Statins and Cognition
A Focus on Mechanisms

Disclosures: SPARCL Steering Committee and past consultant for Pfizer

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Vascular and Non-Vascular Dementia

- No pathological criteria for diagnosis
- No diagnostic “gold standard”
- Other neurodegenerative conditions often co-exist in patients with evidence of ischemic injury or prior hemorrhage

Additional Information for Patients
- Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once the drug was no longer being taken.

Additional Information for Healthcare Professionals
- There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Degenerative and Vascular Pathology

Vascular and Non-Vascular Dementia

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Vascular Ds.</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Smoking</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CHD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diabetes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>apoE4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Inc. Homocysteine</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
<td>+/–</td>
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O’ Brien Am J Geriatr Psych 2006;14 724-733
**Vascular Injury and AD Pathology**

**Pathophysiology**
- Vascular injury → Increased AD pathology
- Arteriosclerosis/ atherosclerosis → Hypoxia/ ischemia
- Reduced perilymphatic drainage → Tau Phosphorylation
- Reduced amyloid clearance → Increased APP Cleavage
- Increased AD pathology

*O’Brien Am J Geriatr Psych 2006;14:724-733*

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**Amyloid Precursor Protein Processing**


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**Cholesterol and APP Processing**


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**Cholesterol in the Brain**

- 25% of cholesterol in humans is in the brain, mostly in myelin.
- Almost all brain cholesterol is a product of local synthesis.
- Blood-brain barrier blocks exchange with the circulation.
- De novo brain synthesis balanced by excretion of oxysterol 24S-hydroxycholesterol which can cross the blood-brain barrier.
- In adults, neurons rely on glia for delivery of cholesterol.

*Bjorkhem & Meaney Arterioscler Thromb Vasc Biol. 2004;24:806-815*

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**Statins**

**Blood-Brain Barrier Permeability**

- Lipophilic
  - Simvastatin
  - Fluvastatin
  - Cerivastatin
  - Lovastatin
  - Atorvastatin
- Hydrophilic
  - Pravastatin
  - Rosuvastatin

*Data from Sierra et al. J Alzheimer's Dis 23 (2011) 307–318*
Statin Effects on Biomarkers

- Blood-brain barrier blocks most statins.
- No difference in the effects of hydrophobic and hydrophilic statins.
- Biomarker studies show inconsistent results.
- Only one found a reduction in the 4S-hydroxycholesterol:cholesterol level.

Statins and Cognition Pathophysiology

- Cholesterol-lowering decreases γ-secretase activity
  - Decreases conversion APP to Aβ
  - Decrease amyloid pathololgy
- Inconsistent evidence of statin effect on CNS biomarkers.
- Little evidence of central effect.
- Little exchange between central and peripheral cholesterol pools.
- Therefore, seems unlikely that statins would affect cognition by affecting amyloid processing.
- Given overlap between vascular disease and AD, effects might be mediated through vascular effects.

Lipid-Lowering and Dementia Canadian Study of Health and Aging

- Case-control
- N=2305>65 yo - Dementia free
- Baseline 1991-92
- Follow-up 1994
- 492 developed dementia
  - Statins, n=57
  - Other LLA, n=15
  - Any LLA, n=71

Statins and Dementia UK General Practice Research Database

- Case-control
- 284 new onset dementia
  - 4.6% on statins
- 1080 matched controls
  - 10.9% on statins
- 71% lower risk with statins

Statins and Cognitive Decline Prospective Cohort Study

- N=1674 older Mexican Americans free of dementia
- Annual cognitive and clinical evaluations
- 5-year follow-up
- DSM-IV, NINDS-ADRDA

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<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<td>Statin use</td>
<td>0.56</td>
<td>(0.37, 0.87)</td>
<td>0.01</td>
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<td>Diabetes</td>
<td>2.01</td>
<td>(1.39, 2.92)</td>
<td>0.0002</td>
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<td>Stroke</td>
<td>1.80</td>
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<td>0.02</td>
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<td>1.67</td>
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Statins and Cognitive Decline Prospective Cohort Study

- 2,356 cognitively intact persons age >65 y
- 13,110 person-years
- 392 used statins
- 312 new onset dementia

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CIND – Cognitive Impairment No Dementia
Statins and Cognitive Decline
Prospective Cohort Study

Design
- 2,356 cognitively intact persons age >65-y.
- 13,110 person-years
- 392 used statins
- 312 new onset dementia

Table showing study results
No effect of statins

Li et al. Neurology 2004;63: 1624–1628

Statins and Dementia
Prospective Cohort Study

- 929 older Catholic clergy.
- 69% women, baseline age 75 years.
- Free of dementia.
- 12.8% statin use at baseline.
- Up to 12 years of follow-up.
- No relationship with incident AD.
- No relationship with cognitive decline.

Arvanitakis et al. Neurology 2008;70:1795-1802

PROSPER
Cognitive Outcomes Substudy

- Prospective
- RCT
- N=5,804
- Age 70-84 years
- 1997-1999
- Pravastatin vs. placebo

Figure showing study results
No effect of statin on cognitive measures

Trompet et al. J Neurol 2010;257:85–90

Atorvastatin for Mild-Moderate AD
Randomized Trial

Figure showing study design

Feldman et al. Neurology 2010;74:956 –964

Atorvastatin for Mild-Moderate AD
Outcome

Figures showing study results
No effect of treatment

ADAS-cog:
Scores range 0-70 points (70 worst)
11 subtests
(memory, language, praxis)

ADCS-CGIC:
Scores range 1-7 points
1. Marked improvement
4. No change
7. Marked worsening

Feldman et al. Neurology 2010;74:956 –964
Statins for Treatment of Dementia
Meta-analysis

Figures showing study results
No effect of statins on ADAS-Cog or MMSE change

McGuinness et al. Cochrane Review

Statins and Dementia

- Case-control studies suggest benefit.
- Prospective cohort studies inconsistent.
- RCTs negative.
  - Pravastatin (no BBB penetration)
  - Atorvastatin (limited BBB penetration)

Lovastatin and Cognitive Function

- 209 healthy adults with LDL-C ≥ 160 mg/dL.
- Randomized to lovastatin 20 mg/d or placebo X 6-m.
  - 25% reduction in LDL-C
- Assessments of neuropsychological performance, depression, hostility, and quality of life
- Practice effect in all domains in placebo patients.
- No psychological distress or substantially alteration in cognitive function with treatment.

- Small decrements on attention and psychomotor speed with treatment, the clinical importance of which is uncertain.