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REVIEW

HMGCoA-Reductase Inhibitors in Dementia: Benefit or Harm

Kalpana P. Padala[1], Jane F. Potter[2] and Tsuneya Ikezu[3]

[1]Department of Family Medicine, University of Nebraska Medical Center, Omaha, NE, U.S.A. [2]Section of Geriatrics and Gerontology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, U.S.A. [3]Department of Pharmacology and Experimental Neuroscience; Center for Neurovirology and Neurodegenerative Disorders, University of Nebraska Medical Center, Omaha, NE, U.S.A. Email: kpadala@unmc.edu.

Abstract: Dementia is a syndrome characterized by a decline in cognitive function. Alzheimer's disease and cerebro-vascular disease are the most common causes of dementia. Many factors (genetic, life style, vascular etc.) appear to play some role in the development of dementia. Statins significantly reduce vascular disease and could reduce cognitive impairment in later life. Although most cross-sectional and longitudinal studies suggested a lower incidence of dementia in long-term statin users, randomized trials of statins in dementia did not slow disease progression. Furthermore, the effect of statins on cognitive performance is not well understood. Case reports suggest that statins may adversely affect cognition in some individuals, and prospective data studying the effects of statins in cognitively normal individuals is limited. Thus, the effects of statins on cognition in late life, remains uncertain.

Keywords: statins, dementia, cholesterol, vascular risk factors, cognition

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Dementia and its Prevalence

The purpose of this article is to give a critical review of the current status of impact of statins on dementia with a focus on Alzheimer's dementia.

Dementia is a syndrome characterized by a decline in cognitive function that includes memory and at least one other cognitive domain such as orientation, attention, and praxis. The decline must be from the individual's previous level of function and cognitive function and severe enough to cause impairment in occupational or social function.

Dementia is a major public health problem. Alzheimer's disease (AD) is the most common cause of dementia in the elderly followed by cerebro-vascular disease. It is estimated that currently around 24 million people have dementia worldwide, with the number being projected to double every 20 years.[1] About 60% of dementia patients live in developing countries, with the proportion expected to increase to more than 70% by 2040.[2]

There are over 5.2 million people diagnosed with AD in the US alone. One in eight persons over age 65 years has the disease while half of persons over age 80 are affected. Every 71 seconds someone in America is diagnosed with AD.[3] Some estimates predict a quadruple increase in the numbers of individuals affected with AD, where as others predict a 3-fold increase by 2050.[4] Owing to the rapid growth of the oldest age groups in the US population, the number who are 85 years and older will more than quadruple to 8.0 million by 2050, and will constitute most of the patients with AD.[5] Some estimate that 70% of all people with AD will be age 85 or older. Thus, dementia is a major public health problem with an increasing prevalence.[6]

The cost of AD in the United States is estimated to be $148 billion per year, ranking third after heart disease and cancer.[7] This cost includes direct medical costs such as medications, physician visits, hospitalization, and nursing home costs; direct non-medical costs such as daycare and other social services; and indirect costs such as the time informal caregivers spend with patients and the associated loss of productivity in the workplace.

Types of Dementia

Dementias are categorized according to their clinical presentation, neuropathology and/or etiology. The major causes of dementia include AD, cerebro-vascular disease, and Lewy Body disease. Less frequent causes include Parkinson's disease with dementia, fronto-temporal dementia, Huntington's disease, head injury, and alcoholism.

AD, which accounts for 60%–70% of all dementias, is a progressive neurodegenerative disease characterized by cognitive and behavioral abnormalities. Cognitive problems in AD include memory disturbance, executive dysfunction, agnosia, and apraxia. Significant decline in functional status resulting in nursing home placement is common with AD.[8] Vascular dementia, which causes 15%–25% of cases, is the second most common form of dementia caused by both small-vessel disease and large-vessel disease. White matter changes are noted in both cases. Dementia with Lewy Body disease is considered to be the second most common type of neuro-degenerative dementia after AD.

