# Remembering Statins: Do Statins Have Adverse Cognitive Effects?

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**The issue of statin-associated cognitive impairment has been a hot topic among both patients and health care providers, especially since the U.S. Food and Drug Administration (FDA) issued a statement regarding rare postmarketing reports of ill-defined cognitive impairment associated with statin use. This statement was based on case reports, and no objective measures of cognitive function were used. Nevertheless, many patients at high risk of cardiovascular disease have expressed concerns about possible cognitive decline and may have opted to forgo statin therapy. In this overview, the evidence leading to the statement by the FDA is reviewed. Potential mechanisms of the effect of LDL cholesterol reduction and statin therapy on cognition are discussed. 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.**

Hydroxymethylglutaryl CoA reductase inhibitors (statins) are a major contributor to cardiovascular disease prevention in patients with diabetes. In a prospective meta-analysis of more than 18,000 people with diabetes (mean age 63 years, with 43% over the age of 65 years) in 14 randomized trials, statins were shown to reduce both cardiovascular morbidity and mortality (1). As a result, both European (2) and U.S. (3) guidelines recommend statin treatment for almost all patients with diabetes. It is estimated that for people over the age of 55 years, statins would be recommended for 96.4% of men and 65.8% of women by the American College of Cardiology/American Heart Association guidelines and 66.1% of men and 39.1% of women by European Society of Cardiology guidelines (4).

With so many people eligible for treatment, even rare adverse effects become important. In 2012, the U.S. Food and Drug Administration (FDA) issued a statement regarding rare postmarketing reports of ill-defined cognitive impairment associated with statin use that was reversible upon statin discontinuation (5). This has led many people, patients and health care providers alike, to erroneously associate statins with dementia and may have contributed to low adherence rates.

This review will deal with the relationship between cholesterol and cognitive function and the possible effects of statins on short- and long-term cognitive function.

## Cholesterol and Cognitive Function

The human brain contains ~25% of the total cholesterol of the body. Cholesterol is a major lipid constituent of the myelin sheath and the membrane lipid rafts in neurons and astrocytes, participating in regulation of ion channel permeability, signal transduction, and other cellular functions (6). Lipoproteins have very limited permeability of the intact blood-brain barrier. Therefore, essentially all brain cholesterol is

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locally synthesized in astrocytes, which are the main source of cholesterol for neurons.

One of the pathological hallmarks of Alzheimer disease (AD) is the development of extracellular senile plaques, composed mainly of a small peptide known as amyloid-β (Aβ), thought to be a major causative agent in the development of AD. Cholesterol is believed to be an important factor in the regulation of Aβ production, with high cholesterol levels being linked to increased Aβ generation and deposition. Lower cholesterol levels shift amyloid precursor protein processing to nonraft regions of the membrane where the benign α-secretase cleavage pathway is favored (6).

Unlike lipoproteins, oxysterols, like 27-hydroxycholesterol, efficiently pass the blood-brain barrier. Hypercholesterolemia is associated with increased brain levels of 27-hydroxycholesterol, which may affect Aβ production. Alternatively, high LDL cholesterol (LDL-C) levels may damage the blood-brain barrier by inflammatory mechanisms, thus enabling leakage of serum cholesterol and other amyloidogenic factors to the brain. Thus, higher levels of LDL-C were associated with greater brain amyloid measured by positron emission tomography using the tracer carbon $^{11}$C-labeled Pittsburgh compound B, which specifically binds to Aβ plaques, independently of apolipoprotein E genotype (7).

