Faculty Disclosure

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Dr. Schima has listed no financial interest/arrangement that would be considered a conflict of interest.

The Role of Statins in Primary Prevention

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December 7th, 2012
ATPIII Goals

- LDL < 100 (highest risk < 70 mg/dL)
- HDL > 40 mg/dL in men, > 50 in women
- Triglycerides < 150 mg/dL
- Non-HDL <130 mg/dL
  - Total Cholesterol-HDL
  - Should be within 30 mg/dL of LDL

LDL Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (CHD or equivalent, 20% 10 yr risk)</td>
<td>&lt;100 mg/dL (optional &lt;70)</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Mod High (2+ risk factors, 10-20% 10 yr risk)</td>
<td>&lt;130</td>
<td>&gt;130</td>
<td>&gt;130 (100-129, consider rx)</td>
</tr>
<tr>
<td>Moderate (2+risk factors, 10% 10 yr risk)</td>
<td>&lt;130</td>
<td>&gt;130</td>
<td>&gt;160</td>
</tr>
<tr>
<td>Low Risk (0-1 risk factor)</td>
<td>&lt;160</td>
<td>&gt;160</td>
<td>&gt;190 (160-189, consider rx)</td>
</tr>
</tbody>
</table>
LDL Goals

- CHD risk equivalents:
  - PAD
  - AAA
  - Carotid artery disease
    - TIA or CVA of carotid origin
    - >50% obstruction of carotid
  - Diabetes
  - 2+ risk factors with 10 yr 20% risk CHD

Guidelines

- Risk factors
  - Smoking
  - Hypertension (>140/90 or on medication)
  - Low HDL (<40 mg/dL)
  - FH of premature CAD
    - <55 male, <65 female
  - Age
    - >45 male
    - >55 female
Evidence for Primary Prevention

- AFCAPS/TexCAPS
- ALLHAT
- ASCOT-LLA
- CARDS
- HPS
- Jupiter
- MEGA
- PROSPER
- WOSCOPS

Evidence for Primary Prevention

- Every major guideline committee has endorsed use of statins in primary prevention in those with risk factors
- 3 meta-analyses of statin primary prevention trials
  - Modest 9-17% RR reduction in all-cause mortality with statins. Statistical significance in 2 of 3 trials
Statin and all-cause mortality in high-risk primary prevention  Arch Int Med 2010

- 11 studies involving > 65,000 pts without known CHD
- Borderline significant 7-9% risk reduction in all-cause mortality
- Average treatment duration 3.7 yrs
- Cardiovascular morbidity analysis not evaluated

The benefits of statins in people without established CVD but with CVD risk BMJ 2009

- 10 trials, included primary prevention arm of HPS. >70,000 pts
- Statins significantly reduced risk of all-cause mortality by 12%
- Benefit remained even when controversial trials eliminated (Jupiter)
- Also analyzed effects on morbidity
  - Signif decrease in major coronary events, cerebrovascular events, non-fatal MI and revascularizations
Statins for primary prevention of CVD
Cochrane database syst rev 2011

• 14 trials
• Statin resulted in 17% reduction in all-cause mortality and 30% reduction in combined fatal and nonfatal CVD endpoints
• 34% reduction in revascularizations (morbidity)

JUPITER NEJM 2008

• Male > 50, female > 60; no CAD; LDL < 130 and CRP > 2
• Rosuvastatin 20 mg v placebo to decrease rate of first major CV event
• 54% reduction in MI, 51% reduction in stroke, 46% reduction in need for revascularization, 40% reduction in thromboembolism and 20% reduction in all-cause mortality
Jupiter sub-studies

- Those who reached LDL < 70 had 55% reduction in vascular events
- hsCRP < 2  62% reduction
- LDL < 70 and hsCRP < 1  79% reduction
- Regardless of lipid profile, lower hsCRP had better prognosis

Jupiter

- Stopped early due to benefit
- “healthy” pt population at high risk and previously ineligible for statin may benefit if hs CRP is elevated even if LDL acceptable
- 58-80% of older adults potentially on statin
JUPITER Questions

- Would a lower-cost, generic statin show similar benefit?
- Is measurement of hsCRP necessary for risk stratification in primary prevention
  - Ridker conflict of interest issues
- Was the benefit due to LDL-C lowering or hsCRP lowering?

Criticism

- Absence of low-hsCRP control arm for comparison
  - Prior trials demonstrated no statin benefit in pts with low LDL and hsCRP
- Benefit exaggerated
  - ARR .59%/yr requires NNT of 500 to prevent major coronary event
  - Cost of rosuvastatin to prevent 1 event = $638,750
  - Generic statin = $24,000
Criticism

• Reply
  ◦ Statin therapy cost effective at $40,457 per QALY
    • Based on model using generic simvastatin 80
  ◦ 5 yr analysis
    ◦ NNT 15 if +FH
    ◦ NNT 25 for general population
    ◦ NNT 50-60 for women or low Framingham risk score
    ◦ 5 yr NNT for BP control btw 80-130

Criticism

• Results will be used to overtreat
  ◦ Concern that study would be used to treat otherwise healthy pts
  ◦ While free of illness, trial population was not healthy
    • 41% metabolic syndrome
    • 16% tobacco use
    • 12% with FH premature CAD
  ◦ Trial population representative of general population
Jupiter Conclusions

- Many so-called healthy people are underdiagnosed and harbor risk factors
- Very low LDL levels generally well tolerated
- FDA approved rosuvastatin for male > 50 and females > 60 who have hsCRP >2 and at least one additional CRF

Criticism of Statins for Primary Prevention

- Improved outcomes can be achieved with interventions other than statins
  - BP treatment, ASA, weight loss, healthy diet

- Safety of statins
  - Meta-analysis of 35 trials showed no significant increase in risk of myalgias, CK elevations, rhabdo
  - Significantly higher risk of transaminase elevations, progression to liver failure rare
  - Small but statistically significant 9% increase in incidence of DM (1 new diabetes event per 1000 person yrs of rx)
  - Cardioprotective benefit outweighs risk of DM
7 Targets of Ideal Cardiovascular Health

- Never smoked or quit more than one year ago.
- Body mass index less than 25 kg/m².
- Physical activity of at least 150 minutes (moderate) or 75 minutes (vigorous) each week.
- Four to five of the key components of a healthy diet consistent with current American Heart Association guideline recommendations.
- Total cholesterol of less than 200 mg/dL.
- Blood pressure below 120/80 mm Hg.
- Fasting blood glucose less than 100 mg/dL.

7 Targets

- 78% reduction for all-cause mortality and 88% reduction for CV mortality for those who had 5 ideal factors compared with those who had none.
- Only 1.7% of adults meet all 7 targets.

"The second half of a man’s life is made up of nothing but the habits he has acquired during the first half.”

- Dostoevsky
Moral Hazard

- People will make less effort to follow a healthy diet and get regular exercise because they are falsely reassured by their medications
- Evidence that statin users are more concerned about lifestyle factors
- Combination of lifestyle modification and pharmacotherapy is more effective than either alone in at-risk patients

Conclusions

- Substantial evidence of use of statins in primary prevention
- Combination of lifestyle adjustment and medical therapy is ideal
- Risk assessment
  - Identify those who stand to benefit the most from statins
  - May result in unnecessary treatment of some
Issues for ATP-IV

1. Should the goals for LDL-C in primary prevention be lowered?
2. What to do with CRP – routine use in risk stratification, secondary target?
3. What about secondary target?
   ▫ Non-HDL-C, HDL-C, apo B, LDL Particle concentration?
4. Move from 10-year to lifetime risk?