Risk Factors for Dementia and Cognitive Decline

Increasing age and positive family history are the two greatest risk factors in AD (Fig. 1). Genetics plays an important role in AD. Presence of the apolipoprotein E epsilon 4 (ApoE4) allele increases the risk of AD. ApoE4 allele is present in 30%–50% of patients with AD. Inheritance of one E4 allele increases the chances of developing AD by two fold, whereas, inheriting both alleles raises the chances by ten-fold. This association is seen in Caucasians but not in African Americans or Hispanics. In late-life AD, having a first degree relative with AD increases the relative risk by 2.6 fold whereas having two first-degree relatives, increases the relative risk by 7.6 fold. Presenilin-1, Presenilin-2 and β-amyloid precursor protein (APP) genes have been identified as causative genes for familial cases of AD and follow an autosomal dominant transmission. Such cases are rare comprising of only 5% of AD and have an onset before age 60 years. In monozygotic twin studies, there is a concordance rate of 40%–60% with wide variation in age of onset.[9]

Life style plays an important role in risk for development of dementia. Higher educational level appears to be protective. In normal cognitively intact older people, participation in leisure activities like reading, playing board games, dancing and playing music appear to be protective against cognitive decline.[10] Stress and depression are independent risk factors

for cognitive decline. Sustained poverty in midlife is associated with late-life dementia.[11] Lower linguistic ability in early life probably related to a lower cognitive development is a risk factor for late-life AD.[12]

There is a strong correlation between vascular disease and cognitive dysfunction. Vascular risk factors such as diabetes, hypertension, smoking, hyperlipidemia, and cerebro-vascular disease are all risk factors for the dementia.[13] The pathophysiology of vascular cognitive impairment is complex. Vascular dementia is caused by both large-vessel disease and small vessel disease. The clinical manifestation of large vessel disease leads to the substantial cognitive impairment that often occurs following a major stroke.[14] The cognitive deficits depend on the anatomical distribution of ischemia.[15] There must be evidence of cerebro-vascular disease, either focal neurological signs and symptoms, and CT or MRI demonstrating vascular lesions in the cortex or subcortex. Small vessel disease represents as white matter changes in the brain, also called leukoaraiosis. Longitudinal studies find that the periventricular white matter lesions (WML) are associated with cognitive impairment whereas the subcortical WML are not. In a large population-based sample study of non-demented elderly persons subjects, de-Groot et al. found that the severity of periventricular, but not subcortical WML, was related to the rate of cognitive decline.[16] After controlling for confounding variables, they found that subjects with severe periventricular WML experienced cognitive decline nearly three times as fast as those with average periventricular WML suggesting a significant effect of small vessel disease on vascular dementia.

Midlife Vascular Risk Factors and Dementia

Midlife vascular risk factors increase the risk of late-life dementia. Uncontrolled hypertension, cholesterol and diabetes in midlife are independent risk factors for late-life dementia.[17] There is also an association between the metabolic syndrome and cognitive decline.[18] Impaired insulin signaling seen in type 2 diabetes is also seen in AD patients. In both of these diseases dysfunctional protein GlcNAcylation/phosphorylation may be important for disease pathology.[19] Several epidemiologic studies have shown an association between midlife systolic and diastolic blood pressure elevation and late-life AD.[20] Better control of hypertension in midlife is associated with lower prevalence of late-life dementia. In the Nun's Study, lacunar infarcts in basal ganglia, thalamus or deep white matter were associated with high prevalence of clinical dementia.[21] In the population-based Rotterdam scan study, silent brain infarcts in elderly people were associated with increased risk of dementia and faster cognitive decline when compared to those without infarcts.[22]

Higher cholesterol in midlife is also a risk factor for late-life dementia.[23,24] However, higher cholesterol in late-life is associated with lower incidence of dementia, especially among non-smokers.[25] Studies of smoking and dementia have shown mixed results. Epidemiological studies have shown protective effect of smoking in dementia, while short prospective studies have shown deleterious effects on dementia.[26–28] However, in another prospective study no significant difference amongst smokers and nonsmokers was found in the onset of dementia. They concluded that smoking may increase the age specific onset rate of dementia.[29]

