Update on Statin Therapy: Is there a minimum (or maximum) age?

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Disclosures

Honoraria
Pfizer, Merck, MSD

Consultant
Merck, CSL

Research
Merck, CSL
Statins and Age
Key Questions

Does the pathophysiology change with age?

Are the risks for treatment different with age?
Statins and Age

Key Questions

Does the pathophysiology change with age?

No but

Younger take longer to manifest events
Older have larger burden of disease

Are the risks for treatment different with age?
Statins and Age

Key Questions

Does the pathophysiology change with age?
No

Are the risks for treatment different with age?
Likely not but
Risk/benefit or cost/benefit over how many years?
Enough time left to accrue benefit?
Very young or very old have more potential for adverse reactions?
Pediatric/young adult
Rationale supporting early treatment

– Bogalusa Heart Study
  • Cohort of children followed over time
  • Autopsy data on accidental deaths

– Findings
  • Fatty streaking increased with aging
  • Prevalence approached 70% in young adults
  • Correlations with fatty streaks
    » TC, LDLc, Tg, low HDL
    » Number of CVD risk factors
    » Obesity

Berensen, NEJM. 1998
## Pediatric - Risk Populations

### First - Risk stratification by disease process

<table>
<thead>
<tr>
<th>High risk*</th>
<th>Moderate risk**</th>
<th>At risk***</th>
<th>Some Risk = CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other CRF (smoke)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Family Hx CAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M ≤ 55 yrs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>W &lt; 65 yrs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(BMI &gt; 85th %ile)</td>
</tr>
</tbody>
</table>

* Manifest CAD < 30 yrs of age
** Accelerated atherosclerosis
*** High-risk setting for accelerated atherosclerosis

Kavey, Circulation. 2006; Pediatrics March 2007
Pediatric - Risk Populations

Next – Match diseases to risk

<table>
<thead>
<tr>
<th>High risk*</th>
<th>Moderate risk**</th>
<th>At risk***</th>
<th>Some Risk = CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous FH</td>
<td>Heterozygous FH</td>
<td>Congenital Heart</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Type I DM</td>
<td>Type II DM</td>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td>Other CRF (smoke)</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>Chronic inflammatory disease</td>
<td>Cancer treatment survivors</td>
<td>Family Hx CAD M ≤ 55 yrs. W ≤ 65 yrs.</td>
</tr>
<tr>
<td>Kawasaki with active aneurysms</td>
<td>Kawasaki regressed aneurysms</td>
<td>Kawasaki without detected aneurysms</td>
<td>Obesity (BMI &gt; 85th %ile)</td>
</tr>
</tbody>
</table>

* Manifest CAD < 30 yrs of age
** Accelerated atherosclerosis
*** High-risk setting for accelerated atherosclerosis

Kavey, Circulation. 2006; Pediatrics March 2007
Pediatric indications

Adjusting risk in at risk populations

Next – Further adjust risk based on comorbidities

- Fasting lipids
- Smoker?
- Family hx (M<55, F<65) of early CAD
- Hypertension (documented 3 measures high)
- BMI
- Fasting glucose
- Physical activity hx

2 or more risk factors call for an upgrade in risk category (eg. Moderate risk to High risk)

Kavey, Circulation. 2006; Pediatrics March 2007
## Treatment of at risk populations

### Tier 1 Highest risk

<table>
<thead>
<tr>
<th></th>
<th>FH</th>
<th>DM 1</th>
<th>CKD</th>
<th>Transp</th>
<th>Kawas</th>
<th>Upgrade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo. diet</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Goal</td>
<td>Low as poss.</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Statin</td>
<td>Yes all</td>
<td>If &gt; 100 age &gt; 10</td>
<td>If &gt; 100 age &gt; 10</td>
<td>If &gt; 100 age &gt; 10</td>
<td>If &gt; 100 age &gt; 10</td>
<td>If &gt; 100 age &gt; 10</td>
</tr>
<tr>
<td>Goal</td>
<td>&lt; 100mg/dl</td>
<td>&lt; 100</td>
<td>&lt; 100</td>
<td>&lt; 100</td>
<td>&lt; 100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Special</td>
<td>Apheresis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Moderate risk disease states with 2 or more CV risk factors

