"Ten Things Statins are Good For"

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Ten Things Statins Are or May Be Good For

- CVD
  - Prevention of MI and related mortality
  - Primary & secondary
  - Thrombotic CVA
    - Secondary
    - Patients with CHD
    - Patients with CVA
  - CHF mortality
- Atrial Fibrillation
- Severe infections and sepsis
- Ophthalmologic disease
  - Cataract
  - Macular degeneration
- Neurosurgery
- Anesthesia
- Osteoporosis
- Dementia
- Contrast-induced nephropathy
- Cancer

Statins and Cancer

"Few strong or consistent associations between statins and cancer incidence overall or for any of the sites reviewed were detected. Data for any effects of statins on cancer prognosis and secondary prevention are lacking; with the exception of consistent evidence that statins are associated with reduced risk of advanced/aggressive prostate cancer. Statins appear safe in relation to cancer risk but any chemopreventive effect in humans remains to be established and should not be recommended outside the context of clinical trials. It is encouraging that numerous trials are ongoing."

**The Pleiotropic Effect of Statins**

- All cells
  - ↓ cholesterol synthesis
  - ↑ LDL receptors
Revised NCEP ATP III LDL-C Goals

<table>
<thead>
<tr>
<th>CHD Risk Category</th>
<th>LDL-C Goal</th>
<th>Consider Drug Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (Very High)</td>
<td>CHD or Risk Equivalent (&gt;20%/10 yrs)</td>
<td>&lt;100 (&lt;70)</td>
</tr>
<tr>
<td>Moderately High</td>
<td>2+ RF (10-20%/10 yrs)</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Moderate</td>
<td>2+ RF (&lt;10%/10 yrs)</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Low</td>
<td>0–1 RF’s</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

* Consider drug options if below goal, but above goal for next higher risk level

Revised NCEP ATP III Non-HDL Goals

<table>
<thead>
<tr>
<th>CHD Risk Category</th>
<th>Non-HDL-C Goal</th>
<th>Consider Drug Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (Very High)</td>
<td>CHD or Risk Equivalent (&gt;20%/10 yrs)</td>
<td>&lt;130 (&lt;100)</td>
</tr>
<tr>
<td>Moderately High</td>
<td>2+ RF (10-20%/10 yrs)</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Moderate</td>
<td>2+ RF (&lt;10%/10 yrs)</td>
<td>&lt;190</td>
</tr>
<tr>
<td>Low</td>
<td>0–1 RF’s</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>

* Consider drug options if below goal, but above goal for next higher risk level

LDL-C Reduction in Statin Trials

Clinical statin trial data
\[ iE_{max} \text{ model, } r^2 = 0.82, \ p=0.01 \]

Statins: The Down Side

- Abnormal AST and ALT
  - < 3X ULN: ~1.3%
  - > 3X ULN: <1.0%
  - Dose related
- Myopathy: Any disease of muscles
  - Myalgias: pain in a muscle of group of muscles
    - ~10%
  - Myositis: muscle symptoms with ↑ CK
    - ~2.5%
  - Rhabdomyolysis: > 50 fold ↑ in CK + renal impairment
    - <0.1%

Bruckert E et al, Cardiov Drugs 19:403, 2005
Onusko E, J Fam Pract 57:449, 2008

What the Clinician Needs to Consider

- Hypothyroidism
- Other drugs
  - Fibrates,azole anti-fungals, cyclosporine, macrolides, diltiazem, HIV protease inhibitors
- Genetic differences in drug-metabolizing enzymes, e.g. OATP1B1
  - SLCO1B1, CYP2D2, 3A4
- Neuromuscular diseases
  - Mitochondrial myopathy, McArdles disease, myotonic dystrophy, polymyositis

Asymptomatic CK in high risk patients only
CK measured < 5 x normal

Mildly Symptomatic
- Symptoms worse: repeat CK & Stop or Reduce statin dose

Moderate to Severely Symptomatic
- Stop Statin: CK measured, hydrate if creatinine ↑
- Symptoms gone: CK ↓ & creatine ↓

Therapeutic Options

- Titrate Statin Dose to reach LDL and non-HDL-C goals
- Ezetimibe and/or BAS

- Fluvastatin or pravastatin, 20 mg per night or every other night
- Fluvastatin XL 80 mg per night
- Rosuvastatin 5 mg daily, every other day or weekly
- Red yeast rice, 600-1800 bid