Cholesterol and Dementia

Cholesterol is insoluble in plasma and is carried around by lipoproteins to different tissues for energy utilization, lipid storage, bile acid formation and for steroid hormone production. The lipoproteins consist of both esterified and non-esterified cholesterol. Twenty-five percent of the total non-esterified cholesterol in the body is found in the central nervous system (CNS).[30] Cholesterol in the CNS is reported to be synthesized locally and to a greater extent is independent of the nutritional intake.[31] However, it has been shown that feeding cholesterol and raising the plasma lipid level is associated with metabolic changes in the brain, suggesting the uptake of small amounts of plasma cholesterol into the CNS, at rates too low to be detected by current methods.

There is continuous recycling of the cholesterol in the brain and this is critical for neuron repair and remodeling. The rest of the body primarily uses low density lipoprotein (LDL) receptor for uptake of lipoprotein-cholesterol but the brain cells use transporters such as those from the LDL receptor family, including LDL receptor itself, LDL receptor related protein (LRP), very low density lipoprotein (VLDL) receptor, ApoE receptor 2, megalin, etc.[32–35]

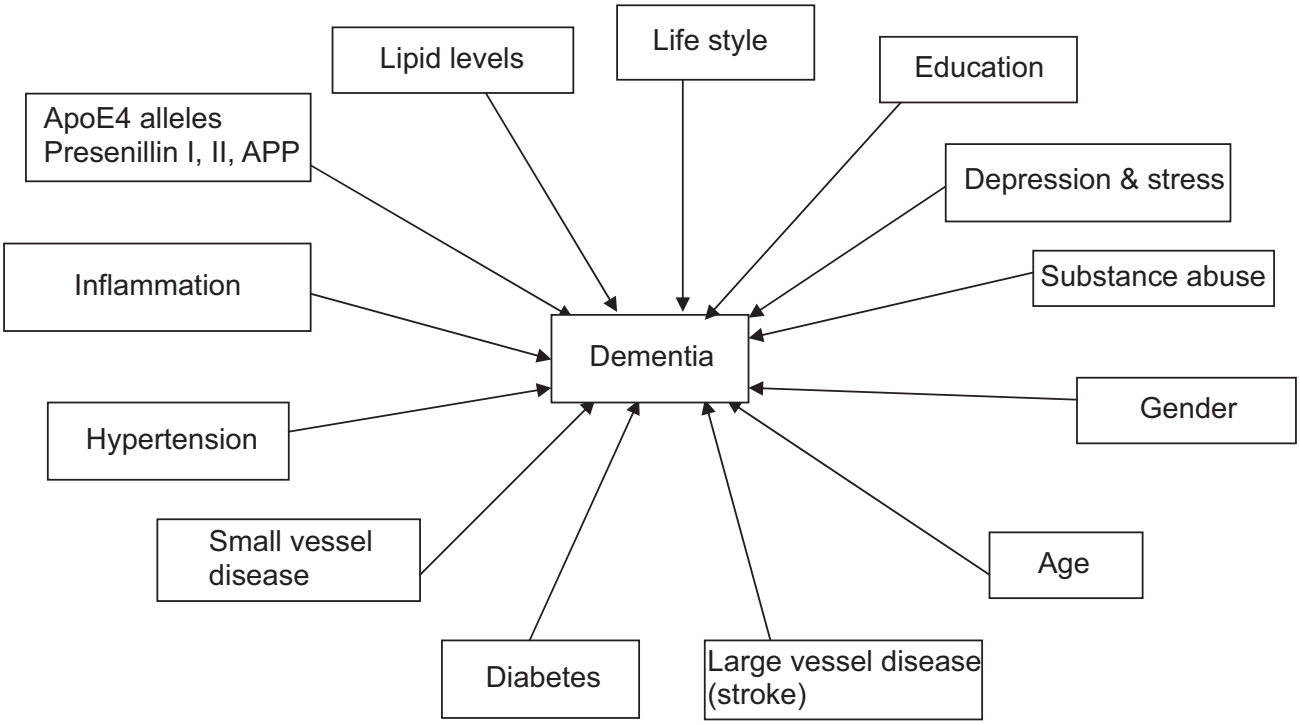

Figure 1. Risk factors for dementia.