Paradoxically, in some epidemiological studies, a low serum cholesterol level was associated with an increased risk of developing AD. However, this finding may be due to reverse causation, since some studies included elderly participants who might have already had AD at enrollment, making it difficult to distinguish between effects of cholesterol on the development of AD and alteration of cholesterol level because of the catabolic state and pathophysiological changes that accompany AD. Indeed, studies finding a negative correlation of cholesterol level with dementia risk were principally conducted in elderly patients, whereas studies finding a positive correlation tended to include younger patients (8). For example, in a study looking at 1,321 people (mean age 50 years, free from dementia at baseline, and followed for 21 years), cognitive impairment or dementia (diagnosed by the DSM-IV criteria) developed in 9% of the subjects. High mid-life total cholesterol levels were a risk factor for more severe cognitive impairment later in life (9). On the other hand, in a study looking at 382 subjects aged 70 years and free from dementia at baseline who were followed for 18 years, 24% developed dementia (diagnosed by the DSM-III-R criteria). High cholesterol levels in late life were associated with decreased dementia risk (10). One way of avoiding the risk of reverse causation is to look at genetic studies. In one small study, patients with familial hypercholesterolemia showed a high incidence of mild cognitive impairment compared with subjects without the disease. Importantly, this did not seem to be due to vascular dementia, since patients with a history of stroke or transient ischemic attack were excluded and the finding was unrelated to findings on brain MRI (11). Another study, using a Mendelian randomization approach, looked at the association between genotype risk scores for four blood lipid phenotypes (including total and LDL-C) and late-onset AD. No such association was found, leading the authors to conclude that genetic predisposition to increased blood cholesterol is not associated with elevated AD risk (12).

## Statins and Cognitive Function

Cholesterol is vitally important for brain function. While the brain represents ~2–3% of total body weight, 25% of the cholesterol in the body is found in the brain, where it plays important roles in membrane function. Because cholesterol synthesis is essential for the normal functioning of the brain, it is theoretically possible that excessive inhibition of cholesterol synthetic pathways may result in neurocognitive adverse effects. Statins may reduce cholesterol synthesis in the brain and interfere with myelin formation and function. In a mouse model, simvastatin impaired remyelination after chemical demyelination (13). Alternatively, statins induced reduction in coenzyme-Q10 levels and may lead to impaired mitochondrial functioning and increased oxidative stress, which may have an adverse effect on cognition.

Statins may affect cognition through their effect on the level of cholesterol. Alternatively, statins may exert pleiotropic effects unrelated to their effect on cholesterol. Several preclinical studies using cell cultures and animal models of AD have demonstrated that statins increase α-secretase activity and decrease Aβ production (8). In humans, lovastatin decreased serum Aβ levels in a dose-dependent manner when given to subjects without dementia (14).

In a study looking at brain autopsies from 110 subjects, ages 65–79 years, neuropathologic findings were compared between statin users and nonusers. The risk for typical AD pathology (Braak stage IV and Consortium to Establish a Registry for Alzheimer's Disease [CERAD] rating moderate) was reduced in statin users (15).

### *Case Reports Concerning Cognitive Effect of Statins*

In 2003, Wagstaff et al. (16), using the MedWatch drug surveillance system of the FDA, found 60 reports of patients who had memory loss associated with statins. Since then, several other case reports and case series have suggested a potential negative association between statins and cognitive function. In most reports, the main symptom related to statins was short-term memory loss that occurred a few months after the start of statin therapy or after a dosage increase. Cognitive impairment was usually reversible upon discontinuation of statin therapy. The cases did not appear to be associated with fixed or progressive dementia, such as AD. No association was found between cognitive impairment and a specific statin (lipophilic or hydrophilic), age, statin dose, or concomitant medications.

It should be noted that causality cannot be determined by this type of study. First, the patient population receiving statins is already at risk for memory loss because of cardiac risk factors and advancing age, which could lead to detection bias. Second, no objective memory tests were performed. In fact, a search of the same FDA postmarketing surveillance databases yielded cognitive-related adverse event reporting rates for statins (1.9 per million prescriptions) similar to those for other commonly prescribed cardiovascular medications, such as losartan (1.6 per million prescriptions) and clopidogrel (1.9 per million prescriptions) (17).

### *Observational Studies Concerning Cognitive Effect of Statins*

Several observational studies have looked into the association between statin use and cognitive function. Most of the studies demonstrated either a beneficial effect or no effect of statins on cognitive function and the risk of dementia.

Ten studies found an association between statin use and improved cognitive function, five studies found no association between statin use and cognitive function, and one study found an association between statin use and an increased risk of cognitive decline (17–32) (Table 1).

A few studies deserve special attention. In an analysis of 57,669 individuals aged >65 years with no history of dementia from Taiwan, adjusted HRs for dementia were significantly inversely associated with total or daily equivalent statin dosage (25). A higher exposure to statins (measured by accumulated dose, mean daily dose, number of days of taking a statin, or % of days taking a statin) was associated with a lower risk of dementia. The use of potent statins (atorvastatin, rosuvastatin) was associated with a lower risk of dementia than the use of less potent statins.

