th graders had TC >200
  - NHANES: 10% of adolescents had TC >200
  - Increase in obesity and metabolic syndrome

- Efficacy and safety of stains similar to that in adults
  - Including prepubertal and between 8 and 10 years
- No effect on sexual or physical maturation
- Impact on atherosclerotic process: FMD and CIMT
- Impact on clinical outcomes lacking: Extrapolation from adult studies
  - No outcome studies to show that treatment in childhood decreases adult CVD
2008 AAP Recommendations

• Population approach to healthful diet to all children >2 years
  – Studies in ages 7 months to adolescents have shown safety of low total fat, saturated fat and cholesterol diets

• Individual approach for those at higher risk for CVD and high LDL
  – Screen earlier between 2 and 10 years
    – FHx of CVD or dyslipidemia (parents or grandparents <55)
    – FHx not known and other RF’s (overweight, obese, HTN, smoking, DM)
  – Fasting lipid profile
  – Retest 3 to 5 years if normal range
2008 AAP Guideline Recommendations

- Earlier start age (for screening and treatment)
- Emphasis on overweight, high TG and low HDL
  - Lifestyle management, weight management
- Change in primary treatment choice: statins rather than resins
- Lower LDL cutpoints dependent on risk

<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>

- For individuals over 8 years of age, pharmacologic therapy considered
  - Fiber up to 20 gm/day/Plant stanols/sterols
- Other high risk patients: Transplantation, HIV, Chronic inflammatory disease (SLE, RA), Renal disease, nephrotic syndrome, Kawasaki Disease, Childhood cancer survivors

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