Cholesterol synthesized in the brain needs to be hydroxylized before it can cross the blood-brain barrier. The cytochrome P450 subfamily CYP46, which is predominantly expressed in brain, hydroxylates cholesterol, forms 24S-hydroxycholesterol, which can readily cross the blood brain barrier and enter blood plasma.[36] Cholesterol output from the whole body also partly depends on formation of oxysterols such as 7a-hydroxycholesterol and 27-hydroxycholesterol, but the major pathway for cholesterol output utilizes cell surface transporter proteins to excrete cholesterol into the feces.[37–39] The role of these latter proteins in the cholesterol output from the CNS remains uncertain. Ninety percent of the plasma 24S-hydroxycholesterol comes from the CNS.[40] 24S-hydroxycholesterol in the plasma is further converted to bile acids in the liver and excreted by the kidneys.[41]

Studies show that 24S-hydroxycholesterol is neurotoxic because of increased generation of free radicals.[42] The mechanism behind the age dependent variation in the levels of circulating 24S-hydroxycholesterol and its relation to cholesterol synthesis is not well established.[36] Cholesterol plays a key role in the accumulation of both β-amyloid plaques and the neurofibrillary tangles.[43,44]

The effect of cholesterol on dementia risk may vary across the life span. High level of total cholesterol in mid life is a risk factor for AD in late life.[17] Cholesterol levels decrease with age.[45] In a twenty-one year longitudinal study, it was found that total cholesterol decreased with age. Also, subjects with a moderate decrease in cholesterol from mid-life to late-life experienced a higher risk of cognitive decline after adjusting for co-morbid conditions and apoE4 allele status.[46] In another longitudinal study, with subjects aged 70 years and older, higher levels of cholesterol were associated with reduced risk of dementia between ages 79 and 88 years.[25]

The National Cholesterol Education Program (NCEP) has guidelines for primary prevention and secondary prevention of coronary heart disease (CHD). For primary prevention the goal is to treat all subjects whose LDL cholesterol is 160 mg/dl or more with statins after an adequate trial with dietary modification. The goal is to reduce LDL to below 160 mg/dl in patients who have up to one risk factor (the 10-year risk for CHD is $<10\%$), to below 130 mg/dl in patients who have multiple (2+) risk factors (10-year risk of CHD is $\leq 20\%$) and below 100 mg/dl in subjects who have CHD or CHD risk

equivalents (10-year risk for CHD is >20%). The CHD risk equivalents comprise of other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm or symptomatic carotid artery disease), diabetes or multiple risk factors. Secondary prevention is done in patients who have existing CHD. The timing of therapy and intensity of therapy are highly important in secondary prevention. Statins are started during hospitalization in patients who have an acute myocardial infarction. The goal is to lower the LDL cholesterol to less than 100 mg/dl. Aggressive management is advised to lower LDL cholesterol. Increasing the dose of statin every 4–6 weeks to achieve the target goal of LDL level is recommended.[47]

Statins and Dementia

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. These are the most common agents used in the treatment of hyperlipidemias since 1987 when lovastatin, the first discovered statin got its FDA approval. Currently available statins include atorvastatin, simvastatin, fluvastatin, lovastatin, pravastatin and rosuvastatin. Statins are generally well tolerated and have a safe side effect profile, except for rare cases of hepatotoxicity and myotoxicity. Each statin differs in its absorption, bioavailability, half-life and metabolism. Fluvastatin has the shortest half life of about 1.5 hours, while atorvastatin has the longest half-life of fourteen hours. All statins undergo hepatic metabolism via the cytochrome P-450 pathway, however, pravastatin is more renally excreted than others.[48]

