ΣΤΑΤΙΝΕΣ ΚΑΙ ΓΝΩΣΙΑΚΗ ΕΚΠΤΩΣΗ

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& Μονάδα Έρευνας του Πανεπιστημίου Αθηνών
Πανεπιστημιακό Γ.Ν “ΑΤΤΙΚΟΝ”
Δήλωση σύγκρουσης συμφερόντων

- Η ομιλία αντανακλά τις απόψεις του ομιλητή

- Η Βαΐα Λαμπαδιάρη έχει λάβει τιμητικές αμοιβές (honoraria) για διαλέξεις σε συνέδρια, επιστημονικές ημερίδες/εκδηλώσεις και συμβουλευτική από τις εταιρίες: Sanofi, Novartis, NovoNordisk, MSD, Boehringer, Eli-Lilly, Vianex, Elpen, Amgen, Boehringer,
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**NORMAL CHOLESTEROL METABOLISM**

- **Synthesis**
  - Primary synthetic sites are extrahepatic, but liver is key regulator of homeostasis

- **Absorption**
  - Largest source is biliary secretion, not diet.
  - Normal absorption: 50%
  - For cholesterol to be absorbed it must:
    - undergo hydrolysis (de-esterification by esterases)
    - be incorporated into micelles
    - be taken up by cholesterol transporter
    - be re-esterified and incorporated into chylomicrons
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NORMAL CHOLESTEROL ABSORPTION

Defect in ABCG5/G8 transporter causes phytosterolemia.
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Statin Therapy and the Mevalonate Pathway

Acetyl-CoA → HMG-CoA → Mevalonate → Geranyl-PP → Farnesyl-PP → Squalene → Cholesterol

- Statins block HMG-CoA Reductase

- Ras, dolichol, coenzyme Q10

- Vitamin D3, estrogen, testosterone, progesterone, cortisol, bile acids

Rab, Rho
Factors Contributing to \([\text{A}\beta_s]\)

Cholesterol regulates the production and clearance of \(\text{A}\beta\).
Decreased clearance of \(\text{A}\beta\) is responsible for the development of AD, rather than increased \(\text{A}\beta\) synthesis.

*Gene.* 2017 Jan 15;597:10-16.

Adapted from Hazzard 2004 AGS annual meeting
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*Gene*. 2017 Jan 15;597:10-16.
Cholesterol & Alzheimer’s

- In human studies there are more β-amyloid plaques in patients dying from heart disease than from other causes (Sparks 1991)

- Cholesterol >240 between age 40-50 predicted higher AD risk 30 years later (Notkolo 1998)

- In animal studies, rabbits fed high cholesterol diet led to plaques that regressed when cholesterol was removed

What do we do with our effective cholesterol lowering drugs?

*Adapted from Hazzard 2004 AGS annual meeting*
As cholesterol cannot be directly exported across the blood–brain barrier (BBB), it is converted to 24-hydroxycholesterol by the enzyme cholesterol 24-hydroxylase, which is encoded by cyp46a1 and expressed in select neuronal populations including cortical and hippocampal pyramidal cells, dentate gyrus granule cells, Purkinje cells, and thalamic neurons.

Neuronal cholesterol homeostasis is intimately linked to cognitive function and to the trafficking and processing of amyloid precursor protein (APP)

the repertoire of lipoproteins found in the CNS differs considerably from that in the circulation

apoA-I on circulating HDL particles may also have beneficial roles in cerebral vessels, thereby providing indirect benefit to brain cells.

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Low Cholesterol during Childhood Promotes “Cycle of Violence”*

“In summary, we found a significant correlation between exposure to violence as a child and expression of violence as an adult (i.e. cycle of violence), only in the group with cholesterol levels below the median.”

*P Asellus et al., Psychiatry Research 215 (2014) 646–650
Low Serum Cholesterol and Suicide*

- Primary prevention trials involving lowering serum cholesterol report increase in deaths due to suicide or violence
- Number of serotonin receptors in mouse brain synaptosomal membrane depends on cholesterol concentration
- Decrease in serotonin leads to aggressive behavior

17 Year Study on Elderly*  Prognostic significance of serum cholesterol, lathosterol, and sitosterol in old age; a 17-year population study

- Begun in 1990: all subjects were at least 70 years old
- Measured serum cholesterol, ability to synthesize cholesterol, and ability to absorb cholesterol through the intestines
- Low values of all three parameters were associated with accelerated mental decline and increased physical frailty
- Subjects with low values on all three had 4 ½ years decreased life span

