The Benefits and Safety of Cholesterol Medicines

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Statin Safety – Overview

• Very safe class of medications
• Primary issues are muscle and liver side effects
• Highest dose of each statin has increased risk of side effects
• Little difference between statins in toxicity
• Muscle aches can occur with any statin, any dose
• Differences in statins with drug interactions
• Recent concern with increased risk of diabetes – but marked risk reduction with statin use in diabetes
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease
Guideline Scope

- Focus on treatment of blood cholesterol to reduce heart disease and stroke risk in adults
- Emphasize adherence to a heart healthy lifestyle
  - See lifestyle guideline recommendations
- Identify individuals most likely to benefit from cholesterol-lowering therapy
  - 4 statin benefit groups
- Identify safety issues
New Guidelines Address 3 Critical Questions

1. What is the evidence for LDL and risk assessment for initiation of treatment? (who to treat)

2. Should we use LDL goals or targets for treatment?

3. What medications have evidence for use in the treatment of cholesterol? (include harm)
Statin Benefit Groups

• Clinical heart disease (includes stroke and artery disease)
• LDL-C $\geq 190$ (without other cause)
• Primary prevention – Diabetes – LDL-C 70-189
• Primary prevention – No DM – CVD risk $\geq 7.5\%$

*Requires risk discussion with the clinician before statin prescription

Statin therapy may be considered if risk decision uncertain after use of heart disease risk calculator.
2013 Update of 2011 Cochrane Review

- 18 primary prevention statin trials (n= 56,934) with data collected between 1994-2008. (update includes four new trials and additional data on 3 trials)

- 60% men and 40% women, majority white, mean age 57

- population not uniformly healthy (DMII, proteinuria, HTN) and some with CVD (did not include if >10% of population)

- Most used pravastatin and all funded by pharmaceutical company

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin Trials, No.</th>
<th>Statin Events, No.</th>
<th>Statin Total No. of Participants</th>
<th>Placebo/Control Events, No.</th>
<th>Placebo/Control Total No. of Participants</th>
<th>Relative Risk (95% CI)</th>
<th>Favors Statins</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>13</td>
<td>1077</td>
<td>24408</td>
<td>1223</td>
<td>23652</td>
<td>0.86 (0.79-0.94)</td>
<td></td>
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</tr>
<tr>
<td>Total CVD events</td>
<td>9</td>
<td>1103</td>
<td>11892</td>
<td>1444</td>
<td>11913</td>
<td>0.75 (0.70-0.81)</td>
<td></td>
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</tr>
<tr>
<td>Total CHD events</td>
<td>14</td>
<td>820</td>
<td>24217</td>
<td>1114</td>
<td>23832</td>
<td>0.73 (0.67-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stroke events</td>
<td>10</td>
<td>345</td>
<td>20302</td>
<td>442</td>
<td>19993</td>
<td>0.78 (0.68-0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>7</td>
<td>286</td>
<td>21166</td>
<td>461</td>
<td>21237</td>
<td>0.62 (0.54-0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>12</td>
<td>5748</td>
<td>20718</td>
<td>5090</td>
<td>19998</td>
<td>1.00 (0.97-1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2</td>
<td>342</td>
<td>12205</td>
<td>290</td>
<td>12202</td>
<td>1.18 (1.01-1.39)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. Needed to Treat for 5 Years (95% CI):
- 138 (92-321)
- 49 (40-66)
- 88 (72-119)
- 155 (106-309)
- 96 (78-129)

Not applicable

99 (46-1778)
Heart Protection Study

**Effects on 1° Endpoint by Baseline Feature**

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>STATIN (N=10,269)</th>
<th>PLACEBO (N=10,267)</th>
<th>RR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI or CHD</td>
<td>1459 (21.8%)</td>
<td>1841 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Prior Coronary Heart Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>172 (18.7%)</td>
<td>212 (23.6%)</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>327 (24.7%)</td>
<td>427 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>279 (13.8%)</td>
<td>367 (18.6%)</td>
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</tbody>
</table>

**ALL PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>STATIN (19.9%)</th>
<th>PLACEBO (25.2%)</th>
<th>RR and 95% CI</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>24% decrease</td>
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</table>

24% decrease

NNT = 19

(p<0.0001)

0.4 0.6 0.8 1.0 1.2 1.4

STATIN better  STATIN worse

Lancet 2002;360:7
Intensity of Statin Therapy

High risk = high intensity treatment

Moderate risk = moderate intensity treatment

Low risk = low intensity (lifestyle / low intensity statin)

Use evidence based treatment
Safety of Medications Benefit vs Risk

• Benefit derives from:
  • How common is the disease
  • Consequences of the disease
  • Reduction in the risk of the disease if treated

• Risk derives from:
  • The percent of adverse events
  • The disability or fatality of the adverse events
  • The reversibility or permanency of the adverse events
  • The consequences of not controlling the disease

• With statins, there is high risk-benefit if used correctly
  • The risk is very low but related to important functional organs such as liver, kidney, muscle and central nervous system
  • There is only reversible side effects, no permanent harm
  • There is permanent benefit, not permanent risk!
Statin – Heart Disease and Stroke Prevention

Reduce Cardiovascular Disease events and total mortality in high-risk patients... but patients must adhere to long-term therapy to derive that benefit.

