The Effects of HMG-CoA Reductase Inhibitors in the Prevention of Dementia in the Elderly Population

Jessica M. Starr
Pacific University
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Abstract

Background: The prevention and treatment of cognitive decline in the elderly population is reaching an increasing significance as people are living longer than they have in the past due to better healthcare services. Dementia is a major contributor to morbidity and mortality in the aging population, and society would greatly benefit from strategies to delay or decrease the progression. It has been suggested that certain medications, dietary measures, mental activity, and exercise may decrease the risk of cognitive impairment in the elderly population. There has been mixed evidence that people who use a specific cholesterol lowering medication, the HMG-CoA reductase class, better known as statins, are less likely to develop dementia. However, direct evidence of statin effects of neuropathologic markers of Alzheimer's disease is lacking. This paper will review recent research on the usage of statins in the treatment of dementia and its efficacy and validity.

Methods: A systematic review of the past six years of published literature was conducted using the search engines MEDLINE, CINAHL, and PubMed using keywords dementia, Alzheimer’s, cognitive decline, and statins. Relevant references were retrieved and reviewed. Original research and cohort studies that included statin usage and cognitive decline were analyzed. Meta-analyses were excluded. Only studies published within the past six years were analyzed. The population included older adults greater than 60 years old who did not have baseline dementia at the time the study was initiated, and who used statin therapy for at least four months, monitored over the course of at least five years. Articles of original research that examined the effects of statin medications on cognitive function were selected. Seven studies were selected that met the above criteria, and were analyzed for quality and significant results.

Results: Results from studies varied as to whether statins had any protective effects in the decline of dementia. Some studies made conclusions based on patient’s function on cognitive tests alone, while other looks into more advanced tests such as cranial MRI scans or even brain biopsies. Of the seven studies reviewed, three concluded a decrease in cognitive decline while taking a statin medication, however four did not. One exam looked into cognitive decline as well as brain biopsies and found that although there was no significant change in cognitive outcome, there were some benefits on brain autopsy of statin users. However, another study where brain biopsies were performed did not find any significant improvement due to statin medications. MRI analysis did not yield any significant benefit from statin drugs.

Conclusion: Based on the above results, there are no significant consistent indications to use statins in the prevention of dementia. Statins may play a role in limiting cognitive decline, however more detailed analysis needs to be performed in order to better understand the role that statins play.

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First Advisor
Annjanette Sommers MS, PA-C

Second Advisor
Rob Rosenow PharmD, OD
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Jessica M. Starr

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Pacific University

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Faculty Advisor: Annjanette Sommers, MS, PA-C
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

Jessica Starr is from Reno, Nevada. She graduated from the University of Nevada, Reno in 2007 with a degree in Biology and minor in Spanish. She spent time studying abroad in Costa Rica and Spain during this time. She comes from a large, loud, and outgoing family, including 2 very inspiring parents Gary and Janet, who both work in the medical field, 2 amazing sisters, Gaylyn and Stephanie, and 3 wonderful brothers Jason, Ryan, and Tjerck. She enjoys anything that has to do with the outdoor especially skiing and mountain biking. She is looking forward to graduating and beginning her career as a PA!
Abstract

Background: The prevention and treatment of cognitive decline in the elderly population is reaching an increasing significance as people are living longer than they have in the past due to better healthcare services. Dementia is a major contributor to morbidity and mortality in the aging population, and society would greatly benefit from strategies to delay or decrease the progression. It has been suggested that certain medications, dietary measures, mental activity, and exercise may decrease the risk of cognitive impairment in the elderly population. There has been mixed evidence that people who use a specific cholesterol lowering medication, the HMG-CoA reductase class, better known as statins, are less likely to develop dementia. However, direct evidence of statin effects of neuropathologic markers of Alzheimer’s disease is lacking. This paper will review recent research on the usage of statins in the treatment of dementia and its efficacy and validity.

Methods: A systematic review of the past six years of published literature was conducted using the search engines MEDLINE, CINAHL, and PubMed using keywords dementia, Alzheimer’s, cognitive decline, and statins. Relevant references were retrieved and reviewed. Original research and cohort studies that included statin usage and cognitive decline were analyzed. Meta-analyses were excluded. Only studies published within the past six years were analyzed. The population included older adults greater than 60 years old who did not have baseline dementia at the time the study was initiated, and who used statin therapy for at least four months, monitored over the course of at least five years.

Articles of original research that examined the effects of statin medications on cognitive function were selected. Seven studies were selected that met the above criteria, and were analyzed for quality and significant results.

Results: Results from studies varied as to whether statins had any protective effects in the decline of dementia. Some studies made conclusions based on patient’s function on cognitive tests alone, while other looks into more advanced tests such as cranial MRI scans or even brain biopsies. Of the seven studies reviewed, three concluded a decrease in cognitive decline while taking a statin medication, however four did not. One exam looked into cognitive decline as well as brain biopsies and found that although there was no significant change in cognitive outcome, there were some benefits on brain autopsy of statin users. However, another study where brain biopsies were performed did not find any significant improvement due to statin medications. MRI analysis did not yield any significant benefit from statin drugs.

Conclusion: Based on the above results, there are no significant consistent indications to use statins in the prevention of dementia. Statins may play a role in limiting cognitive decline, however more detailed analysis needs to be performed in order to better understand the role that statins play.