Low cholesterol is associated with increased frailty and accelerated mental decline, as well as early death

* Tilvis et al., Annals of Medicine, Early Online, 2011
Alzheimer’s and Serum Cholesterol

"Significantly lower lipid levels were found in patients with AD, than in controls. Patients in the late phase of AD had significantly lower entire lipid profile than controls and significantly lower cholesterol and LDL-C levels than patients in the middle stage of AD.”*

*Presečki et al., Coll. Antropol. 35, Suppl. 1: 115–120, 2011.
“Former Use” of Statins is Associated with Increased Risk to Alzheimer’s

"However, former use of statins was associated with an elevated risk of all-cause dementia (HR, 1.88; 95% CI, 1.05-3.36) and AD alone (HR, 2.54; 95% CI, 1.24- 5.20) compared with never users.” *

Hazard ratio 1.21 for Alzheimer’s for “ever used statins” v.s. “never used statins.”

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Memory Loss

- Review of adverse events reported to the FDA from 11/1997 – 2/2002 found 60 reports of memory changes. Most were with lipophilic statins (Atorvastatin and Simvastatin).
- Annals of Internal Medicine (2013) published a review of randomized trials and observational studies that did not suggest that statins harm cognition. Quality of evidence was low to moderate, especially with high-intensity therapy.
Cognitive adverse events

FDA reviewed the AERS database, the published medical literature (case reports and observational studies), and randomized clinical trials to evaluate the effect of statins on cognition. The post-marketing adverse event reports generally described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy. Time to onset of the event was highly variable, ranging from one day to years after statin exposure. The cases did not appear to be associated with fixed or progressive dementia, such as Alzheimer’s disease. The review did not reveal an association between the adverse event and the specific statin, the age of the individual, the statin dose, or concomitant medication use. Data from the observational studies and clinical trials did not suggest that cognitive changes associated with statin use are common or lead to clinically significant cognitive decline.
Reduction in Stroke

- SPARCL: Atorvastatin reduced stroke, CAD events. No reduction in all cause mortality.
- HPS: Simvastatin reduced risk of first stroke (ischemic) compared to placebo.
- CARE: Pravastatin reduced risk of CAD event, CVA and CVA + TIA.
- ASCOTT-LLA: In high risk primary prev. patients with HTN and normal lipids, the risk of CVA was lower with Atorvastatin than placebo.
Pleiotropic benefits

- Plaque stabilization
- Reduces inflammation
- Improves endothelial function
- Promotes angiogenesis
- Repair endothelial injury
- Stabilizes arterial plaque
- Prevents cardiovascular and cerebrovascular events
Prevention of Dementia

• Retrospective studies have shown that statins may prevent dementia.
• The Rotterdam study (n=6992) showed a decreased risk of Alzheimer's Disease.
• Randomized controlled trials with dementia or cognitive decline as a primary endpoint are needed to determine this risk.
Prevalence

- About 50% of U.S. adults have an elevated total cholesterol level
- Majority of patients with atherosclerosis have some form of dyslipidemia
- 70-80% of individuals with dyslipidemia do not meet LDL cholesterol targets despite lipid therapy
- Vascular risk factors, including high cholesterol levels, increase the risk for dementia due to Alzheimer disease and vascular dementia. Some observational studies have suggested an association between statin use and lowered incidence of dementia.
Statins and Cognitive Function: Non-RCT observations favour statin use

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

0.43 (0.31-0.62)

*ALL COHORT STUDIES*

Etminan et al. *Pharmacotherapy.* 2003;23:726-730
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## HPS – Results of Testing for Neuropsychiatric Disorders

<table>
<thead>
<tr>
<th>Measure</th>
<th>Simvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitively Impaired*</td>
<td>23.7%</td>
<td>24.2%</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Psychiatric Disorder</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Suicide</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

### PROSPER – Results of Testing for Cognitive Function

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pravastatin - Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of correct letter digits recalled</td>
<td>-0.01 (-0.24-0.23) p=0.95</td>
</tr>
<tr>
<td>Number of words Remembered</td>
<td>+0.02 (-0.12-0.16) p=0.80</td>
</tr>
<tr>
<td>Time needed to complete Stroop test</td>
<td>+0.8 s (-0.4-2.0) p=0.19</td>
</tr>
<tr>
<td>MMSE score</td>
<td>+0.06 (-0.04-0.16) p=0.26</td>
</tr>
</tbody>
</table>

Conclusions of the NLA Safety Task Force on Neurology

- There is no association between statin use and clinically meaningful peripheral neuropathy
- There is no convincing evidence that statins cause impaired memory or cognitive dysfunction
- Clinical trial data indicate that lowering lipids with statins does not increase risk of cerebral hemorrhage

Brass LM et al. Am J Cardiol. 2006;97:86C-88C
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### Statin Use and the Risk of Parkinson's Disease: An Updated Meta-Analysis.