Statins have definite clinically beneficial effects (Fig. 2). A thorough review of benefits of statins in reduction of vascular risk is beyond the scope of this review. Briefly, benefits are summarized here, to set the context of why there has been interest in examining these agents for therapy for dementia. They decrease coronary heart disease incidence and total mortality. They reduce risk of recurrent myocardial infarction and the need for revascularization procedures. They reduce the risk of stroke and peripheral vascular disease.[49] They decrease platelet activity and decrease platelet deposition on damaged vessel walls.[50] They help in atherosclerotic plaque regression and also plaque stabilization. They regulate the endothelial function by increasing endothelial nitric oxide synthetase and reducing endothelin-I thereby increasing cerebral blood flow (CBF).[51] They act as antioxidants by decreasing free radical injury and reducing lipoprotein oxidation.[52] They have anti-inflammatory properties by reducing pro-inflammatory cytokines such as tumor necrosis factor (TNF) –alpha, acute phase reactants and interleukin (IL)-6 in peripheral blood samples which in turn reduces cell damage.[53] Statins inhibit cholesterol ester accumulation in monocyte derived macrophages. They stimulate alpha-secretase activity for APP processing, which helps in reduction of amyloid-β peptide generation and neuronal protection. Statins deplete downstream isoprenoids and interact with G-proteins such as Rho GTPases, thus protecting the brain from ischemia in experimental stroke models.[54]

Statins are either lipophilic (have affinity for or capable of dissolving in lipids) or hydrophilic (have affinity for or capable of dissolving in water) in nature. Lipophilic statins cross the blood brain barrier easily when compared to the hydrophilic statins. Thus, lipophilicity of a particular statin may dictate the potential direct effects on neurons.[55] Of the available agents, simvastatin, atorvastatin and lovastatin are lipophilic while pravastatin and fluvastatin are hydrophilic.[56] Of the lipophilic statins, simvastatin is the most lipophilic while lovastatin is the least lipophilic. Since cholesterol is essential in the myelination of neurons, it is proposed that excessive inhibition of cholesterol synthesis might lead to decrease in the myelination of neurons further leading to adverse cognitive effects (Fig. 3). Impact on cognition is also hypothesized to be related to the dose of the lipophilic statin. A larger dose of the lipophilic statin will cause greater decline in cholesterol levels in the brain. This will further decrease myelination of neurons and might worsen cognition.[57] Algotsson et al. hypothesized that patients with AD may be more susceptible to adverse effects of statins due to pre-existing defects in cholesterol metabolism.[58] Lipophilic statins have been shown to be pro-inflammatory in human monocytes in vitro and leucocytes in mice in vivo. However, hydrophilic statins do not induce a similar inflammatory response. This pro-inflammatory property of lipophilic statins could be another mechanism through which cognition could be worsened in AD.[59]

Statins have several drug-drug interactions. Use of statins causes increased levels of diclofenac, warfarin, ibuprofen and amitryptiline. Drugs like erythromycin,

