Hyperlipidemia in Kids: To Treat or Not to Treat

CHRIS FEDDOCK, MD, MS, FAAP, FACP

Objectives

- Review the screening recommendations for hyperlipidemia
- Discuss the risk stratification approach to the treatment of hyperlipidemia
- Discuss effective therapy
Childhood Dyslipidemia Screening

- Positive family history of dyslipidemia or premature CVD (< 55 years for men or < 65 years for women)
- Family history is not known
- Other CVD risk factors:
  - Overweight (BMI 85th to <95th percentile)
  - Obesity (BMI 95th percentile)
  - Hypertension (blood pressure > 99th percentile)
  - Cigarette smoking
  - Diabetes mellitus

AAP Guidelines

- Screen between 2 and 10 years of age
- Fasting lipid profile is recommended
- Normal values → retest every 3 to 5 years
Bogalusa Heart Study

- Association between Multiple Cardiovascular Risk Factors and Atherosclerosis in Children and Young Adults

- Risk factors for atherosclerosis:
  - Values > 75th percentile for the study group
  - Body-mass index
  - Systolic blood pressure
  - Triglyceride concentration
  - LDL cholesterol concentrations


The Prevalence of Fibrous-Plaque Lesions

Effect of Multiple Risk Factors

Pday
Pathobiological Determinants of Atherosclerosis in Youth

- Effects of Nonlipid Risk Factors on Atherosclerosis in Youth With a Favorable Lipoprotein Profile
- Risk of advanced plaque in LAD
  - Male sex (n=311) OR=4.09 (1.71–9.81) *
  - Smoking (n=253) OR=0.99 (0.60–1.62)
  - Hypertension (n=78) OR=1.22 (0.67–2.24)
  - Obesity (n=37) OR=3.72 (1.73–8.04) *
  - Elevated HgbAlc (n=20) OR=1.78 (0.64–4.96)
Intimal Surface Involvement

High Risk
Smokers
Hypertensive
BMI > 30 kg/m²
HgbAlc < 8%

Circulation 2001;103:1546-50.

NHANES III (1988-1994) Total Cholesterol

<table>
<thead>
<tr>
<th>Ages</th>
<th>50th Percentile</th>
<th>75th Percentile</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
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<td>4-5</td>
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<td>16-19</td>
<td>158</td>
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</tbody>
</table>

Therapeutic Lifestyle Change

- **Stage 2 diet**
  - Saturated fats < 7% of total calories
  - Cholesterol < 200 mg/d
  - Total fat 25-35% of total calories

- **Therapeutic options for enhancing LDL lowering**
  - Plant stanols/sterols (2 g/d)
  - Increased viscous (soluble) fiber (10-25 g/d)

- **Weight reduction**
- **Increased physical activity**

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**TABLE 2** Lipid and Lipoprotein Distributions in Subjects Aged 5 to 19 Years

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th></th>
<th>Females</th>
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<tbody>
<tr>
<td></td>
<td>5–9 y</td>
<td>10–14 y</td>
<td>15–19 y</td>
<td>5–9 y</td>
<td>10–14 y</td>
<td>15–19 y</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>50th percentile</td>
<td>153</td>
<td>161</td>
<td>152</td>
<td>164</td>
<td>159</td>
<td>157</td>
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<tr>
<td>75th percentile</td>
<td>168</td>
<td>173</td>
<td>168</td>
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<tr>
<td>90th percentile</td>
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<td>183</td>
<td>189</td>
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<tr>
<td>95th percentile</td>
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<td>201</td>
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<tr>
<td>Triglyceride, mg/dL</td>
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<tr>
<td>50th percentile</td>
<td>48</td>
<td>58</td>
<td>68</td>
<td>57</td>
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<td>75th percentile</td>
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<td>112</td>
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<tr>
<td>95th percentile</td>
<td>85</td>
<td>111</td>
<td>143</td>
<td>120</td>
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<tr>
<td>LDL, mg/dL</td>
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<td></td>
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<tr>
<td>50th percentile</td>
<td>90</td>
<td>94</td>
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<td>122</td>
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<tr>
<td>95th percentile</td>
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<td>133</td>
<td>130</td>
<td>140</td>
<td>136</td>
<td>137</td>
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<tr>
<td>HDL, mg/dL</td>
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<td></td>
</tr>
<tr>
<td>5th percentile</td>
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<td>37</td>
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<tr>
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<td>25th percentile</td>
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<td>52</td>
<td>52</td>
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</tbody>
</table>

*Adapted from the Lipid Research Clinic Pediatric Prevalence Study.*
Special Turku Coronary Risk Factor Intervention Project