Keywords: Statins, dementia, Alzheimer’s disease, cognitive decline
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To my parents: Thank you for guiding me and giving me the inspiration to get me through these challenging years. I love you!
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Table 1: Summary Matrix of Reviewed Literature

List of Abbreviations

AD...........................................Alzheimer’s Disease
ApoE........................................Apolipoprotein E
APP.........................................Amyloid Precursor Protein
BMI.........................................Body Mass Index
BBB.........................................Blood Brain Barrier
CASI.........................................Cognitive Assessment Screening Instrument
HR.........................................Hazard Ratio
GMS.........................................Geriatric Mental Scale
MMSE......................................Mini Mental Status Examination
NP.........................................Neuritic Plaques
NFT.........................................Neurofibrillary Tangles
OR..........................................Odds Ratio
3MS/3MSE..................................Modified Mini Mental Status Exam
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BACKGROUND

Dementia is a condition characterized by memory impairment and at least one other cognitive domain (apraxia, agnosia, aphasia, executive function). It is estimated to affect more than four million Americans and up to 3.1 million caregivers of those with Alzheimer’s Disease.\(^1,^2\) To diagnose, there must have been a decline from a previous level of function and it must have been severe enough to interfere with independence and daily function. The major types of dementia include: Alzheimer’s disease, vascular dementia, Lewy Body Dementia, Parkinson disease with dementia, Frontotemporal dementia, and reversible dementias. Alzheimer’s dementia accounts for 60-80% of dementias, with vascular dementia the next most common, accounting for 10-20% of dementia.\(^3\)

Alzheimer’s disease (AD) is a neurodegenerative disorder that primarily affects older adults over age 60, more commonly women, with the prevalence increasing with age. The cause and pathogenesis is uncertain. The cost of caring for one patient with AD is $47,000 per year.\(^2\) Many treatments are available that can alter the course of the disease or lessen the symptoms, but there is no cure, and the disease inevitably advances in all patients.\(^3\)

There are many clinical features that accompany AD. Memory impairment is often the earliest manifestation. Declarative memory for facts and events is profoundly affected, while procedural and motor learning are usually spared until quite late in the
disease. Memory for recent events is controlled by the hippocampus, entorhinal cortex, and other structures in the mesial temporal lobe are usually impaired early in AD.

Memories that are formed over long periods of time (years) are usually spared early on, since they can be remembered without hippocampal function. Language problems also occur with the earliest manifestations including word-finding difficulties, circumlocution, and reduced vocabulary in spontaneous speech with anomia. Later language findings include agrammatism, impoverished speech content, impaired comprehension, and paraphasic errors. Loss of visuospatial skills can also be an early sign, including misplacement of items and difficulty finding their way in unfamiliar terrain, progressing to familiar terrain. Later features include the inability to recognize objects (visual agnosia) or faces (prosopagnosia). Alzheimer’s disease patients may also develop decreased awareness of their deficits, which has been linked to frontal lobe pathology. They underestimate their deficits or offer explanations for them. Difficulty performing learned motor tasks (apraxis) occur later in the disease process after memory and language deficits are apparent. Executive function, in which patients may present with an alteration of personality, poor judgment and planning, and the inability to complete tasks, can be affected. Later in the disease, neuropsychiatric symptoms, including apathy, social disengagement, and disinhibition, become more common. These can progress to more severe behavioral disturbances including wandering, aggression, agitation, and even psychosis.

Hippocampal volume loss of MRI is highly correlated with AD, but does not diagnose. Diagnosis can only be done by autopsy; the brains of those with AD are characterized by extracellular deposition of amyloid-beta proteins, intracellular
neurofibrillary tangles, and loss of neurons. The abnormal processing of amyloid-beta protein is likely to be the cause of AD. A group of amyloid precursor proteins can be cleaved by certain secretases. When the amyloid proteins are cleaved on the amino end by a beta-secretase and on the carboxy end by a gamma-secretase, an Abeta42 protein is released. Abeta42 then accumulates in diffuse plaques, which are thought to change into the thick neuritic plaques. Increased amounts of Abeta42 and Abeta oligomers are found in the cerebrospinal fluid and brain tissue of patients with early dementia and show a relationship with cognitive decline, supporting the hypothesis that small Abeta oligomers rather than amyloid plaques are the mediators of neurotoxicity in Alzheimer’s disease.\textsuperscript{1,4}

When the dense neuritic plaque forms, excitotoxicity, inflammation, and even apoptosis cause damage. Neurofibrillary tangles (NFTs) are a hyperphosphorylated type of microtubule-like protein Tau.\textsuperscript{1}

Alzheimer’s disease progression is typically measured with the Mini-Mental Status Examination (MMSE) and the Clinical Dementia Rating Scale. A number of studies have found that patients decline on average 3 to 3.5 points on the MMSE each year without any specific intervention.\textsuperscript{3}

- MMSE score 20-26: Mild functional dependence (difficulty managing finances)
- MMSE score 10-20: Moderate functional impairment (inability to drive, difficulty with hygiene and shopping, remote memory impairment)
- MMSE score <10: state of total dependence and need for constant supervision. Motor impairments such as gait and balance are affected, as well as incontinence, myoclonus, and total debility.\textsuperscript{3}
After diagnosis of AD, mean survival ranges from three to eight years. Patients often succumb to end stage complication such as dehydration, malnutrition, and infection. A definitive diagnosis of AD requires a histopathologic examination which is rarely done while the patient is alive.\(^3\)

There are many other types of dementia. Vascular dementia is caused by either ischemic or hemorrhagic strokes, commonly due to small vessel cerebrovascular disease. It is usually suggested by onset of cognitive deficits after a stroke, abrupt onset of symptoms, findings on neurological exam consistent with a prior stroke, and infarcts shown on cerebral imaging. Frontotemporal dementia is characterized by atrophy of the frontal or temporal lobe, often manifested by changes in personality, behavior, and executive functioning early in the disease. Typical manifestations, which are prominent early in the course of the disease, include abnormal social behavior, unusual eating patterns, ritualized behaviors, and difficulty finding words, while cognitive disturbance is usually minimal at onset. Lewy Body Dementia is the second most common type of dementia after AD.\(^3\) Features include early appearance of visual hallucinations, spontaneous motor features of Parkinson’s, cognitive changes, dysautonomia, sleep disorders, and neuroleptic sensitivity.\(^3\)