Fig 2. Forest plot in overall analysis.
Statin Use and the Risk of Parkinson's Disease: An Updated Meta-Analysis.

Fig 4. Forest plot in analysis of long-term statin use in relation to the risk of PD.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0152564
In 295 older adults, we compared white matter hyperintensities (WMH) on brain magnetic resonance imaging and, total WM fractional anisotropy (FA) and GM mean diffusivity (MD) on diffusion tensor imaging, of Alzheimer’s disease (AD) relevant regions in statin-exposed and statin unexposed participants stratified by Modified Mini-Mental Status Examination (3MS) score.

There was no overall effect of statin exposure on cerebral structural indices.

Discussion: **Statins may benefit WM in older adults vulnerable to dementia.**
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**HOPE-3: 2 x 2 Factorial Design**

N = 14,000 people at intermediate risk for CVD

- **Rosuvastatin (10mg)**
- **Placebo**
- **Candesartan/HCT (Atacand plus 16/12.5mg)**
- **Placebo**
- **R Rosuvastatin + Candesartan/HCT**
- **R Rosuvastatin + Placebo**
- **Candesartan/HCT + Placebo**
- **Placebo + Placebo**

Follow-up for an average of 6 years
At baseline, mean LDL cholesterol level was 128 mg/dL and mean blood pressure (BP) was 138/82 mm Hg. During median follow-up of 5.6 years, key findings were as follows:

- Compared with placebo, rosvastatin lowered mean LDL cholesterol level by 35 mg/dL, and the antihypertensive drugs lowered mean systolic/diastolic BP by 6/3 mm Hg.
- The first coprimary outcome (CV-related death, nonfatal stroke, or nonfatal myocardial infarction [MI]) occurred significantly less frequently with rosvastatin than with placebo (3.7% vs. 4.8%); absolute reductions were 0.3%, 0.4%, and 0.5% for CV-related death, MI, and stroke, respectively.
- Overall, candesartan/hydrochlorothiazide did not significantly lower the incidence of the first coprimary outcome compared with placebo (4.1% vs. 4.4%); however, it did lower the incidence in a subgroup with highest baseline systolic BP (>143 mm Hg; 4.8% vs. 6.5%).
- Overall, outcomes with rosvastatin plus candesartan/hydrochlorothiazide were not significantly better than outcomes with rosvastatin alone.
- All-cause mortality was not lowered by active therapies compared with placebo.
- Neither treatment increased risk for diabetes; a small excess of muscle pain was noted with rosvastatin and dizziness with candesartan/hydrochlorothiazide.

April 2016, NEJM
NEW ORLEANS — A large substudy of the HOPE-3 trial found no benefit relating to cognitive function in patients who took cholesterol or blood pressure-lowering drugs.

A HOPE-3 substudy, presented at the American Heart Association meeting in New Orleans, examined the effect of the study drugs on cognitive and functional decline in 1,626 patients over more than 5 years of followup. There were no significant differences in any of cognitive and functional outcome measures in the study. However, there was a trend toward improvement in a post hoc analysis that looked at the small number of patients (n=93) who at baseline were in the highest tertile of blood pressure (over 145 mm Hg) and LDL (over 140 mg dL). One potentially important finding of the study is that there was no evidence of any sort for cognitive decline in patients taking rosvastatin.

- it was difficult to detect a difference in a population that was somewhat healthier than expected.
- hope that significant benefits might be found by treating, on the one hand, higher risk populations or, on the other hand, younger patients for a longer period of time
- earlier intervention may be the best way to achieve a beneficial effect.

AUG 2016 AHA
two trials with **26,340 participants aged 40 to 82 years** of whom 11,610 were aged 70 or older. All participants had a history of, or risk factors for, vascular disease. The studies used different statins (simvastatin and pravastatin).