The one study that found an association between statin use and an increased risk of cognitive decline looked at the acute effects of statin treatment. This study compared 482,543 statin users with two control groups: 482,543 matched nonusers of any lipid-lowering drugs (LLDs) and 26,484 users of nonstatin LLDs. Compared with nonusers of any LLDs, statin users had an increased risk of acute memory loss but only during the 30-day window immediately after the first exposure (fully adjusted odds ratio [OR] 4.40). However, a similar pattern was found in users of nonstatin LLDs, leading the authors to speculate either that all LLDs cause acute memory loss or, more likely, that the association is the result of a detection bias caused by a higher likelihood of ascertainment of memory loss in patients receiving preventive therapies because of increased physician contact (33).

All of these studies suffer from the known limitations of nonrandomized trials. First, although most of these trials adjusted for various confounders, observational research is prone to bias and confounding. The results could be influenced by a "healthy user" effect and closer monitoring. Second, publication bias is possible, since observational studies with significant outcomes are more likely to be published and, therefore, overrepresented. Third, the methods of diagnosing

**Table 1—Observational studies of cognitive effect of statins**

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

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.

dementia and cognitive impairment varied widely, and some studies used computer-recorded diagnosis, which is prone to both over- and underdiagnosis.

#### *Randomized Controlled Trials Concerning Cognitive Effect of Statins*

Two large randomized controlled trials have examined the effect of statins on cognitive function as a secondary end point.

In PROSPER (Prospective Study of Pravastatin in the Elderly at Risk for Vascular Disease), pravastatin (40 mg daily) was compared with placebo in 5,804 elderly participants (34). The subjects were 70–82 years old (mean age 75 years). Cognitive function was assessed repeatedly at six different time points during the study using four neuropsychological performance tests. After a mean follow-up period of 42 months, a significant cognitive decline was observed in both groups, with no difference between pravastatin- and placebo-treated subjects. No adverse events such as memory loss or confusion were reported to be more common with pravastatin use compared with placebo.

In the Heart Protection Study (HPS), simvastatin (40 mg daily) was compared with placebo in 20,536 participants (35). The subjects were 40–80 years old (5,806 were at least 70 years of age at study entry). Similar numbers were reported to have developed dementia during follow-up (0.3% in both groups). The modified Telephone Interview for Cognitive Status (TICS-m) was administered to participants during their final follow-up after a mean of 5.3 years of treatment. There were no differences between the treatment groups in the percentages of patients classified as cognitively impaired, in the overall mean TICS-m score, in the scores for any of the four separate domains of TICS-m (including the one representing memory), or in a separate verbal fluency score. It should be noted that cognitive function was measured only once at the end of the study, so dropout due to cognitive impairment during the study could have biased the results.

In the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study, no differences in cognitive function were found between rosuvastatin and placebo users at the end of the trial, as measured by adverse event reports from the sites (including the terms dementia, dementia Alzheimer type, amnestic disorder, global amnesia, senile dementia, cognitive disorder, and vascular dementia). Eighteen rosuvastatin-treated versus four placebo-treated subjects reported a confusional state (36). However, unlike PROSPER and HPS, neurocognitive status was not measured in a systematic way, and therefore the clinical significance of these data are unclear.

Twelve small randomized controlled trials have looked at the relationship between statin use and cognitive function as a primary outcome (37–48) (Table 2). Eight of these studies found no change in cognitive function between statin and placebo users, two found a detrimental effect of statin use on some tests, and two found a benefit in other tests. It is important to note that these trials were small and of short duration and used different tests to assess cognitive function. This is important because some cognitive tests appear to be more sensitive to the effect of statins (43).

Statins were tested as a means of slowing cognitive decline in patients with AD in two randomized controlled trials.

In the LEADe study (Lipitor's Effect in Alzheimer's Dementia), 640 patients with mild-to-moderate probable AD were randomized to receive 80 mg/day atorvastatin or placebo for 72 weeks. No difference between the groups was found in the co–primary end points of changes in cognition (Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog]) and global function (Alzheimer's Disease Cooperative Study Clinical Global Impression of Change [ADCS-CGIC]) or any of the secondary end points (50).

In another study, 406 patients with mild-to-moderate AD were randomized to receive 40 mg/day simvastatin or placebo for 18 months. Simvastatin had no effect on change in the primary end point of ADAS-Cog score or any of the secondary outcome measures (51).