Risk factors for dementia include smoking, hypertension, Diabetes Mellitus type 2, high homocysteine levels, insulin resistance, hypercholesterolemia, and obesity. Being positive for the allele Apolipoprotein E epsilon 4 also is a risk factor for Alzheimer’s, however this allele has a low prevalence. ApoE plays a role in lipid metabolism and is the main transport protein for cholesterol into the brain.\(^5,6\) Factors that have been shown to decrease the risk of dementia include: higher education, physical exercise, mental
exercise, diets high in fish, fruits, and vegetables, antioxidants (Vitamin E), and B Vitamins (Folate, B6, and B12). Contributors to chronic dementia include medications (such as antihistamines), alcohol, depression, central nervous system neoplasms, hematomas, or meningitis, and metabolic disorders and deficiencies.

Alzheimer’s disease (AD) is the most common type of dementia accounting for 69.9%, while vascular dementia (VaD) is the next most common at 17.4%. The other 12.7% included Parkinson’s dementia, Lewy body dementia, normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury.

Alzheimer’s disease is a degenerative disorder that begins insidiously and progresses gradually over time. Detection of early stage dementia, or Mild Cognitive Impairment (MCI), can be the imperative time to begin treatment to slow the progression of the disease. The rate of progression to clinically diagnosable Alzheimer’s disease from MCI is 10-15% per year, relative to 1-2% in the normal elderly population. Since dementia is a progressive disease, benefit can be measured not only with improvement on a test, such as the MMSE, but also by stabilization or a decrease in the rate of decline. So even though there may still be a decrease in cognition, the rate of decline may indicate a benefit when compared to a placebo group. An expected decline in the placebo group is an important factor in order to compare the change in the subject’s mentation.

Statins are a commonly used cholesterol lowering medication that work by reducing the cholesterol production by the liver. They block the enzyme, hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA reductase) that is responsible for making cholesterol. The mechanism by which statins may affect the pathogenesis of
dementia is uncertain. Cholesterol is essential for normal function of the brain, so this was originally thought to be an underlying mechanism, however, the brain cholesterol is synthesized in situ, and the BBB prevents exchange of cholesterol with the periphery.\textsuperscript{10} It was originally hypothesized that only lipophilic statins would play a role in this, since they are able to cross the BBB, however this theory has not been proven.\textsuperscript{5}

**Purpose of the Study**

The purpose of this study is to systematically review recent research regarding the usage of statins in the prevention of cognitive decline. The ideal research would control for potential confounders, and have a large enough number of participants to permit clinically significant results.

**Clinical Question**

Alzheimer’s disease and other forms of dementia have become so pervasive in our communities affecting more and more people both directly and indirectly and heavily impacting the healthcare system. It is imperative that the causes and treatments for such a widespread problem be addressed. There are many well established preventative measures, but the use of statin drugs in still one that is under investigation. There have not been any consistent results that statins are indeed a good prevention option for Alzheimer’s disease.

**METHODS**

**Search Strategy**

A systematic review of the past six years of published literature was conducted using the search engines MEDLINE, CINAHL, and PubMed using keywords dementia, Alzheimer’s, cognitive decline, and statins. Relevant references were retrieved and
reviewed. Original research and cohort studies that looked at statin usage and cognitive decline were analyzed. Meta-analyses were excluded. Only studies published within the past six years were analyzed.

**Inclusions/Exclusions**

The population of interest included adults greater than 60 years old who did not have baseline dementia at the time the study was initiated. The search was limited to English language publications.

Inclusion criteria included human studies, subjects greater than 60 years old at the time the study began, mental examination of patients at least once per year, and statin usage for greater than four months. Included studies contained greater than 100 participants, and followed patients for more than five years. Age, sex, smoking status, presence of diabetes of high blood pressure, education, and the presence of the ApoE allele were adjusted for in each study.

Exclusion criteria included studies in which patients were not physically examined at least once per year, patients who had baseline dementia at the start of the study, studies which tried statin therapy for less than 4 months, and studies which included other drugs than statins for the treatment of dementia. Animal studies were also excluded.

**RESULTS**

Articles of original research that examined the effects of statin medications on cognitive function were selected. Seven studies were selected that met the above criteria, and were analyzed for quality and significant results. Table 1 shows a summary matrix of selected studies. These various studies demonstrated variations on whether statins had
any protective effects against the decline of dementia. Some studies made conclusions based on patient’s function on cognitive tests alone, while other looked into more advanced tests such as cranial MRI scans or even brain biopsies. Of the seven studies reviewed, three concluded there was a decrease in cognitive decline while taking a statin medication, however four saw no effect, positive or negative. One study looked into cognitive decline as well as brain biopsies and found that although there was no significant change in cognitive outcome, there were some benefits on brain autopsy of statin users. However, another study that performed brain biopsies did not find any significant improvement while on statin medications. MRI analysis did not reveal any significant benefit from statin drugs either.