There were no differences between statin and placebo groups on five different cognitive tests. **Statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia.** Statins could prevent dementia due to their role in cholesterol reduction and initial evidence from observational studies was very promising. However, indication bias may have been a factor in these studies and the evidence from subsequent RCTs has been negative. There were limitations in the included studies involving the cognitive assessments used and the inclusion of participants at moderate to high vascular risk only.
a retrospective cohort study compared **482 543 statin users** with **2 control groups**: 482 543 matched nonusers of any LLDs and all 26 484 users of nonstatin LLDs.

Both statin and nonstatin LLDs were strongly associated with acute memory loss in the first 30 days following exposure in users compared with nonusers but not when compared with each other. **Thus, either all LLDs cause acute memory loss regardless of drug class or the association is the result of detection bias rather than a causal association.**

*JAMA Intern Med. 2015;175(8):1399-1405.*
Table 3. Acute Memory Loss Comparing Statin Users With Nonusers of Any LLDs and With Users of Nonstatin LLDs

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Patients With Incident Acute Memory Loss After First Exposure, No. (%)</th>
<th>Statin vs Nonuse of LLD, Adjusted OR (95% CI)</th>
<th>Statin vs Nonstatin LLD, Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin Users (n = 482,543)</td>
<td>Adjusted for Matching Variables&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Adjusted for Matching and All Other Confounding Variables&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any time after first exposure</td>
<td>14,637 (3.03)</td>
<td>1.33 (1.30-1.37)</td>
<td>1.23 (1.18-1.28)</td>
</tr>
<tr>
<td></td>
<td>Matched Nonusers of Any LLDs (n = 482,543)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11,138 (2.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unmatched Users of Nonstatin LLDs (n = 26,484)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>724 (2.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30 d After first exposure</td>
<td>376 (0.08)</td>
<td>3.30 (2.67-4.07)</td>
<td>4.40 (3.01-6.41)</td>
</tr>
<tr>
<td></td>
<td>Matched Nonusers of Any LLDs (n = 26,484)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>114 (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unmatched Users of Nonstatin LLDs (n = 26,484)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (0.07)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LLD, lipid-lowering drug; OR, odds ratio.

<sup>a</sup> Indicates conditional logistic regression used.

<sup>b</sup> Matching variables were sex, age group, and enrollment duration. The patient's general practitioner was a matching variable but not included in the model because stratifying on 533 practices would have destabilized the model.

<sup>c</sup> Indicates ordinary logistic regression used.

<sup>d</sup> Other confounding variables included indication variables (diabetes mellitus, hypercholesterolemia, cardiovascular disease, hypertension, stroke, and antihypertensive drugs) and other confounders (Cushing syndrome, alcohol abuse, drug abuse, smoking or chronic obstructive pulmonary disease, depression, electroconvulsive therapy, or anxiety disorders; menopausal symptoms; retinopathy; vitamin B<sub>12</sub> deficiency or supplementation; thiamine deficiency; vitamin D deficiency; mercury exposure; human immunodeficiency virus, cytomegalovirus, or herpesvirus; liver disease; kidney disease; and use of antidepressants, antipsychotics, anxiolytics, stimulants, antiepileptics, antihistamines, chemotherapy, corticosteroids, antiretroviral therapy or highly active retroviral therapy, estrogens, barbiturates, or indomethacin) except for the matching variables.

Table 4. Acute Memory Loss Comparing Nonstatin LLDs With Their Own Matched Nonusers of Any LLDs

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Patients With Incident Acute Memory Loss After First Exposure, No. (%)</th>
<th>Conditional Logistic Regression, Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Users of Nonstatin LLDs (n = 26,484)</td>
<td>Adjusted for Matching Variables&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Matched Nonusers of Any LLDs (n = 26,484)</td>
<td>Adjusted for Matching and All Other Confounding Variables&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any time after first exposure</td>
<td>724 (2.73)</td>
<td>1.51 (1.34-1.69)</td>
</tr>
<tr>
<td></td>
<td>Matched Nonusers of Any LLDs (n = 26,484)</td>
<td>0.96 (0.79-1.17)</td>
</tr>
<tr>
<td>0-30 d After first exposure</td>
<td>18 (0.07)</td>
<td>3.60 (1.34-9.70)</td>
</tr>
<tr>
<td></td>
<td>Matched Nonusers of Any LLDs (n = 26,484)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: LLD, lipid-lowering drug; OR, odds ratio.

<sup>a</sup> Indicates conditional logistic regression used.

