Statins and Primary Prevention in the Elderly
What the HDL???
Sarah Earle
November 21st, 2013

Objectives

- Screening
- Are we biased against older adults?
- Secondary Prevention
- Primary Prevention
- Treatment
USPSTF

*strongly recommends* screening >35
recommends screening aged 20-35, if increased CAD risk

*strongly recommends* screening >45, if increased CAD risk
recommends screening 20-45, if increased CAD risk

No recommendation for or against routine screening for lipid disorders in men aged 20 to 35, or in women aged 20 and older *who are not at increased risk* for coronary heart disease.

---

**ATP III**
Adult Treatment Panel

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dl)

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-100</td>
<td>Optimal</td>
</tr>
<tr>
<td>100-129</td>
<td>Near optimal/above optimal</td>
</tr>
<tr>
<td>130-159</td>
<td>Borderline high</td>
</tr>
<tr>
<td>160-189</td>
<td>High</td>
</tr>
<tr>
<td>≥190</td>
<td>Very high</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-200</td>
<td>Desirable</td>
</tr>
<tr>
<td>200-230</td>
<td>Borderline high</td>
</tr>
<tr>
<td>≥240</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL Cholesterol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>Low</td>
</tr>
<tr>
<td>≥50</td>
<td>High</td>
</tr>
</tbody>
</table>
Table 4. Three Categories of Risk that Modify LDL Cholesterol Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Multiple (2+) risk factors*</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Zero to one risk factor</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

RISK FACTORS
Tobacco
HTN or on BP Rx
HDL <40
FHx CAD

NEGATIVE RISK FACTOR
HDL >60

FRAMINGHAM-10 year risk

Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person’s chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

Age:
Gender:
Total Cholesterol:
HDL Cholesterol:
Smoker:
Systolic Blood Pressure:
Are you currently on any medication to treat high blood pressure.

Calculate Your 10-Year Risk.
**FRAMINGHAM-10 year risk**

<table>
<thead>
<tr>
<th>Age:</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td>female</td>
</tr>
<tr>
<td>Total Cholesterol:</td>
<td>195 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol:</td>
<td>55 mg/dL</td>
</tr>
<tr>
<td>Smoker:</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure:</td>
<td>155 mm/Hg</td>
</tr>
<tr>
<td>On medication for HBP:</td>
<td>No</td>
</tr>
<tr>
<td>Risk Score*:</td>
<td>?</td>
</tr>
</tbody>
</table>
## FRAMINGHAM-10 year risk

<table>
<thead>
<tr>
<th>Age:</th>
<th>81</th>
</tr>
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<tbody>
<tr>
<td>Gender:</td>
<td>male</td>
</tr>
<tr>
<td>Total Cholesterol:</td>
<td>195 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol:</td>
<td>55 mg/dL</td>
</tr>
<tr>
<td>Smoker:</td>
<td>No</td>
</tr>
<tr>
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</tr>
<tr>
<td>On medication for HBP:</td>
<td>No</td>
</tr>
<tr>
<td>Risk Score*</td>
<td>21%</td>
</tr>
</tbody>
</table>

### FRAMINGHAM-10 year risk

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<tr>
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<tr>
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<tr>
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<td>No</td>
</tr>
<tr>
<td>Risk Score*:</td>
<td>29%</td>
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FRAMINGHAM-CAD 10 year risk

Individuals with:
- **low risk** have 10% or less
- **intermediate risk** 10-20%
- **high risk** 20% or more.

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<tr>
<th>AGE</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>79</th>
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</thead>
<tbody>
<tr>
<td>SBP 130</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>SBP 110</td>
<td>6</td>
<td>8</td>
<td>11</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>BP Rx @ 130</td>
<td>6</td>
<td>9</td>
<td>13</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>BP Rx @ 110</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>11</td>
<td>13</td>
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Optimal
TC 170
HDL 50

New Recommendations
Focus on ASCVD Risk Reduction
New perspective on Treatment Goals
Global Risk for Primary Prevention

Focus on...