The Rotterdam Study,\(^5\) published in 2008, is a prospective, population-based cohort study of age related diseases. Between 1990 and 1993, 6992 participants were entered in the study, all free of dementia. Patients were monitored in 1993-1994, 1997-1999, and 2000-2004 using MMSE and GMS screening and clinical work up for dementia. Pharmacy records of all patients were tracked. Only patients who proved they had taken medications for at least six months were included in the study. Cholesterol medications were monitored, particularly statins, and grouped into lipophilic or hydrophilic categories. Lipophilic medications, including simvastatin, pravastain, flucastatin, atorvastatin, rosvustatin) are known to pass the BBB more efficiently. Hydrophilic statins include pravastatin, fluvastatin, and rosvustatin which do not cross the BBB.\(^5\)

The diagnosis of dementia was based on a 3 step protocol. Screening procedures included the Mini-Mental Status Examination (MMSE) and Geriatric Mental State
Schedule (GMS). Positive results included MMSE <26 or GMS >0. These patients with positive results underwent Cambridge examinations for mental disorders, and those who were suspected of having dementia underwent a more extensive neurological testing. Imaging data was used as needed. The diagnosis of dementia was made according to criteria from the DSM-III-R, and Alzheimer’s disease and vascular dementia criteria consisting of a panel of a neurologist, neurophysiologist, and a research physician, who were all blinded to the drug exposure. Characteristics that were looked at included age, with the average being 69.4 years, sex (60% female), smoking, DM, Blood Pressure, cardiovascular disease, stroke, total cholesterol, BMI, education level, and presence of the ApoE4 allele (+25.6%).

A total of 6992 patients who were all free of dementia who had taken medications for at least six months were examined at baseline. Patients followed up to 15.3 years, with the average being 9.2 years. Of these, 739 developed dementia (582 were Alzheimer’s, 81 were vascular dementia, 76 other types of dementia). The total number of prescriptions filled was 30 241. Simvastatin was the most frequently used statin (the most lipophilic statin) followed by pravastatin (the most hydrophilic statin). It was found that the use of statins was associated with a lower risk of AD than those who had never used statin medications. However, there was no strong evidence for lipophilic statins providing stronger protection than a hydrophilic statin (adjusted OR: 0.61, 95% CI 0.36 to 1.03 for lipophilic and 0.38; 95% 0.15 to 0.99 for hydrophilic). There was no dose dependent relationship detected; doses both above and below the mean were associated with a decreased risk of Alzheimer’s. The protective effect was seen regardless of the length of time statins were used. Data was collected from those patients over age 65
years, with similar results of AD and HRs (HR statin 0.61; 95% CI 0.38 to 0.98) (HR non statin 1.14; 95% CI 0.49 to 2.68).\textsuperscript{5}

The use of statin, but not non-statin cholesterol medication, was found to be associated with a lower risk of AD compared with the patients who did not take any types of cholesterol medication. No difference was observed between lipophilic and hydrophilic medications.\textsuperscript{5}

Arvanitakis et al,\textsuperscript{4} evaluated the usage of statin therapy in relation to Alzheimer’s disease. This study included 929 older Catholic clergy members (68.7% women, mean age 74.9, mean MMSE 28.5) who were all free of dementia at baseline. All participants agreed to annual structured clinical evaluations consisting of 19 neuropsychological tests and also consented to brain autopsy at time of death. 314 patients died, and 294 had a brain biopsy performed.\textsuperscript{4}

Cognition was assessed at baseline and at each follow up appointment and data reviewed by a neurophysiologist. There were a total of 19 tests were used to assess global cognition on five separate cognitive domains: episodic memory, somatic memory, working memory, and visuospatial ability. The MMSE was used. Medications taken by participants, including statins, were recorded. Statins were evaluated based on their lipophilic properties in relation to possible effects on BBB. The time period during which statins were used by the participant was also reviewed. More than 900 older patients without baseline dementia for up to 12 years with annual follow-up and did not find any relation of AD with statins, no changes in global cognition on five separate cognitive domains.\textsuperscript{4}
After death, a blinded neurologist reviewed all clinical data. Brain autopsies were performed and cut into 1 cm samples and examined for AD pathology using a silver stain to visualize any pathologic signs of AD. The number of diffuse plaques, neuritic plaques (NPs), and neurofibrillary tangles (NFT) in each region was counted. A neuropathologic diagnosis of definite AD, probable, possible, or no AD was made. Amyloid-beta was measured using a microscope. To quantify the amount of tangles present, the protein Tau was labeled with AT8, and tangles were quantified by serology using a microscope.4

The relation of statin usage to neurofibrillary tangles was examined. It was found that of the 929 patients, 119 used statins (12.8%) at baseline, and 810 did not (87.2%). Of the statin users, 67 were taking more lipophilic statins (simvastatin and lovastatin). During the 12 year follow up period, 191 patients developed AD, 16 of these patients used statins at baseline (8.4%). Using a Cox proportional hazards model, it was shown that baseline statin usage was not associated with a risk of AD compared to the non-statin users (HR=0.91; 95% CI 0.54, 1.52). The presence of ApoE4 did not change this finding and there was no interaction of statins seen with ApoE4.4 The relationship between lipophilic versus hydrophilic statins were examined (HR=1.05, 95% CI 0.57 to 1.95, and HR=0.71; 95% CI 0.29 to 1.74 respectively). There was no relationship found between the cumulative statin variable to incident AD (HR=0.93, 95% CI 0.56 to 1.55). The relation of cognition of statin was examined and was found that statins were not associated with level (p>0.09 in all tests) or change (p>0.20) in global cognition or cognitive domains. In patients who developed dementia, there was no relation of statins to change in global cognition (p=0.32).4
The mean age of death was 85.4 years (SD=6.8). The mean MMSE was 23.5 at the last clinical evaluation (with the mean time to death of 6.5 months). 1/3 had clinical dementia before death. Nearly all 262 subjects who underwent brain biopsy had some pathology of AD with a mean global AD score of 0.59 (range 0 to 1.50) in statin users and 0.70 (range 0 to 1.59) in those who did not use statins. Of the 199 patients who had amyloid data present on biopsy, 16.6% were statin users, statin users had less immunoreactivity compared to nonusers (0.92 vs. 1.97 units, p<0.01). Of the patients, 231 were found to have NFT evidence, with a mean age of 85.5 years. There was no difference between statin and non-statin users. Results showed that 81 of the 262 patients had cerebral infarctions, which were present in 23.4% of statin users and 32.6% of nonusers (p=0.22).4