<sup>b</sup> Other confounding variables included indication variables (diabetes mellitus, hypercholesterolemia, cardiovascular disease, hypertension, stroke, and antihypertensive drugs) and other confounders (Cushing syndrome, alcohol abuse, drug abuse, smoking or chronic obstructive pulmonary disease, depression, electroconvulsive therapy, or anxiety disorders; menopausal symptoms; retinopathy; vitamin B<sub>12</sub> deficiency or supplementation; thiamine deficiency; vitamin D deficiency; mercury exposure; human immunodeficiency virus, cytomegalovirus, or herpesvirus; liver disease; kidney disease; and use of antidepressants, antipsychotics, anxiolytics, stimulants, antiepileptics, antihistamines, chemotherapy, corticosteroids, antiretroviral therapy or highly active retroviral therapy, estrogens, barbiturates, or indomethacin) except for the matching variables.

<sup>c</sup> Indicates ordinary logistic regression used.
We examined the medical and pharmacy claims of a 20% sample of Medicare beneficiaries from 2006 to 2013 and compared rates of Alzheimer disease diagnosis for 399,979 statin users 65 years of age or older with high or low exposure to statins and with drug molecules for black, Hispanic, and non-Hispanic white people, and men and women of Asian, Native American, or unknown race/ethnicity who are referred to as “other.”

The reduction in Alzheimer disease risk varied across statin molecules, sex, and race/ethnicity. Clinical trials that include racial and ethnic groups need to confirm these findings.

- Simvastatin was associated with lower Alzheimer disease risk for white women, white men, Hispanic women, Hispanic men, and black women.
- Atorvastatin was associated with a reduced risk of incident Alzheimer disease diagnosis for white women, black women, Hispanic men, and women.
- Pravastatin and rosuvastatin were associated with reduced Alzheimer disease risk for white women only.
- High statin exposure was not associated with a statistically significant lower Alzheimer disease risk among black men.
certain patients, facing multiple, otherwise equal statin alternatives for hyperlipidemia treatment, may reduce AD risk by using a particular statin. **The right statin type for the right person at the right time may provide a relatively inexpensive means to lessen the burden of AD.**
We investigated the association between LDL-C variability and 4 cognitive domains at month 30 in 4428 participants of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk). Additionally, we assessed the association of LDL-C variability with neuroimaging outcomes in a subset of 535 participants.

**Conclusions**: We found that higher visit-to-visit variability in LDL-C, independently of mean LDL-C levels and statin treatment, is associated with lower cognitive performance, lower cerebral blood flow, and greater white matter hyperintensity load.
7484 men and women (63%) with mean age 73.9 years and no known history of vascular events at entry. Mean follow-up was 9.1 years.

**Lipid lowering drug users were at decreased risk of stroke compared with non-users (hazard ratio 0.66, 95% confidence interval 0.49 to 0.90);** hazard ratios for stroke were similar for statin (0.68, 0.45 to 1.01) and fibrate (0.66, 0.44 to 0.98)

Analyses stratified by age, sex, body mass index, hypertension, systolic blood pressure, triglyceride concentrations, and propensity score did not show any effect modification by these variables, either for stroke or for coronary heart disease.

**Conclusion**

In a population based cohort of older people with no history of vascular events, use of statins or fibrates was associated with a 30% decrease in the incidence of stroke.

*BMJ 2015;350:h2335*
## Table 2 | Association between risk of vascular events and lipid lowering drug therapy

<table>
<thead>
<tr>
<th>Baseline lipid lowering drug use</th>
<th>No of events</th>
<th>Adjusted hazard ratios (95% CI) for vascular events*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td><strong>Coronary heart disease or stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lipid lowering drug</td>
<td>545</td>
<td>Reference</td>
</tr>
<tr>
<td>Statins or fibrates</td>
<td>187</td>
<td>0.98 (0.83 to 1.16)</td>
</tr>
<tr>
<td>Statins</td>
<td>92</td>
<td>1.01 (0.81 to 1.26)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>95</td>
<td>0.96 (0.77 to 1.19)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lipid lowering drug</td>
<td>234</td>
<td>Reference</td>
</tr>
<tr>
<td>Statins or fibrates</td>
<td>58</td>
<td>0.71 (0.53 to 0.95)</td>
</tr>
<tr>
<td>Statins</td>
<td>29</td>
<td>0.74 (0.51 to 1.08)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>29</td>
<td>0.70 (0.48 to 1.01)</td>
</tr>
<tr>
<td><strong>Coronary heart disease†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lipid lowering drug</td>
<td>311</td>
<td>Reference</td>
</tr>
<tr>
<td>Statins or fibrates</td>
<td>129</td>
<td>1.18 (0.96 to 1.45)</td>
</tr>
<tr>
<td>Statins</td>
<td>63</td>
<td>1.19 (0.91 to 1.56)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>63</td>
<td>1.17 (0.90 to 1.53)</td>
</tr>
</tbody>
</table>
Experimental studies support links between cholesterol intake and amyloid synthesis, whereas observational studies indicate that patients receiving statins have a reduced risk of dementia. No evidence indicates a direct association between LL-therapy with statins and/or PCSK9 inhibitors and the risk of cognitive disorders. The evidence does not yet support routine administration of serial bedside memory tests in otherwise healthy patients receiving statins. The CV benefits of statin, and possibly of PCSK9 inhibitors are well documented and a small number of case reports of memory loss should not discourage their appropriate administration.
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the Statin Safety Expert Panel reaffirms the general safety of statin therapy.