- Statins
- Randomized Control Trials
- Systematic Reviews/Meta-Analyses
- Excluded observational studies
- No recommendation on
  - NYHA class II-IV
  - ESRD on HD
### Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Atorvastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
<th>Pravastatin</th>
<th>Lovastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td><strong>40-80</strong></td>
<td><strong>20-40</strong></td>
<td><strong>20-40</strong></td>
<td><strong>40-80</strong></td>
<td><strong>40</strong></td>
</tr>
<tr>
<td>Low</td>
<td><strong>10-20</strong></td>
<td><strong>5-10</strong></td>
<td><strong>10</strong></td>
<td><strong>10-20</strong></td>
<td><strong>20</strong></td>
</tr>
<tr>
<td>Moderate</td>
<td><strong>10-20</strong></td>
<td><strong>5-10</strong></td>
<td><strong>10</strong></td>
<td><strong>10-20</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

**Notes:**
- **High** intensity Therapy lowers LDL by >50%.
- **Moderate** intensity Therapy lowers LDL by 30-50%.
- **Low** intensity Therapy lowers LDL <30%.

**Statin Dosages:**
- **Atorvastatin:** 40-80 mg
- **Rosuvastatin:** 20-40 mg
- **Simvastatin:** 20-40 mg
- **Pravastatin:** 40-80 mg
- **Lovastatin:** 40 mg

---

**Figure:** Major recommendations for statin therapy for ASCVD prevention.

- **ASCVD Statin Benefit Group:**
  - Adult age ≥75 y and candidates for aspirin therapy.
  - Age ≥75 y. Moderate-intensity statin if not available for high-intensity statin.
  - Age 55-74 y. Estimated 10-year ASCVD risk ≥1% and LDL-C ≥70 mg/dL.

- **LDL-C Reduction:**
  - High-intensity statin: LDL-C <50 mg/dL
  - Moderate-intensity statin: LDL-C <70 mg/dL

- **Estimated 10-year ASCVD Risk:**
  - Moderate-intensity statin: <10% or <1% with preventive risk factors.

- **ASCVD Prevention:** Statin therapy may be less clear in other groups.
  - Consider additional factors:
    - Age ≥65 y
    - Risk factors for ASCVD
What about everyone else?

- **Clinical ASCVD**
  - No
  - LDL-C ≥190 mg/dL
    - No
    - **Diabetes**
      - Type 1 or 2
      - Age 40-75 y
        - No
        - Yes
          - Moderate-intensity statin
  - Yes
    - Age ≤75 y
      - **High-intensity statin**
        - Moderate-intensity statin if not candidate for high-intensity statin
    - Age >75 y OR if not candidate for high-intensity statin
      - **Moderate-intensity statin**

- **Estimated 10-y ASCVD risk ≥7.5%**
  - Yes
    - **High-intensity statin**
  - No
    - **Moderate-to-high intensity statin**

- **ASCVD prevention benefit of statin therapy may be less clear in other groups**
http://my.americanheart.org
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Optimal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>170</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>50</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>110</td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N</td>
</tr>
<tr>
<td>Smoker</td>
<td>N</td>
</tr>
</tbody>
</table>

**RISK CALCULATORS**

7.6

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>60</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>170</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>50</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>130</td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N</td>
</tr>
<tr>
<td>Smoker</td>
<td>N</td>
</tr>
</tbody>
</table>
A G E 5 5 6 0 6 5 7 0 7 5 7 9

<table>
<thead>
<tr>
<th>AGE</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>79</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP 130</td>
<td>4.8</td>
<td>7.6</td>
<td>11.7</td>
<td>17.1</td>
<td>24</td>
<td>30.8</td>
</tr>
<tr>
<td>SBP 110</td>
<td>3.6</td>
<td>5.7</td>
<td>8.8</td>
<td>13</td>
<td>18.6</td>
<td>24</td>
</tr>
<tr>
<td>BP Rx @130</td>
<td>5.6</td>
<td>8.9</td>
<td>13.6</td>
<td>19.8</td>
<td>27.7</td>
<td>35.1</td>
</tr>
<tr>
<td>BP Rx @110</td>
<td>4.2</td>
<td>6.7</td>
<td>10.2</td>
<td>15.1</td>
<td>21.3</td>
<td>27.4</td>
</tr>
</tbody>
</table>

Optimal
TC 170
HDL 50

Objectives

Screening

Are we biased against older adults?