All the models were adjusted for sex, education, and age at death. It was found in a linear regression analysis that statins were not associated with the global AD score. Compared to non-statin users, higher or lower lipophilic properties was not associated with global AD pathology (p=0.28 for more lipophilic, p=0.76 for less lipophilic). It was however found that higher lipophilic statin users were less likely to have amyloid buildup in the brains (p=0.03). There was no connection found between statins and infarctions (p=0.19). More lipophilic statins were associated with lower likelihood of amyloid. The relationship between statins and cerebral infarction was examined, and no relationship was found (OR=0.9, 95% CI: 0.4, 1.8).4

Li et al,1 who started their study in 1994, also performed brain biopsies to evaluate the effect of statins on cognitive decline. Typically AD related neuropathologic outcomes were monitored: including neurofibrillary tangles and neuritic plaques (NPs).
Statins were not widely used before the mid 1990s so older subjects were not treated with statins in their early older ages. Brain biopsies were performed on 110 subjects, from 65 to 79 years old, who were cognitively normal at baseline. Comparisons were made between statin users who took more than 4 months of statins and those who did not.

Each subject had a baseline neurocognitive examination and was followed twice per year for cognitive decline on the Cognitive Abilities Screening Instrument scale (CASI). Decline was detected by a score of less than 86. Those who showed decline had an evaluation with a neuropsychological test battery and a physical and neurological examination by a neurologist or a geriatrician. Laboratory values and brain CT or MRI scans were obtained as needed. Total cholesterol and HDL values were measured although patients were generally not always fasting. By 2006, 24% of the eligible sample had died, with the mortality rate being lower in the statin users than non-users (19 vs. 26%, p<0.01). Exposure to medications was determined from the GHC pharmacy database. All assessments were performed blind to clinical diagnosis and risk factors. All brains were evaluated for gross lesions, atherosclerosis, cystic infarcts, ventricle enlargement, NPs, NFTs, and microvascular lesions.

Of the 110 subjects underwent brain biopsy, 36 (33%) had received greater than three prescriptions for statins. Statin users were more likely male, and had a higher prevalence of cardiovascular disease or diabetes mellitus at enrollment and had higher total cholesterol levels. Statin users were found to have slightly lower CASI scores at enrollment; however the incidence of dementia did not differ between the 2 groups. Subjects received their first statin prescription at an average age or 76 (range 64 to 87) and the average number of prescriptions filled was 30 (range to 90). Most participants
received simvastatin or lovastatin. There was found to be no association between statin usage and dementia based on the CASI scores.\textsuperscript{1}

Brain autopsies showed statin users had a lower amount of both NFTs and NPs compared with non-users. After controlling for age at death, CASI score, gender, brain weight, presence of MVL, it was found that statin users had a significantly decreased risk for typical AD neuropathology findings. Findings were consistent with statin usage associated with a decreased NFT burden on autopsy. Alzheimer’s typical neuropathology, using the Braak and CERAD scores, were significantly less common in statin users than in non-users.\textsuperscript{1}

Cramer et al,\textsuperscript{11} examined the efficacy of statins in prevention of dementia over a five year period of time. The population based cohort comprised of 1674 Mexican American patients over the age of 60 who were dementia free at baseline. Cognitive and clinical evaluations were performed every 12 to 15 months. Cox proportional hazard models were used to evaluate the association between statins and dementia. Over a five year period of time, 130 participants developed dementia. Statin dose, duration, frequency, and source were monitored at each patients home by inspection of all prescribed medications. A semiannual phone call to and annual direct examination were made to each participant. Covariates included DM, CVA, education, nativity, smoking status, insurance, and ApoE genotype. Cognitive testing and evaluations were performed yearly. Dementia was diagnosed based on DSM-IV and NINCDS-ADRDA. MMSE, Spanish and English verbal learning tests, and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) were used to evaluate cognitive decline. A case review team included a geriatrician, neurologist, and a neuropsychologist who arbitrated all
potential dementia cases. Diagnoses were based on the patient’s mental tests and findings from neurologic examination, Cases with dementia were referred for an MRI and certain laboratory tests.11

Of the 1674 patients free of dementia at the beginning of the study, 452 (27%) took statins at some point during the study. Patients who took other cholesterol medications that were not in the statin class were not included in this category. Of the patients that took statins, 263 (58%) used them for longer than 2 years during the study. Participants in the statin class were found to be slightly younger, have increased education, more likely to have been born in the United States, and more likely to have medical insurance, as well as a higher percentage of patients with diabetes and higher baseline MMSE exam scores.5,9 A total of 130 participants developed dementia over the five year follow up. Of those diagnosed with dementia: 48% had possible/probable AD, 23% undetermined etiology, 13% ischemic vascular dementia, 13% had mixed AD or vascular dementia, and 3% had other types.11

Cox proportional hazard models were used to examine the relationship between dementia and the use of statins. Baseline diabetes, stroke, education, smoking status, ApoE4 allele, and MMSE were all associated with dementia in unadjusted models. Two adjusted models, diabetes and stroke were associated with statin use and included in the Model 1, and all significant covariates were included in Model 2. There were no significant interactions between statin use and any covariates.5 In the adjusted analysis, statin use was associated with a 43% lower rate of dementia (HR 0.577, 95% CI 0.376, 0.886). In Model 1, statin use was associated with a 48% lower rate of dementia (HR 0.518, 95% CI 0.336, 0.797). In Model 2 with all covariates included, there was a 44%
lower rate of dementia in statin users (HR 0.564, 95% CI 0.365, 0.872). Baseline MMSE did not predict statin use, and there was found to be no interaction between the 2 variables. Statin use was found to be associated with a significant decrease in the incidence of dementia.11