The potential benefits of statin therapy outweigh the potential risks.

In general terms, the number needed to treat in preventing non-fatal myocardial infarction, revascularization, stroke, and CVD mortality, far outweighs needed to harm.

Because the absolute benefit of statins is related to an individual’s baseline risk, it is only in those individuals whose baseline risk is very low that the benefits of statin therapy may not outweigh the risk of adverse events.

However to date, based on the Cholesterol Treatment Trialists meta-analysis of 26 clinical trials and 170,000 patients, a value for the concentration of LDL-C or for total CVD risk has not yet been defined that is without relative benefit during statin therapy.
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Larger and better-designed studies are needed to draw unequivocal conclusions about the effect of statins on cognition.

Published data do not suggest an adverse effect of statins on cognition; however, the strength of available evidence is limited, particularly with regard to high-dose statins.
The only serious adverse events that have been shown to be caused by long-term statin therapy are myopathy, new-onset diabetes mellitus, and, probably, haemorrhagic stroke.

Typically, treatment of 10 000 patients for 5 years with an effective regimen (eg, atorvastatin 40 mg daily) would cause about 5 cases of myopathy (one of which might progress, if the statin therapy is not stopped, to the more severe condition of rhabdomyolysis), 50–100 new cases of diabetes, and 5–10 haemorrhagic strokes.

Placebo-controlled randomised trials have shown definitively that almost all of the symptomatic adverse events that are attributed to statin therapy in routine practice are not actually caused by it (ie, they represent misattribution).
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Similar proportional reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics.

Lancet 2016; 388: 2532–61
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Lancet 2016; 388: 2532–61

Figure 6: Effects of lowering LDL cholesterol with statin therapy on cause-specific mortality in meta-analyses of randomised trials of statin therapy
Adapted from CTT Collaboration website. Combined comparisons in randomised trials of routine statin therapy versus no routine statin therapy and of more versus less intensive statin therapy. RR=rate ratio.
The basis for the FDA 2012 decision was post-marketing event reports from individuals of ill-defined memory loss or impairment that appeared to be reversible after discontinuing statin therapy, and not because there was high quality evidence for a causal link.

Indeed, a subsequent assessment of FDA surveillance databases found the reporting rates of cognition-associated adverse events for statins to be similar to those of other drugs used in patients with atherosclerotic disease.

Consequently, given the weight of evidence against adverse effects of statin therapy on memory or other aspects of cognition, it would now be appropriate for regulatory authorities to consider their removal from lists of potential adverse effects on the drug labels so that patients are not inappropriately deterred from using statin therapy.
Evidence from observational and prospective randomized trials is summarized, leading to the conclusion that as for now, there is no good evidence that statins cause cognitive impairment to a significant degree.

Reported cases seem to be rare, and a causal relationship has not been established.
Table 1—Observational studies of cognitive effect of statins