Secondary Prevention

Primary Prevention

Treatment
Bias against treatment in older adults?

• Life expectancy
• Comorbidity
• Safety of drugs
• Cost-benefit
• Quality of Life

Life Expectancy at Selected Ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>16.0</td>
<td>19.2</td>
</tr>
<tr>
<td>70</td>
<td>12.8</td>
<td>15.5</td>
</tr>
<tr>
<td>75</td>
<td>10.0</td>
<td>12.2</td>
</tr>
<tr>
<td>80</td>
<td>7.5</td>
<td>9.2</td>
</tr>
<tr>
<td>85</td>
<td>5.5</td>
<td>6.7</td>
</tr>
<tr>
<td>90</td>
<td>4.1</td>
<td>4.9</td>
</tr>
<tr>
<td>95</td>
<td>3.0</td>
<td>3.6</td>
</tr>
</tbody>
</table>

National Center for Health Statistics: DHHS 1998
Cardiovascular Risk Factors in the elderly
Am J Cardiol 1989

ACC/AHA Guidelines for Elderly

EXPERT OPINION:
• For Individuals taking any dose of statins, it is reasonable to use caution in individuals >75yo, as well individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (ie HIV, Transplant).
ACC/AHA Guidelines for Elderly

Few elderly in RCTs
Does support continuation of current statin

Secondary Prevention:
- Support moderate intensity
- Few data did not clearly support high intensity

Primary Prevention:
- Few data to support event reduction benefit

Objectives

Screening
Are we biased against older adults?

Secondary Prevention
Primary Prevention
Treatment
Secondary Prevention

- **4S=Scandinavian Simvastatin Survival Study**
  - 1993
  - 1021/4444 were >65yo followed for 5.4 yr
  - Simvastatin 20-40mg or placebo
  - All cause mortality RR 0.66 or 34% risk reduction
  - CHD mortality RR 0.57 or 43% risk reduction

  NNT=30, in older adults NNT=22

---

Secondary Prevention

- **LIPID=**
  - *Long-Term Intervention with Pravastatin in Ischemic Disease*
  - 1989
  - 3514/9014 Australian/Kiwis ages 65-75 over 6 yr
  - Pravastatin 40mg or placebo
  - All cause mortality RR 0.79 or 21% risk reduction
  - CHD mortality RR 0.76 or 24% risk reduction

  NNT=46, in older adults NNT=22
  NNT=71, in older adults NNT=35
Secondary Prevention-elder specific

- PROSPER, age 70-82, @3 yr
- Pravastatin 40mg vs placebo
- HR 0.85 (0.74-0.97)
- HR 0.97 (0.87-1.14) All-Cause Mortality
- SAGE, age 65-85, @ 1yr
- Atorvastatin 80mg vs Pravastatin 40mg
- Duration of ischemia on 48hr holter
- HR 0.71 (0.46-1.09) Major events
- HR 0.33 (0.13-0.83) All-Cause Mortality

Risk Interpretation

<table>
<thead>
<tr>
<th></th>
<th>% Deaths</th>
<th>% Deaths on Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simva 20-40</td>
<td>Prava 40</td>
</tr>
<tr>
<td>LIPID</td>
<td>Prava 40</td>
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</tr>
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<td>PROSPER</td>
<td>Prava 40</td>
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Objectives