Bernick et al,13 examined the association of statin drug use on cognitive and MRI changes in older adults. They performed a longitudinal study of participants over age 65, and were grouped into 3 categories according to whether they took statins continuously, intermittently, or not at all. Patients who had a history of TIA or stroke or 3MS scores less than 80 were excluded. Participants were monitored over an average of seven years based on their 3MS scores, along with changes in white matter and measures of atrophy on MRI.13

A total of 5888 participants were eligible for the study. It was a community based prospective epidemiologic study in adults over age 65. Patients underwent yearly cognitive testing and some underwent cranial MRIs. Data was collected by a baseline clinical visit, semiannual updates that alternated between phone calls and clinic visits, standard questionnaires, physical examinations, and laboratory testing. Participants were followed for ten years, cognitive function was assessed using the 3MS, which assesses cognition in greater detail than the MMSE and ranges from 0 to 100. Scores of less than 80 have a high specificity for dementia. Certain participants underwent cranial MRI scans at two time points, generally four to five years apart. Imaging was interpreted by a neuroradiologist with training in this protocol and without knowledge of the subject’s clinical information. The white matter changes and ventricular and sulcal size of each patient was assessed.13
Patients were excluded from statistical analysis if they: had incomplete lipid data, a baseline 3MS<80, less than two years of cognitive testing, no baseline 3MS, missing information of statin usage, or an incidental stroke or TIA. The remaining participants were divided into 3 groups:

1. Untreated group who had received none or less than 2 years of statin therapy.
2. Intermittent group who received between 2-4 years of continuous treatment or 3-5 years of noncontinuous statin treatment.
3. Continuous group who received greater than 4 years of continuous statin therapy.13

Cognitive decline was measured as the rate of change in 3MS per year. The rate was modeled in a linear regression as the response variable. A multivariate regression was used to adjust for factors that might have contributed to the relationship between cognitive decline and statins, including age, sex, ApoE4, education, and cholesterol. Univariate ANOVA was used to test the effect between treatment categories.13

A total of 3660 participants underwent MRI examinations. After cross sectioning those who had an MRI at years five and ten with statin data, there were 1823 participants with an average interval of 5.1 years between scans for analysis of change. MRI analysis included white matter, ventricular, and sulcal grade which were treated as continuous variables. Linear regression was used to examine the association of statin usage with the difference between first and second MRI results, after adjusting for covariates (white matter grade, ventricular size, sulcal size).13

The baseline 3MS scores and other characteristics were similar among all groups. The adjusted and unadjusted mean in cognitive decline were evaluated. The adjusted model uses the covariates that were associated with cognitive decline and displays the
rate of change per year in treatment categories. The unadjusted difference in mean rate of
3MS between the continuous statin group and the intermittent statin group was 0.48 (95%
CI 0.06, p=0.024). After adjusting for age, sex, ApoE, race, cholesterol and education, the
difference in 3MS was 0.40 points per year (95% CI -0.03, 0.87, p=0.069). The
unadjusted differences in 3MS between continuous statin compared with the untreated
group was 0.49 (95% CI 0.12, 0.85 p=0.009), which remained significant even after
adjustments (0.49, 95%CI 0.04, 0.95’ p=0.026). In MRI results, there was no
significant difference in white matter, ventricular, or sulcal changes between continuous
statin groups and untreated groups. However, there was a fourfold increase in silent
infarcts in the untreated group compared to the statin group.13

The use of statin drugs was found to be associated with a slight decrease in
cognitive decline in elderly patients. In serial MRIs taken five years apart, there was no
measurable difference in changes in white matter or atrophy between treatment groups.10

Li et al14 examined the association between statin therapy and the risk of AD in a
prospective cohort study with incident dementia and documented statin exposure. A total
of 2356 cognitively intact participants greater than 65 years of age when the study was
started in 1994 were recruited. Subjects were randomly selected from a HMO and were
assessed for dementia twice per year. A total of 312 participants were identified with
incident dementia, and of these 168 had probable AD. Participants were screened using
the Cognitive Abilities Screening Instrument (CASI) and those who scored higher than
86 out of 100, and without evidence of baseline dementia were allowed into the cohort.
ApoE genotyping was completed.14
A total of 312 participants developed dementia or probable AD, 363 participants died, and 186 refused participation, leaving 1496 cognitively normal participants at the end of the study in 2002. Prescription history was obtained through a pharmacy database including dosage and frequency of statin medications. Subjects were screened using the CASI assessment every two years, and those who scored less than 86 underwent dementia diagnostic evaluation including a physical and neurologic examination by a neurologist, geriatrician or internist, and a one hour battery of neuropsychological testing. Laboratory tests and brain CTs or MRIs were obtained as needed. Diagnoses were made using criteria from the DSM-IV and NINCDS-ADRDA. Those diagnosed with dementia underwent at least one annual follow up visit to verify dementia and to assess cognitive decline.14

Age at study entrance was found to be inversely associated with risk of dementia with a hazard ratio of 0.88 (95% CI 0.84-0.94). The corresponding HR for probable AD was 0.91 (95% CI 0.84-0.98). These results show that a one year increase in age at entry was associated with a 12% decrease in relative risk for dementia and 9% decrease in relative risk for AD. Each year of education was also found to be inversely related to the risk of dementia (HR 0.95, 95% CI 0.92-0.99) and probable AD (HR 0.92, 95% CI 0.87-0.97). The presence of the Apo4 allele was also associated with increased risk of dementia (HR=2.24, 95% CI 1.75 to 2.85) and probable AD (HR=2.57, 95% CI 1.85 to 3.56). Sex, race, BMI, and other vascular co morbidities were not found to have a significant association with dementia or probable AD.14