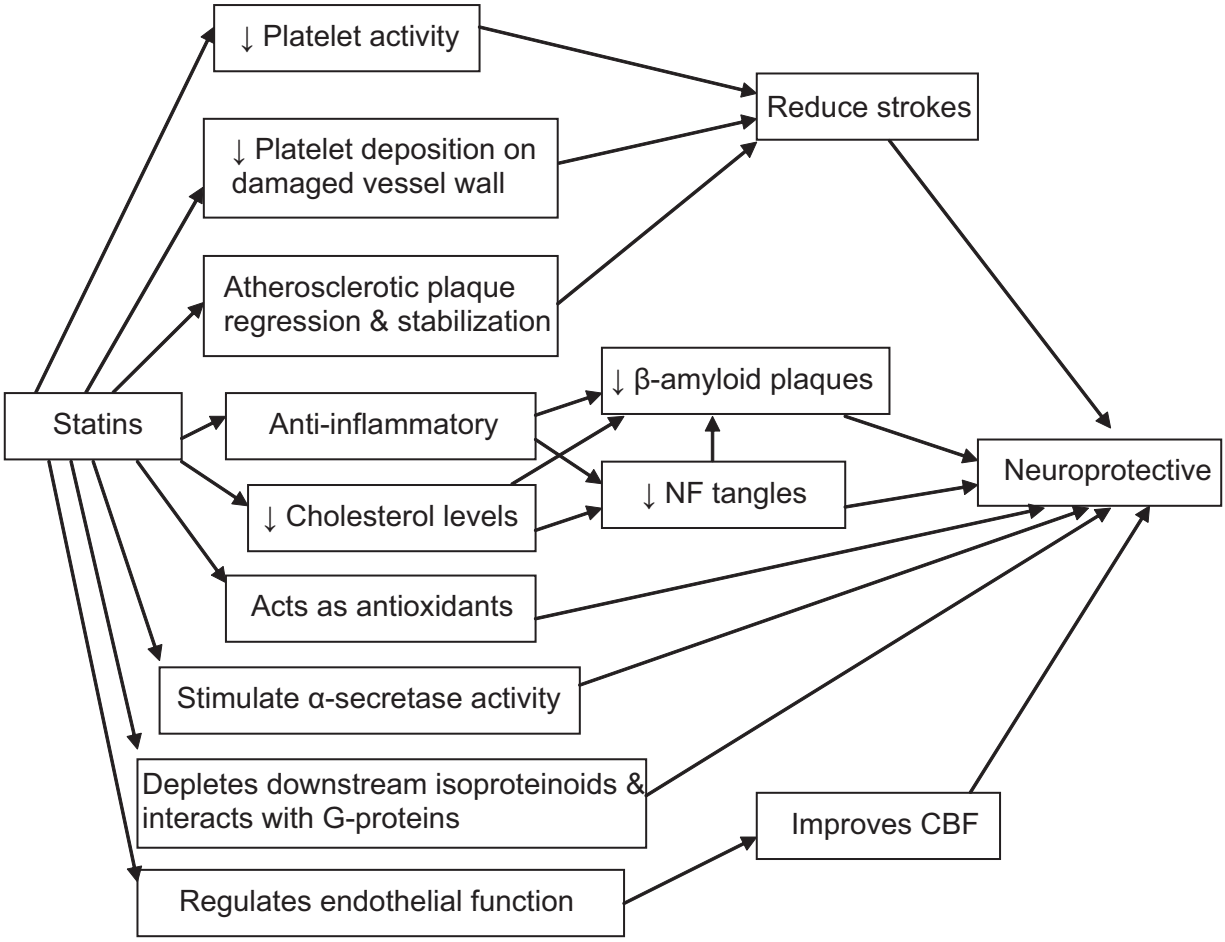

Figure 2. Possible beneficial effects of statins in dementia.

omeprazole, clarithromycin and cimetidine inhibit statin metabolism and raise levels of statins.[48]

Studies Done in Animals

Animal studies of statins done in APP mice have yielded both positive and negative effects on β-amyloidosis. Preclinical studies have also shown differential effects of statins (such as lovastatin and pravastatin) on β -amyloidosis, inflammation, and liver toxicity. Simvastatin reduced levels of β 42 and β 40 amyloid precursors both in vivo and vitro.[60] Fassbender et al. showed reduction of Aβ levels in cerebrospinal fluid and brain tissue in guinea pigs with high doses of simvastatin.[60] They also demonstrated reduction in intracellular and extracellular levels of Aβ40 and Aβ42 in primary rat hippocampal neurons, with simvastatin and lovastatin. Yet, in another preclinical study, lovastatin use enhanced β-amyloid production and thus senile plaque deposition in female mice brains.[61] Another study compared the effects of lipophilic statin lovastatin to a hydrophilic statin pravastatin in APP mice over a three month period. Both drugs reduced the amyloid burden in the brain, however lovastatin potentiated inflammation in the brain and also caused liver and muscle histotoxicity while pravastatin did not have any adverse effects.[62]