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Design</th>
<th>No. of subjects</th>
<th>Age (years)</th>
<th>Follow-up (years)</th>
<th>Diagnosis of dementia</th>
<th>Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Nested case control</td>
<td>1,364</td>
<td>50–89</td>
<td>N/A</td>
<td>Computer-recorded clinical diagnosis</td>
<td>RR 0.29 (0.13–0.63)</td>
</tr>
<tr>
<td>18</td>
<td>Case control</td>
<td>655</td>
<td>Mean 78.7</td>
<td>N/A</td>
<td>Clinical diagnosis and MMSE</td>
<td>OR 0.23 (0.1–0.56)</td>
</tr>
<tr>
<td>19</td>
<td>Case control</td>
<td>2,305</td>
<td>≥65 (average 70.3)</td>
<td>N/A</td>
<td>Clinical diagnosis and MMSE</td>
<td>OR 0.26 (0.08–0.88)</td>
</tr>
<tr>
<td>20</td>
<td>Prospective observational</td>
<td>1,037</td>
<td>Mean 70</td>
<td>4</td>
<td>MMSE</td>
<td>OR 0.67 (0.42–1.05)</td>
</tr>
<tr>
<td>21</td>
<td>Retrospective cohort</td>
<td>1,290,071</td>
<td>≥65 (average 74.6)</td>
<td>N/A</td>
<td>ICD-9</td>
<td>HR 0.46 (0.44–0.48)</td>
</tr>
<tr>
<td>22</td>
<td>Prospective observational</td>
<td>1,674</td>
<td>≥60 (mean 70)</td>
<td>5</td>
<td>DSM-IV</td>
<td>HR 0.52 (0.34–0.80)</td>
</tr>
<tr>
<td>23</td>
<td>Prospective observational</td>
<td>6,992</td>
<td>Mean 69.4</td>
<td>Mean 9</td>
<td>DSM-III-R</td>
<td>HR 0.57 (0.37–0.90)</td>
</tr>
<tr>
<td>24</td>
<td>Propensity analysis</td>
<td>57,669</td>
<td>≥65 (mean 72.9)</td>
<td>Median 11.8</td>
<td>ICD-9</td>
<td>HR 0.385–0.829 depending on exposure</td>
</tr>
<tr>
<td>25</td>
<td>Prospective cohort</td>
<td>478</td>
<td>80</td>
<td>69</td>
<td>MHT</td>
<td>F = 5.78 for IQ change from childhood</td>
</tr>
<tr>
<td>26</td>
<td>Retrospective cohort</td>
<td>13,626</td>
<td>30–85 (mean 61)</td>
<td>7</td>
<td>ICD-9</td>
<td>OR 1.56 (1.19–2.03) in nonpersistent vs. persistent statin users</td>
</tr>
<tr>
<td>27</td>
<td>Cross-sectional</td>
<td>24,595</td>
<td>≥45</td>
<td>N/A</td>
<td>SIS</td>
<td>OR 1.03 (0.86–1.24)</td>
</tr>
<tr>
<td>28</td>
<td>Case control</td>
<td>548</td>
<td>≥65 (median 72)</td>
<td>N/A</td>
<td>Various tests</td>
<td>OR 0.8–1.5 depending on test, P = NS</td>
</tr>
<tr>
<td>29</td>
<td>Retrospective cohort</td>
<td>2,798</td>
<td>≥65 (56.7% &gt;80)</td>
<td>N/A</td>
<td>Various tests</td>
<td>HR 0.57 (0.77–1.52)</td>
</tr>
<tr>
<td>30</td>
<td>Prospective observational</td>
<td>3,587</td>
<td>Mean 72.8</td>
<td>3.4</td>
<td>CDR-SOB, MMSE</td>
<td>P = NS for deterioration</td>
</tr>
<tr>
<td>31</td>
<td>Observational cohort</td>
<td>756</td>
<td>Mean 74.2</td>
<td>N/A</td>
<td>Trail Making Test Part B</td>
<td>P = NS</td>
</tr>
<tr>
<td>32</td>
<td>Retrospective cohort</td>
<td>991,570</td>
<td>Mean 63.8</td>
<td>30 days</td>
<td>Computer-recorded clinical diagnosis</td>
<td>OR 4.40 (3.01–6.41)</td>
</tr>
</tbody>
</table>

CDR-SOB, Clinical Dementia Rating Sum of Boxes; IQ, intelligence quotient; MHT, Moray House Test; N/A, not applicable; NS, nonsignificant; RR, relative risk; SIS, Six-Item Screener.
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### Table 2—Randomized controlled trials with the relationship between statin use and cognitive function as a primary outcome