Kavey, Circulation. 2006; Pediatrics March 2007
Pediatric indications for lipid Rx
High Risk Populations

Tier 2 - Moderate risk or At Risk with 2 or more CRF
Diet if LDL > 130mg/dl for 6 mo.
If repeat is > 130mg/dL then statin if age > 10

Tier 3 At Risk
Diet if LDL > 160mg/dL for 6 mo.
If repeat is > 160mg/dL then statin if age > 10

Kavey, Circulation. 2006; Pediatrics March 2007
Pediatric indications for lipid Rx
Some risk - who and when to screen

Screen children between ages of 2 and 10 with

• Fam. Hx. dyslipidemia
• Fam. Hx. premature (M<55, W< 65) CVD
• Children with other CVD risk factors
  – BMI > 85\textsuperscript{th} percentile
  – Hypertension (BP> 95\textsuperscript{th} percentile)
  – Smokers

If in range re-test every 3-5 years

Daniels, Pediatrics. 2008
Pediatric indications for lipid Rx
Some Risk - when to treat

Children 8 years and older who
Fall out of range
> 190mg/dL
> 160mg/dL with family hx or 2 or more CRF
Then fail to reach target with 6 mo. diet therapy
Target < 160mg/dL or
Target < 130mg/dL with strong fam. Hx or multiple CRF

Daniels, Pediatrics. 2008
Pediatric indications for lipid Rx
Some risk when to use statins

– Children 8 years and older who fail to reach target with dietary therapy are excellent candidates for statin therapy. Goals are as outlined on the last slide

– Who will not tolerate this (or should not be prescribed)
  Family hx of not being tolerant to a statin
  -10x increase likelihood of intolerance as well
  Sexually active girls who could become pregnant

Indications for statins in younger adults

How NCEP can help

No trial data in patients under 50 years of age

Potential options

Pediatric approach of degree of risk over time is reasonable
My own approach to help identify those at future risk
What is the absolute risk? – NCEP Calculator

<table>
<thead>
<tr>
<th>Age</th>
<th>LDL @160</th>
<th>LDL, smoke</th>
<th>LDL, BP 140</th>
<th>LDL, smk, BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 yo man</td>
<td>&lt;1%</td>
<td>4%</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>35 yo man</td>
<td>1%</td>
<td>7%</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>45 yo man</td>
<td>4%</td>
<td>12%</td>
<td>6%</td>
<td>20%</td>
</tr>
<tr>
<td>45 yo woman</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Indications for statins in younger adults

How NCEP can help

Age drives NCEP risk more than any other factor
The remainder of the NCEP risks can be modified

IF the risk were not present –
I evaluate the potential change in residual risk
I use this to motivate behavior changes

<table>
<thead>
<tr>
<th>Age</th>
<th>LDL @160</th>
<th>LDL, smoke</th>
<th>Smoke only &lt;130</th>
<th>Smoke only &lt;100</th>
<th>No Smoke &amp; &lt;130</th>
<th>No Smoke &amp; &lt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 yo man</td>
<td>4%</td>
<td>12%</td>
<td>8%</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>55 yo man</td>
<td>8%</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCEP risk calculator hp2010.nhlbihin.net/atp iii/calculator.asp
Indications for statins in younger adults – Are there other risks

• hsCRP
  – May be of most benefit in those with intermediate risk between 5-15%

• Lp(a)
  – Mostly genetic
  – Looking for the very high level and (+) fam hx

• Imaging
  – Coronary calcium most predictive in the young
  – Intimal thickening?

(Ridker, JACC 2007)
NCEP III Recommendations—Treatment of Dyslipidemia in Older Adults

Primary prevention in older adults

• Therapeutic lifestyle changes (TLC)
• Standard risk assessment may not be adequate in older adults
• Consider lipid lowering in patients with 2+ risk factors or subclinical atherosclerosis
• Similar targets of LDL < 130 mg/dL with 2 or more risk factors

Secondary prevention in older adults

• No age restrictions for LDL-lowering therapy in patients with established CHD
• Similar targets of LDL < 100 mg/dL with known CV disease or high risk

NCEP Expert Panel. NCEP ATP III Guidelines. NIH 02–5215; 2002
Statins Demonstrate Age-gradient in Post-MI Discharge Care