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Secondary Prevention

Primary Prevention

Treatment

Data from 3 exclusively primary prevention RCTs

AFCAPS/TexCAPS
• Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women of average Cholesterol levels

MEGA
• Primary Prevention of Cardiovascular Disease with Pravastatin in Japan

JUPITER
• Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated CRP
### Data from 3 exclusively primary prevention RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women of average Cholesterol levels</td>
<td>58</td>
<td>221</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>MEGA</td>
<td>Primary Prevention of Cardiovascular Disease with Pravastatin in Japan</td>
<td>58</td>
<td>198</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvasatin to Prevent Vascular Events in Men and Women with Elevated CRP</td>
<td>66</td>
<td>150</td>
<td>36</td>
<td>52</td>
</tr>
</tbody>
</table>

### AFCAPS/TexCAPS-1998

- 5608 men and 997 women followed for 5.2 years
- ~TC 221
- ~LDL-C 150 → reduced LDL-C by 25% to 115
- ~HDL-C 36men/40women → increased HDL by 6% to 39
- Lovastatin (20-40 mg daily) or placebo in addition to a low-saturated fat, low-cholesterol diet.

- First acute major coronary event defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death.
AFCAPS/TexCAPS-1998

RR=0.63 or 37% less
10.9 per 1000 patient years vs 6.8 per 1000 patient years
NNT=50 over 5 years to prevent 1 event

MEGA Study-2006

- 2476 men and 5356 women in Japan for 5.3 years
- ~TC 242 → decreased by 2.1% in diet, 11.5% in pravastatin
- ~LDL 156 → decreased by 3.2% in diet, 18% in pravastatin
- ~HDL 57
- Pravastatin 10-20mg plus diet or diet alone

- First occurrence of coronary heart disease, including fatal and non-fatal MI, angina, cardiac and sudden death and revascularization.
MEGA Study-2006

HR=0.67 or 33% less

5 per 1000 patient years vs.
3.3 per 1000 patient years

NNT=115 over 5.3 years to prevent 1 event

JUPITER-2008

- 11001 men and 6801 women followed for 1.9 years
- LDL <130 → reduced by 50% to median 47
- CRP>2.0 → reduced by 37%
- Rosuvastatin 20 mg daily or placebo

- First acute major coronary event defined as MI, CVA, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.
**JUPITER-2008**

HR 0.56 or 44% less

13.6 per 1000 person years vs. 7.7 per 1000 person years

Abs RR=0.01
NNT=95 over 2 years to prevent 1 event

**Views from Above**
18 RCTs total
n= 56,934
28-97yo, average 57

Threshold for 10% of participants with CVD

Trial endpoints were all-cause mortality, fatal and nonfatal CVD events, LDL levels and revascularizations

**COCHRANE SUMMARIES**
Independent high-quality evidence for health care decision making

---

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<th>Statin Therapy</th>
<th>Cardiovascular Events</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td></td>
<td>n=38,437</td>
<td>n=974</td>
<td>1.14</td>
<td>0.97-1.34</td>
</tr>
<tr>
<td></td>
<td>n=28,504</td>
<td>n=328</td>
<td>1.10</td>
<td>0.94-1.27</td>
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Total (95% CI):

264868 / 281524 = 0.93 (0.90, 0.96)

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<tr>
<th>Study subgroup</th>
<th>Statin Therapy</th>
<th>Cardiovascular Events</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=38,437</td>
<td>n=974</td>
<td>1.14</td>
<td>0.97-1.34</td>
</tr>
<tr>
<td></td>
<td>n=28,504</td>
<td>n=328</td>
<td>1.10</td>
<td>0.94-1.27</td>
</tr>
</tbody>
</table>

Total (95% CI):

264868 / 281524 = 0.93 (0.90, 0.96)
All-cause mortality:

**RR 0.86** (95% CI 0.79 to 0.94)

5 yrs NNT=96

Combined fatal and non-fatal CHD events:

**RR 0.73** (95% CI 0.67 to 0.80)

5 yrs NNT=56
CTT
Meta-Analysis

• Cholesterol Treatment Trialists’ Collaboration
• Established in 1994 after it was identified that no single ongoing trial would have sufficient statistical power to address some key uncertainties about the effects of lowering cholesterol
• 2 Cycles-2010, 2012

CTT

• Difference in LDL cholesterol at 1 year:
  1mmol/L
  =38.6mg/dL
• Greater proportional reductions in major vascular events being associated with greater LDL reductions
• Proportional reductions in major vascular events per mmol/L LDL cholesterol reduction were found in all types of patient studied
• reduced risk of major vascular event RR 0.79
• All-Cause Mortality RR 0.91 CI(0.88-0.97)
The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease
Cholesterol Treatment Trialists-2012

6 (<5% group)
15 (5-10% group)

events avoided per
1000 people treated for 5 years

NNT: 167 and NNT: 67

ASCVD Benefits
ASCVD Benefit

**AFCAPS/TexCAPS**
- RR 0.63
- NNT=50 over 5 years to prevent 1 event

**MEGA**
- HR 0.67
- NNT=115 over 5.3 years to prevent 1 event

**JUPITER**
- HR 0.56
- NNT=95 over 2 years to prevent 1 event

**Cochrane**
- RR 0.73
- NNT=56 over 5 years to prevent 1 event

Risk Interpretation??

![Bar chart showing % Deaths and % Deaths on Statin for AFCAPS, MEGA, JUPITER, and COCHRANE]
Before initiating a statin for primary prevention, it is reasonable to engage in a discussion:

- ASCVD Benefit
- Adverse Effects
- Drug-drug Interaction
- Patient Preferences
When To Treat

Lifestyle as the Foundation

“It must be emphasized that lifestyle modification (i.e. adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies.”

2013 ACC/AHA guideline
**Adverse Effects**

LFTs
- 0.5 to 3.0%
- Primarily occurred during the first 3 months

Should a baseline ALT be checked prior to initiating statin?

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**Adverse Effects**

Grade B recommendation
- Baseline measurement of ALT should be performed prior to initiating statin
Adverse Effects

Myopathy
• 2 to 11% for myalgias
• 0.5% for myositis
• <0.1% for rhabdomyolysis.

• CK does not have to go up
• Usually begin within weeks to months
• Pravastatin and fluvastatin have less muscle toxicity
• More susceptible if AKI/CKD, Liver dx, hypothyroid

Should we follow CK for increase?

Adverse Effects

Grade A recommendation
• CK should not routinely be measured in individuals receiving a statin
Adverse Effects

Cognition
• 60 FDA case reports 1997-2002
• Simva (36) Atorva (23) Prava (1)
• 14/25 improved when discontinued
• 4 had recurrence on re-challenge

Adverse Effects

Expert Opinion
• Individuals presenting with confusional state or memory impairment it may be reasonable to evaluate for nonstatin causes, such as exposure to other drugs, as well as systemic and neuropsychiatric causes in addition to the possibility of adverse effects associated with statin drug therapy
Drug-Drug Interaction

- Most statins metabolized with CyP-450 3A4
- Lovastatin, simvastatin, atorvastatin
- Prefer Pravastatin, fluvastatin, rosuvastatin

**Inhibitors:** Azoles, HIV Rx, Ciprofloxacin, verapamil, haloperidol, sertraline, Tamoxifene

**Inducers:** Carbamazepine, dexamethasone, phenytoin, nafcillin, primidone

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**Patient Preferences**
Take home points

Age is a strong factor in risk calculators (old/new)
Highly unlikely that our patient will be <7.6 risk

• Secondary prevention
  - 1 RCT that is elder specific
• Primary Prevention
  - No data that is elder specific
  - Does the data correlate to my patients

Risk Interpretation??
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- http://www.telegraph.co.uk/finance/jobs/9877132/Career-change-how-to-make-it-happen.html