• 1062 healthy infants in Finland
• Intervention group
  o Breastmilk or formula for the first 12 months
  o After: protein 10-15%, carbohydrates 50-60%, and fat 30-35%
    × Skim milk 0.5-0.6 liters daily
    × Replace milk fat with 2-3 teaspoons of oil or soft margarine daily
    × Encouraged lean meat products (fish 1-2x per week)
    × Low-fat dairy
    × Ample vegetables
• Control group
  o At least 2% milk after the first 12 months


STRIP Study Follow-Up

• Throughout childhood and adolescence
  o Dietary intake
  o Serum cholesterol values
  o Somatic growth
  o Development

• Outcomes
  o Reduced total and saturated fat intake
  o Decreased serum cholesterol
  o Normal cognitive, motor & psychosocial development
  o Normal growth and pubertal development

Dietary Intake

Total Serum Cholesterol

Dietary Options

- **Low-Fat Diet**
  - 1500 kcal per day for women and 1800 kcal per day for men
  - 30% of calories from fat (10% of calories from saturated fat, 300 mg of cholesterol per day)

- **Mediterranean Diet**
  - 1500 kcal per day for women and 1800 kcal per day for men
  - 35% of calories from fat: 30-45 g of olive oil and < 20 g of nuts daily
  - Replace beef and lamb with poultry and fish

- **Low-Carbohydrate Diet**
  - 20 g of carbohydrates per day for the 2-month induction phase
  - Gradual increase to a maximum of 120 g per day
  - Intakes of total calories, protein, and fat were not limited
  - Counseled to choose vegetarian sources of fat and protein

Hyperlipidemia Therapy

- **Overweight or Obese with ↑ triglyceride or ↓ HDL**
  - Improvement of diet with nutritional counseling
  - Increased physical activity
- **Pharmacotherapy for patients 8 years and older**
  - LDL > 190 mg/dL
  - LDL > 160 mg/dL
    - Family history of early heart disease
    - 2 additional risk factors present
  - LDL > 130 mg/dL if diabetes mellitus

Goals of Pharmacotherapy

- Initial goal is to lower LDL to <160 mg/dL
- Targets as low as 130 mg/dL or even 110 mg/dL
  - Strong family history of CVD with other risk factors
    - Obesity
    - Diabetes mellitus
    - Metabolic syndrome
### Drug Class Effects

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>↓15-30%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>↓10-25%</td>
<td>↑15-35%</td>
<td>↓25-30%</td>
</tr>
<tr>
<td>Statins</td>
<td>↓20-60%</td>
<td>↑5-10%</td>
<td>↓10-33%</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>↓10-15%</td>
<td>↑15-25%</td>
<td>↓35-50%</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓6-20%</td>
<td>↑18-33%</td>
<td>↓41-53%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓17%</td>
<td>0</td>
<td>0</td>
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</table>

### Studies of Statins in Children

## Treatment Effects of Statins in Children

<table>
<thead>
<tr>
<th>N=</th>
<th>Condition</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>Heterozygous FH</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>Heterozygous FH</td>
</tr>
<tr>
<td>3</td>
<td>132</td>
<td>Heterozygous FH</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>FHx of hyperlipidemia or premature CVD</td>
</tr>
<tr>
<td>5</td>
<td>173</td>
<td>Heterozygous FH</td>
</tr>
<tr>
<td>6</td>
<td>187</td>
<td>FH, LDL &gt; 190, LDL &gt; 160 + risk</td>
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<tr>
<td>7</td>
<td>214</td>
<td>Familial Hypercholesterolemia</td>
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<td>8</td>
<td>54</td>
<td>Heterozygous FH</td>
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<td>9</td>
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<td>Heterozygous FH</td>
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<td>10</td>
<td>25</td>
<td>Kidney Disorders</td>
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## Treatment Effects of Statins in Children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1 Pravastatin 20mg vs. placebo</td>
<td>12 weeks</td>
<td>LDL ↓ 33%</td>
</tr>
<tr>
<td>2 Lovastatin 10, 20, 30 or 40 mg</td>
<td>8 weeks</td>
<td>LDL ↓ 21-36%</td>
</tr>
<tr>
<td>3 Lovastatin 40mg vs. placebo</td>
<td>48 weeks</td>
<td>LDL ↓ 25%</td>
</tr>
<tr>
<td>4 Pravastatin 10mg + colestipol vs. colestipol</td>
<td>18 weeks</td>
<td>LDL ↓ 17%</td>
</tr>
<tr>
<td>5 Simvastatin 40mg vs. placebo</td>
<td>48 weeks</td>
<td>LDL ↓ 41%</td>
</tr>
<tr>
<td>6 Atorvastatin 10/20 vs. placebo</td>
<td>26 weeks</td>
<td>LDL ↓ 40%</td>
</tr>
<tr>
<td>7 Simvastatin 20/40 vs. placebo</td>
<td>2 years</td>
<td>LDL ↓ 24%</td>
</tr>
<tr>
<td>8 Lovastatin 40mg vs. placebo</td>
<td>20 weeks</td>
<td>LDL ↓ 27%</td>
</tr>
<tr>
<td>9 Simvastatin 40 mg vs. simvastatin + ezetimibe</td>
<td>53 weeks</td>
<td>LDL ↓ 50%</td>
</tr>
<tr>
<td>10 Simvastatin 10/20 vs. placebo</td>
<td>3 months</td>
<td>LDL ↓ 34%</td>
</tr>
</tbody>
</table>
Carotid Intima Media Thickness (IMT)