Aspirin:
- 65-74
- 75-84
- ≥85

Beta Blocker:
- 65-74
- 75-84
- ≥85

ACE Inhibitor:
- 65-74
- 75-84
- ≥85

Clopidogrel:
- 65-74
- 75-84
- ≥85

Lipid Lowering:
- 65-74
- 75-84
- ≥85

Adj. OR c/w age < 65

Alexander, JACC 2005
NCEP III Recommendations—
Treatment of Dyslipidemia in Older Adults

• Subgroup analysis strongly suggested LDL-lowering therapy significantly reduces risk for CHD in older adults

• PROSPER and ASCOT support use of statins for primary prevention in older adults at high-risk

• Heart Protection Study and PROSPER justify intensive LDL-lowering in older adults with established CVD (optional goal of LDL < 70 mg/dL in high-risk persons)

Heart Protection Study (HPS)

Benefit Greater in Older pts (2717 age ≥ 65 years) and regardless of LDL

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>RR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group (y)</strong></td>
<td>Statin better</td>
<td>Statin worse</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>838</td>
<td>1093</td>
<td>Het(C^2) = 4.4</td>
</tr>
<tr>
<td>65–69</td>
<td>516</td>
<td>677</td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>550</td>
<td>628</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>138</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL (mg/dL)</strong></td>
<td>Statin better</td>
<td>Statin worse</td>
<td>(\chi^2) = 0.8</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>285</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>100-130</td>
<td>670</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>≥ 130</td>
<td>1087</td>
<td>1365</td>
<td></td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>24% SE 3 reduction ((P &lt; .00001))</td>
</tr>
</tbody>
</table>

HPS, Lancet, 2002
Evidence ends at 85 - PROSPER

5804 men and women Pravastatin 40 or Placebo

- Age 70-82 at entry
- Hx. vascular disease or risk factors - 57% of placebo and 55% of pravastatin subjects with CRF only
- Average follow up of 3.2 years

HR 0.85 p=0.014 for primary endpoint of coronary death, non-fatal MI, fatal or non-fatal stroke.

- No vascular disease absolute RR of 0.7 and HR 0.94
- Vascular disease absolute RR of 4.3 and HR 0.78

Shepherd, Lancet. 2002
Evidence ends at 85 – PROSPER Safety

Serious adverse events balanced between Pravastatin and placebo at 55% and 56%

No difference in decline in cognitive function between the groups.

No cases of rhabdomyolysis, similar number of reported myalgia (36 and 32) and only 1 subject with elevated LFT in each group.

Trend toward more new cancers with pravastatin

Shepherd, Lancet. 2002
PROSPER - Post Hoc lipid analysis
Low HDLc or LDLc/HDLc ratio

No relationship between pretreatment LDLc or on treatment LDLc and risk of primary endpoint in PROSPER

Neither achieved LDLc or HDLc predicted outcome

HDLc was inversely associated with risk in subjects on placebo but not on Pravastatin

Benefit of Pravastatin
   Found in subjects in the bottom 2 quintiles of HDLc (HDLc < 1.15mmol/L)

   Found reduced risk was associated with LDLc/HDLc to > 3.3

Packard, Circulation. 2005
SAGE – Intensive vs. Moderate Rx

• 893 patients with CAD 65-85 years of age
  – More than 1 episode of ischemia on 48 hr. ambulatory ECG at screening
  – Atorvastatin 80 vs. Pravastatin 40 for 12 mo.

• Intensive therapy
  – No significant change in total duration of ischemia
  – Trend toward reduced MACE (8.1% vs. 11.2%)
  – 77% reduction in all cause mortality with Atorvastatin
  – LFT in Atorvastatin 19 vs. 1 in Pravastatin
  – Myalgia not significantly different 3.1% vs. 2.7%

Deedwania, Circulation. 2007
Conclusions

• For pediatric patients
  – Treat potential risk with statins aggressively when the potential is very high
  – Consider those at lower future risk when multiple CRF are present

• For young adults
  – Consider combining the pediatric approach with estimates of relative risk using NCEP scenarios for motivation
  – Consider adding newer risk factors – hsCRP, Lp(a), imaging

• For the oldest patients
  – Their absolute risk is highest especially if disease has already manifested
  – Data for efficacy is sparse but the physiology is unchanged
  – Treatment appears to be safe and should not be withheld