Patient Types
Diagnostic Strategies

Eckel RH, JCEM In Press, 2010
The Pleiotropic Effect of Statins

- All cells
  - ↓ cholesterol synthesis
  - ↑ LDL receptors
- Endothelial cells
  - ↓ platelet activation & aggregation
  - ↑ eNOS
  - ↑ progenitor cells
- Smooth muscle cells
  - ↓ proliferation
  - ↓ migration
  - ↑ apoptosis

The Pleiotropic Effect of Statins

- Macrophages/monocytes
  - ↓ proliferation
  - ↓ MMP expression
  - ↓ oxLDL uptake
- Vascular inflammation
  - ↓ MHCII expression
  - ↓ hsCRP

The Effect of Statins on Leukocyte Adhesion and Migration and Endothelial Cell Immune Function.

Statins in Hospitalized Patients: Are They Beneficial?

• ACS
• Sepsis
• Contrast-induced nephropathy
• Peri-operative
• CHF
• Neurosurgical

Statins and the Acute Coronary Syndrome

• There is evidence that early statin administration following an acute coronary syndrome is beneficial.  
  (Schwartz GG et al., MIRACL, JAMA, 2001)
• It is unclear if this benefit is due to lipid changes, or other factors, such as effects on inflammatory markers.
Simvastatin and hsCRP in Hypercholesterolemia
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n = 40)</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Age, years</td>
<td>49.8 ± 3</td>
<td>48.2 ± 3</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>261 (11)</td>
<td>252 (10)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>176 (47)</td>
<td>269 (47)</td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>170 (10)</td>
<td>159 (8)</td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>69 (4)</td>
<td>46 (2) **</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>3.39 (0.6)</td>
<td>1.48 (0.2) *</td>
</tr>
<tr>
<td>Lp(a), nmol/L</td>
<td>74 (17)</td>
<td>45 (18)</td>
</tr>
</tbody>
</table>

**p < 0.01        * p < 0.05
Mean ± SEM

Effect of Simvastatin on log(hsCRP) in Hypercholesterolemic Subjects

* p = 0.011


Effect of Simvastatin on LDL Cholesterol in Hypercholesterolemic Subjects

**p < 0.001

Simvastatin and hsCRP in Patients with Type 2 Diabetes

• Patients with Type 2 diabetes:
  – Have higher baseline levels of hsCRP
    Schulze, et al., Diabetes Care, 2004
  – Are at increased risk for CVD events
    Haffner S et al., NEJM, 1998

Design

• Randomized, cross-over, double-blind
• Study phases
  – Simvastatin 40 mg every evening x 28 days
  – Placebo every evening x 28 days
  – Minimum 28-day washout between phases
• Highly-sensitive CRP (hs-CRP) was measured on days 0, 1, 3, 7, 14, 21, and 28
• 12-hour fasting lipid levels were measured on days 0, 7, 14, 21, and 28

Subjects with Type 2 Diabetes

\( n = 35 \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Value (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>13/22</td>
</tr>
<tr>
<td>Age, y</td>
<td>54 ± 2</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>Waist Circumference, Umbilicus, cm</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>103 ± 4</td>
</tr>
<tr>
<td>Women</td>
<td>108 ± 4</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>7.3 ± 0.2</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>219 ± 5</td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>133 ± 4</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>197 ± 14</td>
</tr>
</tbody>
</table>
**LDL Cholesterol**

- Placebo
- Simvastatin

*** p < 0.001

**Baseline hsCRP**

*Centers for Disease Control and Prevention/American Heart Association, 2003*

**Log(hsCRP) over 28 Days**

- Placebo
- Simvastatin

** Levels of Risk: hsCRP**
- hsCRP < 1.0 mg/L - "Low"  
- hsCRP 1.0-3.0 mg/L - "Average"  
- hsCRP > 3.0 mg/L - "High"
Clinical Values of HsCRP

Treatment with Simvastatin

** p < 0.01, log-transformed values, compared to placebo


Statins in Acute Coronary Syndrome

• ↓ ischemia
• ↑ vascular reactivity
• ↓ vascular inflammation
• ↓ plaque stability
  Rosenson RS, Tangney CC, JAMA 279:1643, 1998
• ↓ thrombotic tendency
  Rosenson RS, Tangney CC, JAMA 279:1643, 1998
• ↓ myocardial remodeling
• ↓ mortality at 2 yrs, not at 4 mo
  Briel M et al, JAMA 299:2046, 2006

Death & Nonfatal MI During 30-day after an ACS for Patients with Continued Statin Therapy, Withdrawn Statin Therapy, and Without Statin Therapy.