A total of 392 of the 2356 participants had used statin drugs; some also used another non-statin form of lipid lowering medications. Simvastatin was the most
commonly used followed by pravastatin. Unadjusted HR for statin users were 1.33 for dementia and 0.90 for probable AD, with confidence intervals that included 1.0, the null value. Models that included ApoE, age, and education gave essentially unchanged results. There was no dose-dependent relationship evident between statin use and dementia.14

Zandi et al15 examined the association of statins with dementia on a total of 5092 patients ages 65 and older. Participants were assessed in 1995-1997, and again in 1998 to 2000. Direct visual inspection of medications, including statins, was conducted at each visit. Screening for dementia was done with the modified Mini-Mental Status Exam (3MS). Patients who scored less than 87 on the 3MS at wave 1, or less than 84 on wave 2 were further evaluated with the Dementia Questionnaire. Those whose results suggested cognitive impairment were examined by physical assessment, structured neurological examination, and a one hour battery of neuropsychological tests. Results were reviewed by a geriatric psychiatrist and neuropsychologist and the diagnosis of dementia was determined by the DSM-III-R. Patients were then examined by a geriatric psychiatrist or neurologist and referred for neuroimaging and laboratory studies. A consensus panel of experts in neurology, geriatric psychiatry, neuropsychology, and cognitive neuroscience, reviewed all data and assigned final diagnoses to patients.15

During the first wave, 4895 patients were assessed with the number of demented patients found to be 255, which included 200 AD diagnoses. 99.4% of participants provided medication information and 292 (6%) were taking statin drugs, most commonly lovastatin, fluvastatin, and pravastatin. During the second wave, 1232 patients were lost to death, relocation, or refusal to participate. Among the 3308 remaining, 185 had
developed dementia, including 104 with AD. The number of statin users had grown to 481 (14.7%), most commonly simvastatin, atorvastatin, and fluvastatin. More than half (298) were prescribed statins between the 2 waves.\textsuperscript{15}

There was found to be a significant inverse in the effect of statin use with dementia at wave 1. After adjusting for age and sex, the OR shifted towards the null but remained significant (OR 0.45, 95% CI 0.18-0.95). After adjusting for education, ApoE these results did not significantly change. In adjusted analysis the hazard ratios were above the null of 1.0 for both dementia (HR=1.19, 95% CI 0.53-2.34) and AD (HR=1.19, 95% CI 0.35-2.96). Further analysis was performed which showed some reduced risk of dementia with longer usage of statins but results were not significant (p>0.40). These results did not show any significant association between the use of statins and dementia or AD.\textsuperscript{15}

**DISCUSSION**

The results of statin therapy used for prevention of dementia in the elderly population is inconsistent and unconvincing. While three studies found benefits with statin usage, four studies found no significant benefits. MRI results did not show significant variation in statin users versus non-users. Brain autopsy results were also inconsistent, however, one study reported a decrease in the incidence of amyloid plaques and the other reported a decreased incidence in NPs and NFTs, which may play a role in the progression of dementia. However, this decrease in pathological findings did not have a significant effect on patient’s cognitive functioning during the end of their lifetime.

All studies took into account variables that could have altered results and adjusted for these in their calculations. These variables included age, race, education, and ApoE
presence. All studies eliminated patients with baseline dementia. These studies were cohort studies so did not involve randomization.

Since neither hydrophilic nor lipophilic has been shown to affect AD more than the other, it is proposed that many other factors determine the drug’s distribution into other tissues in the body. They may act through a mechanism in which brain penetration is irrelevant. Statins also affect other tissues by ways of endothelial functioning, atherosclerosis and oxidative stress reactions. There was not shown to be any affect of statins and the ApoE4 genotype.

In more than 250 brains that were biopsied in the study performed by Arvanitakis et al, there was no connection found between statins and AD. However, it was seen that patients taking statins are less likely to have amyloid plaques than those who were not. These results could be better tested by brain autopsies in subjects who started taking statin drugs earlier in life to determine if a significant change was seen with cognitive testing. Overall, the results shown in this study do not support a protective effect of statins on AD or cognitive decline.

Other studies have yielded findings that statins may influence metabolism of the amyloid-precursor protein, by activation of an alpha secretase activity, and have other effects that may decrease amyloid beta production. Statins have also been found to calm cerebral inflammatory pathways by preventing glial production of cytokines, decreasing oxidative stress, and increasing cerebral circulation, and decreasing cholesterol in plasma membranes.

The mechanisms by which statins function in the brain is still unclear. Animal studies have shown that high levels of cholesterol in the brain could alter amyloid
precursor protein (APP) processing, which results in accumulation of Beta-amyloid and the formation of NPs, and that statins can reverse these changes. However, trials in humans have failed to demonstrate a consistent effect of statins in altering CSF APP processing or beta-amyloid levels, or in slowing the progression of AD. Animal studies have also shows that statins may inhibit Tau phosphorylation from either inhibition of a possible amyloid cascade or via anti-inflammatory effects.

Bernick et al found that it was possible to slightly decrease cognitive decline with statin usage. Previous multiyear treatment trial with pravastatin and simvastatin failed to show benefits in cognitive decline. There have been multiple proposed mechanisms on how statins effect cognition: some are able to cross the blood brain barrier and may play a role in brain cholesterol modulation, which may play a role in neurotransmission and synaptic plasticity. Statins may also decrease oxidative stress and inflammation, increase endothelial nitric oxide synthase, and improve endothelial function and blood flow. Subclinical vascular disease may also play a role in cognition which can be improved with statin therapy.