Fear of risk can influence long-term adherence.

A number of case reports of serious side effects exist in the literature and on the internet, motivating a need for serious evaluation of all the literature.

Focus on: Liver, Muscle, CNS, Kidney
Conclusions of the Expert Liver Panel

*Routine monitoring of liver biochemistries in asymptomatic patients is not necessary, because:*

- Irreversible liver damage resulting from statin therapy is exceedingly rare.
- Routine monitoring is not likely to identify the very rare individual who may develop significant liver injury.
- Routine monitoring will detect isolated increases in aminotransferase levels, causing physicians to alter or discontinue statin therapy.

*Cohen DE et al. Am J Cardiol. 2006;97:77C-81C*
# Incidence of Muscle AEs

<table>
<thead>
<tr>
<th>Muscle Adverse Events</th>
<th>Incidence above placebo (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias <em>(sore muscles)</em></td>
<td>1,500 to 3,000</td>
</tr>
<tr>
<td>Myopathy <em>(Symptoms + increased enzymes)</em></td>
<td>5</td>
</tr>
<tr>
<td>Rhabdomyolysis <em>(muscle damage)</em></td>
<td>1.6</td>
</tr>
</tbody>
</table>

Law M, Rudnicka AR. *Am J Cardiol.* 2006;97:52C-60C
38% of Severe muscle damage patients Associated With Gemfibrozil & Statins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Gemfibrozil</td>
<td>38%</td>
</tr>
<tr>
<td>Miberfradil</td>
<td>2%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4%</td>
</tr>
<tr>
<td>Macrolide Antibiotics</td>
<td>3%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5%</td>
</tr>
<tr>
<td>Azole Antifungals</td>
<td>1%</td>
</tr>
</tbody>
</table>

Thompson PD et al. JAMA. 2003;289:1681-1690
Statins and Cognitive Function

60+ cases of “reduced cognition” have been reported in patients taking a statin

- Average age 62
- Most complained of memory loss
- Sx began within 6 months of starting the statin
- Implicated are atorvastatin, pravastatin, and simvastatin
- No relationship with cholesterol level
- Most reported no specific memory test results
- 14 of 33 cases (42%) memory loss resolved with DC of statin (11 no improvement)
- 4 out of 4 cases had recurrence of sx with rechallenge

Wagstaff LR et al. Pharmacotherapy. 2003;23:871-880
Statins and Cognitive Function

Results of 7 observational studies

Rockwood K et al. *Arch Neurol.* 2002;59:223-227
Wolozin B et al. *Arch Neurol.* 2000;57:1439-1443
Yaffe K et al. *Arch Neurol.* 2002;59:378-384

ALL COHORT STUDIES 0.43 (0.31-0.62)

Etminan et al. *Pharmacotherapy.* 2003;23:726-730
Trial of Patients with Mild to Moderate Alzheimer Disease


n = 31 in placebo; n = 32 in atorvastatin 80 mg/day for 1 year; mean age = 79

MMSE = 12-28; LDL-C reduction by atorvastatin: 54%

• There is no evidence that statins are a common or significant cause of peripheral neuropathy

• There is no evidence of a causal relation between impaired memory and/or cognition dysfunction and statin therapy

Brass LM et al. *Am J Cardiol.* 2006;97:86C-88C
Statins and Diabetes Mellitus

New studies suggest an increase in DM incidence of patients on statins – not a consistent finding

Systematic reviews inconclusive*

Effect is very small if present (Odds Ratio 1.09)**

Notable marked reduction in risk of CHD and other outcomes in patients with DM, metabolic syndrome, obesity ***

Note that risk may be increased, it is small, and the medicine is still beneficial and important

*Current Medical Research and Opinion; 2008:24;1359-1362

**Lancet 2010; 375:735-742.

Other Cholesterol Medicines

Zetia / Ezetimibe
Welchol / Colestipol / Cholestyramine
Niacin
Fenofibrate / Gemfibrozil
Fish oil
Benecol
Others
CONCLUSIONS

Statin are as safe as aspirin and at least as beneficial, if not more so, in reducing CVD risk

If a million at-risk patients with high cholesterol were treated with a statin:

- about 10,000 heart attacks or strokes could be prevented each year
- 1-2 patients might experience a serious side effect

The problem is not that too many patients are having adverse effects with statins – the problem is that too many people may be avoiding statins because of an unnecessary fear of adverse effects

If a side effect develops on statin therapy, consider a medication holiday, recurrence of therapy, or after medication holiday a change in class or change in type of cholesterol treatment

Talk to your doctor or other clinician first!
Thank you!
~24% Risk Reduction Regardless of LDL-C

LDL-C = 65 mg/dL

Baseline LDL-C

- Placebo
- Simvastatin 40 mg

Lancet 2002;360:7

*P=0.0006
†P<0.0001