However the impact of statins on Aβ formation is complex. Statins have both cholesterol dependent and cholesterol independent (isoprenoid dependent) effects on APP cleavage and Aβ formation. Low cellular cholesterol levels favor the α-secretase pathway and decrease Aβ secretion.[63] In contrast, low isoprenoid levels result in the accumulation of APP, amyloidogenic fragments, and Aβ.[63] Importantly, low cholesterol and low isoprenoid levels appear to have completely independent effects on APP metabolism and Aβ formation.[63] In another in vitro study done by Ostrowski et al. statins selectively inhibited GTPase isoprenylation

at clinically relevant doses, leading to reduced Aβ production in an isoprenoid-dependent manner.[64]

Highlights of Studies on Statins and Dementia

Because statins have at least theoretical effects on pathways important in brain function, human population studies sought to determine the effects of statins on cognitive health. These epidemiologic and observational studies showed mixed results. Notkola and Kivipelto found that high serum cholesterol levels predicted AD in longitudinal, population based studies.[23,24] The average age of the population was 50.4 years at initial survey and mean length of follow up was 21 years. These subjects underwent magnetic resonance imaging (MRI) scans which showed no evidence of appreciable vascular pathology, ruling out the existence of vascular dementia.[24] In another longitudinal study of over 3000 subjects aged 65 and older, statin therapy was associated with slower rate of cognitive decline at 7 years compared to both the untreated group where statin therapy was either recommended or not. However, the 5-year MRI scans did not show any significant change in white matter lesions or atrophy grades amongst the groups.[65] Other longitudinal studies have shown decreased prevalence of dementia with use of statins.[66–70]

Cognitive effects of statins have also been studied in ethnic minorities. In a community based cohort study of African Americans aged 70 years and older, statin use was associated with reduced incidence of cognitive decline at three year follow up period as measured by Community Screening Interview for Dementia(CSI-D).[71] Another cohort study of Mexican Americans aged 60 years and older revealed lesser rates of incident dementia or cognitive impairment at five year follow up among statin users compared to non-statin users.[72] These studies generally favored statins as agents to improve cognitive outcomes.

Randomized studies, however, did not show beneficial effects of statins on cognition. In the PROSpective Study of Pravastatin in the Elderly at Risk of vascular disease (PROSPER), subjects with vascular disease were randomized to receive pravastatin or placebo and followed for 3.2 years. Though the treatment arm showed decreased coronary mortality, there was no difference in cognition between the treatment and control groups as measured by mini mental state exam (MMSE) and psychometric tests.[73] In the Heart Protection Study, subjects were randomized to get simvastatin or placebo. No difference in cognition was noted between the two groups.[74] In a prospective double blind study, which studied the effects of atorvastatin versus placebo in Alzheimer's patients, improvement in cognition was noted in the atorvastatin group when compared to the placebo group at six months and sustained at one year.[75] In another study, use of statins was associated with lower rates of prevalent dementia but had no impact