#### *Systematic Reviews and Meta-analyses Concerning Cognitive Effect of Statins*

Several meta-analyses have tried to summarize the data on the effects of statins on cognition.

One systematic review, looking at 3 randomized controlled trials, 16 cohort studies, 4 case-control studies, and 4 cross-sectional studies arrived at the conclusion that low-quality evidence suggests no increased incidence of AD and no difference in cognitive performance related to procedural memory, attention, or motor speed associated with statin use. Moderate-quality evidence suggested no increased incidence of dementia or mild cognitive impairment or any change in cognitive performance related to global cognitive performance scores, executive function, declarative memory, processing speed, or visuoperception (17).

Another systematic review performed separate analyses for short-term ($<$1 year after drug initiation) and long-term ($\geq$1 year after drug initiation) effects of statins on cognition. Short-term studies (including 3 randomized controlled trials using validated objective measures of cognition as end points) did not show a consistent effect of statin therapy on cognitive end points. In the long-term studies (8 randomized controlled trials and prospective cohort studies of any statin with an end point of dementia) there was a 29% reduction in incident dementia in statin-treated patients (52).

Another systematic review performed separate analyses for cognitively normal subjects and cognitively impaired patients. In 14 studies of cognitively normal subjects, no statistically significant differences were found between statin and no statin groups for the global, attention, executive, memory, processing speed, and working memory domains. In four studies of cognitively impaired patients, there was a trend toward benefit in statin-treated patients in ADAS-Cog and Mini-Mental State Examination (MMSE), which failed to reach statistical significance (53).

Two Cochrane meta-analyses looked at statins as a means of preventing or treating dementia. For prevention of dementia, only two double-blind randomized placebo-controlled trials were considered (PROSPER and HPS). The authors concluded that there is good evidence that statins given in late life have no effect on AD or dementia (54). For treatment of dementia, four double-blind randomized placebo-controlled trials with 1,154 participants were

**Table 2—Randomized controlled trials with the relationship between statin use and cognitive function as a primary outcome**

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

NS, nonsignificant.

included. No effect of statins was found on the primary outcome measures of ADAS-Cog or MMSE (55).

## Conclusions

Statin-associated cognitive impairment seems to be rare, and there is no evidence for a causal relationship. The warning issued by the FDA relied on case reports, and no objective measures of cognitive function were used. Furthermore, even with use of the FDA postmarketing surveillance databases, the report rate for cognitive impairment associated with statins is not different from other drugs commonly used in similar populations at high cardiovascular risk.

Although observational studies suggested that statins may exert a beneficial effect on the prevention and treatment of dementia, thus far randomized controlled trials have failed to demonstrate such an effect. The discrepancy might stem from the known limitations of nonrandomized trials, such as unknown confounders, a "healthy user" effect, publication bias, and the different methods used to diagnose dementia and cognitive impairment.

Future trials may give us more information concerning cholesterol lowering, statins, and cognitive function.

The Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE) (clinicaltrials.gov identifier: NCT02099123) is aiming to recruit 12,000 patients aged 70 years or older without cardiovascular disease, diabetes, or dementia and randomize them to either 40 mg atorvastatin or placebo. The primary end point is all-cause mortality or need for permanent residential care, with dementia being a prespecified secondary end point (56).

The new proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors reduce LDL-C to very low levels. In the Long-term Safety and Tolerability of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia (ODYSSEY LONG TERM) study, neurocognitive disorders (including amnesia, memory impairment, and confusional state) occurred in 1.2% of patients treated with alirocumab for 78 weeks (mean LDL-C 48 mg/dL), a nonsignificant difference from the control group (57). In the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) study, neurocognitive events (including confusion, cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders) were reported more frequently in patients treated with evolocumab for a mean period of 11 months (mean LDL-C 48 mg/dL): 0.9 vs. 0.3% in the standard therapy

group (58). Ongoing, large prospective studies of PCSK9 inhibitors (ODYSSEY Outcomes, clinicaltrials.gov no. NCT01663402; FOURIER, NCT01764633; and SPIRE 1 and 2, NCT01975376 and NCT01975389) will include dedicated neurocognitive substudies that will provide more information on the safety of achieving very low levels of LDL-C.

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