Heeshen CC et al, Circulation 105:1446, 2002
hsCRP and Uncontrolled Risk Factors in PROVE IT-TIMI 22 Trial: Pravastatin vs. Atorvastatin

Ray KK et al, JACC 46:1417, 2005

Effect of Pravastatin vs. Atorvastatin on MACE in Patients with ACS: PCI-PROVE IT:PROVE IT-TIMI 22:

Gibson CM et al, JACC 54:2290, 2009

Effect of Pravastatin vs. Atorvastatin on Revascularization in Patients with ACS: PCI-PROVE IT:PROVE IT-TIMI 22:

Gibson CM et al, JACC 54:2290, 2009
Statins in Hospitalized Patients: Are They Beneficial?

- ACS
- Sepsis

Mortality from Any Cause in Sepsis: Effect of Statins

Randomized Clinical Trials of Statins and Infections
Statins Do Not Protect Against Influenza Morbidity

ORs for Statin Use and Pneumonia Hospitalization (A), 30-day Pneumonia Mortality (B), and All-Cause Mortality (C), by Influenza Season: Patients on Statins vs. No Statins.

Statins in Hospitalized Patients: Are They Beneficial?

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- Sepsis
- Contrast-induced nephropathy
Statin Pretreatment and Contrast-Induced Nephropathy


Statins in Hospitalized Patients: Are They Beneficial?

• ACS
• Sepsis
• Contrast-induced nephropathy
• Peri-operative

ARMYDA Trial: Incidence of Periprocedural MI in the Atorvastatin vs. Placebo

Pasceri V et al, Circulation 110:674, 2004
Peri-Operative Statins

• Prospective observational study of n=418 undergoing CABG
  – 73 no statins
  – 87 LDL cholesterol ↓ by 45% (estimated)
  – 258 LDL cholesterol ↓ by <45% (estimated)
• Outcomes: In-hospital CHF, malignant arrhythmias, or cardiac death
• OR of statins 0.56 (0.32-0.96, p<0.05)
  – High dose vs. lower dose 0.62 (0.41-0.93, p<0.05)

Quattara A et al, J Cardiothor Vasc Anesth 5:633, 2009

Statins in Hospitalized Patients: Are They Beneficial?

• ACS
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• Contrast-induced nephropathy
• Peri-operative
• CHF

Event-Free Survival from Atrial High Rate Episodes with Duration ≥1 min (A) and 10 min (B) in Patients with Bradyarrhythmias an Pacemakers: Effect of Atorvastatin

Tsai CT et al, Am Heart J 158:65, 2008
Kaplan-Meier Survival-Free CHF: Effect of Statins

Kaplan-Meier Survival: Effect of Statins

Statins in Hospitalized Patients: Are They Beneficial?

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- Neurosurgical
Subarachnoid Hemorrhage: Effect of Pravastatin

[Graph showing effect of pravastatin on clot retraction]


Functional Deficits and Lesion Size in Mice at Day 5 after Cerebral Ischemia and IV Treatment with Rosuvastatin

[Images showing functional deficits and lesion size]


Summary and Conclusions: Benefit of Statins

<table>
<thead>
<tr>
<th>Condition</th>
<th>Benefit of Statins</th>
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<tbody>
<tr>
<td>Acute Coronary Syndromes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Perhaps – randomized trials needed</td>
</tr>
<tr>
<td>Contrast-Induced Nephropathy</td>
<td>Questionable – randomized trials needed</td>
</tr>
<tr>
<td>Peri-operative or Peri-procedural</td>
<td>Perhaps – randomized trials needed</td>
</tr>
<tr>
<td>CHF</td>
<td>Perhaps – randomized trials needed</td>
</tr>
<tr>
<td>Neurosurgery</td>
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