Hypercholesterolemia is known to be associated with vascular disorders, and is thought to play a role in the increased risk of dementia. High cholesterol may also influence dementia pathogenesis. Experiments in vivo and in vitro have shown that cholesterol accelerates the production of Alzheimer amyloid by shifting amyloid precursor protein (APP) metabolism from alpha to beta cleavage products. Statins might inhibit this process by lowering the amount of cholesterol available. They may also prevent atherothrombotic events via the action of smooth-muscle function, macrophages, or platelets, and may play a role in reduction of inflammatory responses that are thought
to work in Alzheimer’s pathogenesis by inhibiting nitric oxide synthase.\textsuperscript{15} Amyloid was found to be decreased after the use of statins in one study after brain biopsy. More research is needed to determine the effects of statins on long term brain anatomy. There was no proven benefit to the efficacy of MRI on the diagnosis of dementia.\textsuperscript{15}

**Limitations of Study**

These studies were all cohort studies, no studies randomly assigned treatments to patient. Patient statin usage was recorded based on the honor system. Patients were prescribed medications, however, whether patients flowed through and took their medication is another question. This is a large flaw that can affect the results of any study if the statin user group was not compliant with their medication. In forming groups for the studies, any statin usage was usually grouped in the same group regardless of whether they took statins for as little as six months or as long as ten years. Baseline medications patients were taking prescribed by their individual providers were not altered or changed during the course of the studies. Other factors that may affect the initiation of statins in elderly is that physicians may be less likely to start a new long term medication on demented patients, since they have a reduced ability to be compliant with their medications and are at greater risk of treatment related complications due to polypharmacy issues that may already be in effect. Different studies used different measures and scales to examine the rate of cognitive decline so it is difficult to compare one study with the next. It is also difficult to compare one study with the next when different grading scales and limitations are used in each study. With a more consistent, monitored study, the effect of statins in the treatment of dementia could better be monitored.
CONCLUSION

Any treatment option that is available to prevent or reduce dementia is an important option for the patient as well as the health care provider. Based on the results above, the evidence that statins decrease the incidence of dementia is unconvincing. However, none have shown to be harmful to the patient and the use of statins has great positive effects on other processes in the body such as cardiovascular events and the use of statins should be a consideration in all patients’ healthcare. More trials need to be done for longer periods of time and looking into the outcomes of statins and dementia when participants begin statins at middle ages, long before signs of dementia may begin to manifest themselves.

REFERENCES


TABLE 1: Summary Matrix of Reviewed Literature

<table>
<thead>
<tr>
<th>Study/Design</th>
<th>Population Exams Done</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.(^1) (2007) Population based study</td>
<td>110 &gt;65yrs Brain biopsies</td>
<td>Statin vs. no statins.</td>
<td>Neurofibrillary tangle burden and neuritic plaques on brain autopsy</td>
<td>Decreased association between statin use and NFTs and NPs on autopsy. Dementia did not differ between groups. OR=0.44, 95% CI 0.20-0.95</td>
<td>5/5</td>
</tr>
<tr>
<td>Haag, et al.(^5) (2009) Prospective population based</td>
<td>6992 &gt;55yrs MMSE GMS</td>
<td>Statins vs No-statins. Lipophilic statins vs. hydrophilic statins</td>
<td>Prevalence of AD Statin use was assoc w/ a decreased risk of AD (HR 0.57, 95% CI 0.37 to 0.90) HRs were equal for both lipophilic and hydrophilic statins (HR 0.54 both, 95% CI: 0.32-0.89, and 0.26-1.11) respectively</td>
<td>4/5</td>
<td></td>
</tr>
<tr>
<td>Cramer et al.(^11) (2008) Population based cohort</td>
<td>1789 &gt;60yrs 3MSE</td>
<td>Statin usage vs. no-statin usage</td>
<td>Prevalence of AD based on 3MSE. Statins were associated with signif decrease in dementia. HR 0.577 (95% CI 0.376-0.886) p=0.012</td>
<td>3/5</td>
<td></td>
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<tr>
<td>Arvanitakis et al.(^4) (2008) Longitudinal clinical pathologic study</td>
<td>929 &gt;65yrs Brain Autopsy</td>
<td>Statin vs. no-statin</td>
<td>Prevalence of AD and Brain composition in statin users vs. non-users. Statin use at baseline (12.8%) was not assoc w/ incident AD, change in global cognition, or change in cognitive domain. Statin use prior to death was not related to global AD pathology. Those taking statins were less likely to have amyloid (p=0.02). Statins were not related to NFTs or infarctions. HR=0.91, 95% CI 0.54-1.52. p=0.32</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>Bernick et al.(^13) (2005) Community based prospective Epidemiologic cohort</td>
<td>3334 pts. &gt;65yrs BrainMRI 3MSE</td>
<td>Continuous statin usage vs. Intermittent statin use vs. No statin usage</td>
<td>Prevalence of AD. Changes in Cranial MRI between statin users and non-statin users Rate of decline of cognition for statin users was 0.48/yr less than untreated group. MRI results show no sig changes in white matter grade or atrophy in statin users. 95%CI 0.06-0.89, p=0.024</td>
<td>4/5</td>
<td></td>
</tr>
<tr>
<td>Li et al.(^14) (2004) Community based prospective cohort</td>
<td>2356 &gt;65yrs Neuro assessment</td>
<td>Statin vs. no statin in dementia</td>
<td>Prevalence of dementia Statins not found to prevent dementia HR 1.19, 95% CI 0.82-1.75</td>
<td>4/5</td>
<td></td>
</tr>
<tr>
<td>Zandi et al.(^15) (2005) Cross sectional prospective study</td>
<td>4895 &gt;65yrs</td>
<td>Statin tx vs. no statin</td>
<td>Prevalence of dementia and AD Statins was inversely assoc w/ dementia prevalence, however 3 years later when pts reexamined, statin use was not found to predict incidence of dementia or AD. OR 1.19, 95%CI 0.53-2.34</td>
<td>3/5</td>
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</tbody>
</table>