  - 214 children with heterozygous FH followed for 2 years
    - Randomized to pravastatin vs. placebo
  - Outcomes
    - 24% decrease in LDL
    - IMT change = 0.041 mm with pravastatin (p = 0.02)

  - 85 children with heterozygous FH followed for 2 years
    - All given fluvastatin 80mg daily
  - Outcomes
    - 34% decrease in LDL
    - No change in IMT

Comparative Efficacy

*UpToDate. May 2008.*
Childhood Risk Factors for Premature Death

- 4857 children & adolescents (5-19 years)
  - Gila River Indian Community in Arizona
  - At least 4/8 Pima or Tohono O’odham Indians
  - 1394 (28.7%) were obese (BMI > 95th percentile)

- 559 (11.5%) premature deaths (< 55 years of age)
  - 59 from alcoholic liver disease
  - 22 from cardiovascular disease
  - 21 from infections
  - 12 from cancer
  - 10 from diabetes or diabetic nephropathy
  - 9 from acute alcoholic poisoning or drug overdose


Incidence Risk Ratios for Endogenous Death

<table>
<thead>
<tr>
<th></th>
<th>2nd Quartile (95% CI)</th>
<th>3rd Quartile (95% CI)</th>
<th>4th Quartile (95% CI)</th>
<th>P-value (95% CI)</th>
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<tbody>
<tr>
<td>BMI</td>
<td>1.24 (0.77-2.00)</td>
<td>1.28 (0.78-2.09)</td>
<td>2.30 (1.46-3.62)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>OGTT</td>
<td>1.43 (0.88-2.30)</td>
<td>1.24 (0.75-2.04)</td>
<td>1.73 (1.09-2.74)</td>
<td>0.12</td>
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<tr>
<td>SBP</td>
<td>0.75 (0.43-1.30)</td>
<td>1.26 (0.77-2.07)</td>
<td>1.34 (0.83-2.15)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.11 (0.71-1.75)</td>
<td>1.11 (0.71-1.75)</td>
<td>1.28 (0.81-2.02)</td>
<td>0.77</td>
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</table>

BMI & Premature Death


Statin Primary Prevention Studies

- West of Scotland Coronary Prevention Study Group
  - Pravastatin 40 mg
  - 6595 patients – all men
- AFCAPS/TexCAPS trial
  - Lovastatin 20/40 mg
  - 6605 patients
- ASCOT-LLA trial
  - Atorvastatin 10 mg
  - 10,305 patients
West of Scotland