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of subjects</th>
<th>Age (years)</th>
<th>Follow-up</th>
<th>Diagnosis of cognitive function</th>
<th>Statin tested (mg)</th>
<th>Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>25</td>
<td>Average 23.8</td>
<td>4 weeks</td>
<td>Digit symbol substitution test</td>
<td>Simvastatin 40, pravastatin 40</td>
<td>P = NS</td>
</tr>
<tr>
<td>38</td>
<td>22</td>
<td>36–65</td>
<td>6 weeks</td>
<td>Rey Auditory Learning, Trail Making Test, Embedded Figures, Benton Visual Retention, Verbal fluency</td>
<td>Lovastatin 40, pravastatin 40</td>
<td>P = NS</td>
</tr>
<tr>
<td>39</td>
<td>36</td>
<td>Mean 51</td>
<td>4 weeks</td>
<td>Digit symbol substitution, auditory vigilance, selective reminding word recall, choice reaction time, finger tapping</td>
<td>Simvastatin 20, pravastatin 40</td>
<td>P = NS</td>
</tr>
<tr>
<td>40</td>
<td>36</td>
<td>Mean 50</td>
<td>4 weeks</td>
<td>Digit symbol substitution, choice reaction time, auditory vigilance, selective reminding word recall, finger tapping</td>
<td>Lovastatin 40, pravastatin 40</td>
<td>P = NS</td>
</tr>
<tr>
<td>41</td>
<td>367</td>
<td>Mean 71</td>
<td>6 months</td>
<td>Digit symbol substitution</td>
<td>Lovastatin 20–40</td>
<td>P = NS</td>
</tr>
<tr>
<td>42</td>
<td>308</td>
<td>Mean 54</td>
<td>6 months</td>
<td>12 neuropsychological tests</td>
<td>Simvastatin 10–40</td>
<td>Detrimental effect on recurrent words, Elithorn maze, and 4-word short-term memory tests</td>
</tr>
<tr>
<td>43</td>
<td>209</td>
<td>Mean 46</td>
<td>6 months</td>
<td>10 neuropsychological tests</td>
<td>Lovastatin 20–40</td>
<td>Detrimental effect on attention and psychomotor speed domains, as well as digit vigilance, recurrent words, Elithorn maze, and grooved pegboard tests</td>
</tr>
<tr>
<td>44</td>
<td>82</td>
<td>Mean 34</td>
<td>4 weeks</td>
<td>10 neuropsychological tests</td>
<td>Lovastatin 40, pravastatin 40</td>
<td>P = NS</td>
</tr>
<tr>
<td>45</td>
<td>1,016</td>
<td>&gt;20</td>
<td>6 months</td>
<td>Recurrent words, Elithorn maze, digit vigilance, grooved pegboard tests</td>
<td>Simvastatin 20, pravastatin 40</td>
<td>P = NS</td>
</tr>
<tr>
<td>46</td>
<td>97</td>
<td>Mean 57</td>
<td>6 months</td>
<td>8 neuropsychological tests</td>
<td>Atorvastatin 10</td>
<td>Beneficial effect on all domains</td>
</tr>
<tr>
<td>47</td>
<td>57</td>
<td>Mean 62</td>
<td>73 weeks</td>
<td>Digit Symbol Coding subtest, Trail Making Test, Stroop Color-Word Reading Test</td>
<td>Atorvastatin 10</td>
<td>P = NS</td>
</tr>
<tr>
<td>48</td>
<td>30</td>
<td>45–75</td>
<td>30 weeks</td>
<td>8 neuropsychological tests</td>
<td>Atorvastatin 30–80</td>
<td>Beneficial effect on verbal memory</td>
</tr>
</tbody>
</table>

NS, nonsignificant.
Atorvastatin attenuates cognitive deficits through Akt1/caspase-3 signaling pathway in ischemic stroke

Jie Yang, Ying Pan, Xuejing Li, Xianying Wang*

The Third Hospital of Hebei Medical University, PR China

Atorvastatin could protect neurons and reduce the impairment of learning and memory by blocking the activation of the caspase-3 through stimulating Akt1 (ser473) phosphorylation during reperfusion after cerebral ischemia.
The positive FOURIER Outcomes results are based on approximately 27,500 patients who had an MI, ischemic stroke, or symptomatic peripheral artery disease and an LDL cholesterol ≥70 mg/dL or a non-HDL cholesterol ≥100 mg/dL despite optimal statin therapy. The Trial met its primary end point—a composite of CV death, MI, stroke, and hospitalization for unstable angina or coronary revascularization—and a key secondary end point—a composite of CV death, MI, or stroke. And, according to the company, no new safety signals were observed.

The noninferiority EBBINGHAUS trial involves about 1900 patients enrolled in FOURIER Outcomes. The primary outcome was the Spatial Working Memory strategy index of executive function; secondary end points include working memory, memory function, and psychomotor speed as assessed with a tablet-based tool. The trial also met its primary end point, demonstrating that evolocumab was noninferior to placebo with regard to its effect on cognitive function.
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