- 6595 Men
  - Cholesterol > 252 mg/dl
    - Mean cholesterol 272 mg/dl
  - LDL > 155 mg/dl despite diet
    - Mean LDL cholesterol 192 mg/dl
- **Pravastatin 40mg qday**
  - Cholesterol ↓ 20%
  - LDL ↓ 26%
  - Triglyceride ↓ 12%
  - HDL ↑ 5%
- **5-Year Follow-Up**


```
<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=3293)</th>
<th>Pravastatin (n=3302)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD-related death or nonfatal MI</td>
<td>7.9%</td>
<td>5.5%</td>
<td>2.4%</td>
<td>42</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>6.5%</td>
<td>4.6%</td>
<td>1.9%</td>
<td>53</td>
</tr>
<tr>
<td>CHD-related death</td>
<td>1.7%</td>
<td>1.2%</td>
<td>0.5%</td>
<td>NS</td>
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</tbody>
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West of Scotland Long-Term Follow-Up

- **10-year follow-up after trial completion**
  - 38.7% of statin group taking a statin
  - 35.2% of placebo group taking a statin

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=3293)</th>
<th>Pravastatin (n=3302)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD-related death or nonfatal MI</td>
<td>15.5%</td>
<td>11.8%</td>
<td>3.7%</td>
<td>27</td>
</tr>
<tr>
<td>CHD-related death or hospitalization</td>
<td>25.8%</td>
<td>20.5%</td>
<td>5.3%</td>
<td>20</td>
</tr>
<tr>
<td>Stroke (fatal or nonfatal)</td>
<td>6.8%</td>
<td>5.9%</td>
<td>1.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>


AFCAPS/TexCAPS

- **6605 patients – 997 postmenopausal women**
  - Men ages 45-73 OR Women ages 55-73
  - Cholesterol 180-264 mg/dl
    - Mean cholesterol 221 mg/dl
    - Mean LDL cholesterol 150 mg/dl
  - HDL < 45 mg/dl (men) or < 47 mg/dl(women)
  - Triglycerides < 400 mg/dl
- **Lovastatin 20 to 40 mg daily**
  - Cholesterol ↓ 18%
  - LDL ↓ 25%
  - Triglyceride ↓ 15%
  - HDL ↑ 6%
- **Follow-up 5.2 years (0.2-7.2 years)**

### AFCAPS/TexCAPS

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Placebo (n=3301)</th>
<th>Lovastatin (n=3304)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event – MI, unstable angina, sudden cardiac death</td>
<td>10.9%</td>
<td>6.8%</td>
<td>4.1%</td>
<td>24</td>
</tr>
<tr>
<td>MI (fatal and nonfatal)</td>
<td>5.6%</td>
<td>3.3%</td>
<td>2.3%</td>
<td>43</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>5.1%</td>
<td>3.5%</td>
<td>1.6%</td>
<td>63</td>
</tr>
<tr>
<td>Revascularization</td>
<td>9.3%</td>
<td>6.2%</td>
<td>3.1%</td>
<td>32</td>
</tr>
</tbody>
</table>


### ASCOT-LLA

- **10,305 patients – 1942 women**
  - Hypertensive
  - Cholesterol < 251 mg/dl
    - Mean cholesterol — 213 mg/dL
    - Mean LDL cholesterol — 131 mg/dL
    - Mean HDL cholesterol — 50 mg/dL
  - 3 or more risk factors:
    - Left ventricular hypertrophy
    - Type 2 diabetes
    - Peripheral vascular disease
    - Previous stroke or transient ischemic attack
    - Age 55 or older
    - Microalbuminuria or proteinuria
    - Smoking
    - Ratio of total to HDL cholesterol of 6 or higher
    - Family history of CHD
    - Male Sex
- Follow-up 3.3 years (stopped early)

ASCOT-LLA

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=3301)</th>
<th>Lovastatin (n=3304)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death and Nonfatal MI</td>
<td>9.4%</td>
<td>6.0%</td>
<td>3.4%</td>
<td>29</td>
</tr>
<tr>
<td>Total CV events and procedures</td>
<td>30.6%</td>
<td>24.1%</td>
<td>6.5%</td>
<td>15</td>
</tr>
<tr>
<td>Stroke (fatal and nonfatal)</td>
<td>7.4%</td>
<td>5.4%</td>
<td>2.0%</td>
<td>50</td>
</tr>
</tbody>
</table>


Cholesterol (NCEP)

- **Screen all adults aged 20 years or older with a fasting lipoprotein profile**
  - If the testing opportunity is nonfasting, only the values for total cholesterol and HDL cholesterol will be usable
  - In such a case, if total cholesterol is 200 mg/dL or HDL is <40 mg/dL, a follow-up lipoprotein profile is needed for appropriate management based on LDL.
- **Repeat testing once every 5 years**
Cholesterol (USPSTF)

- **Men**
  - Strong recommendation for > age 35 “A”
  - Recommendation for aged 20 to 35 if at increased risk for CAD “B”

- **Women**
  - Strong recommendation for > age 45 “A”
  - Recommended for aged 20 to 45 if at increased risk for CAD “B”


Muscle Injury with Statins

- **Myalgias** – 5%
- **Myositis** – 0.1-0.5%
  - CK > 100x ULN
  - Discontinue statin use
- **Rhabdomyolysis** – 0.01%
### Rhabdomyolysis with Statins

- **Incidence 4 per 100,000**
  - Atorvastatin
  - Simvastatin
  - Lovastatin
- **Incidence of 1 per 100,000**
  - Fluvastatin
  - Pravastatin
- **Gemfibrozil has incidence of 28 per 100,000**
  - 15x greater risk than fenofibrate

*Am J Cardiol. 2006;97:52C–60C.*

### Liver Disease with Statins

- **Elevated ALT (> 3x ULN or > 120 mg/dl)**
  - 300 per 100,000 with any statin
  - 200 per 100,000 with placebo
- **Elevated ALT on 2 or more checks**
  - 110 per 100,000 with any statin
  - 40 per 100,000 with placebo
- **Liver Failure Incidence 0.1-0.5 per 100,000**

*Am J Cardiol. 2006;97:52C–60C.*
Other Adverse Effects of Statins

- **Peripheral Neuropathy**
  - Incidence of 12 per 100,000
  - Discontinue statin if develops

- **Hemorrhagic Stroke**
  - Association with low LDL
  - 19% increase compared to placebo
  - 15% reduction in ischemic stroke
  - Avoid statins in individuals with hemorrhagic stroke?

*Am J Cardiol. 2006;97:52C–60C.*