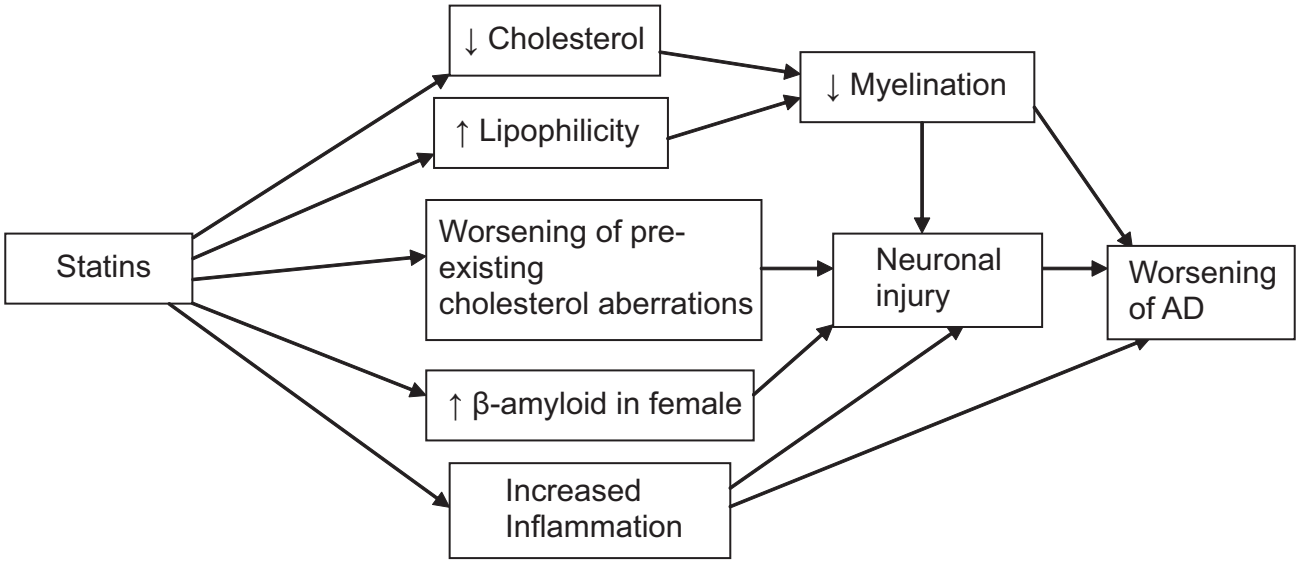

Figure 3. Possible adverse effects of statins in dementia.

on the rates of incident dementia.[76] In the LEADe trial done in mild to moderate subjects with AD, rates of decline in both cognition and global function were the same for the atorvastatin plus donepezil group and the placebo plus donepezil groups.[77] While these studies showed no benefit, they also did not show harmful effects on cognition.

A series of case reports, on the other hand, have raised concern about possible adverse effects of statins on memory. Wagstaff et al. reviewed 60 case reports of memory loss associated with statins. These subjects self reported memory loss. No specific memory tests were documented in any of these patients. Of these, 36 received simvastatin, 23 received atorvastatin and 1 pravastatin. About 50% of patients were noted to have cognitive adverse effects within 2 months of initiation of statin therapy. About 56% of the patients noted improvement when the statin was discontinued. There were only four subjects who were re-challenged with statins and memory loss recurred in all four patients.[78]

Lipophilic statins have been shown to cause CNS adverse effects like insomnia and headaches.[79] Deficits in neuropsychological testing have been reported with use of statins. Muldoon et al. found deficits in attention and psychomotor speed with use of lovastatin without an associated decline in cognition.[80] In another double blind placebo controlled trial, a small decline in neuropsychological performance was noted in the simvastatin group compared to the placebo group.[81] Thus it is possible that some individuals may be susceptible to significant cognitive adverse effects from statins, and that a larger group may experience at least subtle cognitive changes when carefully tested.

Summary

Statins are in wide use because of their known significant beneficial effect in vascular disease. They decrease the incidence of coronary heart disease and total mortality. They have been shown to reduce the risk of recurrent myocardial infarction. They have also been shown to reduce risk of strokes and peripheral vascular disease. The same population at risk for vascular disease is also at risk for cognitive decline and dementia. The impact of statins in AD is variable. Although observational studies have found a strong signal of lower rates of prevalent dementia in statin users, prospective studies have failed to show benefit of statin use on incident dementia or the rate of progression of dementia consistently.

Future Directions

In theory, the differences in lipophilicity among the various statins may be important. Of the individual properties of statins, lipophilicity may have the most influence on the cognitive effects, therefore, studies need to separate the cognitive effects of statins based on their lipophilicity or hydrophilicity. In addition, future studies need to delineate cognitive effects of statins based on subject characteristics, disease markers, stage of disease, and individual properties of the statins. Subject characteristics of interest are the age comparison: young-old (65–75 years) vs. the old-old (>85 years), functional status: (community dwelling vs. institutionalized), and gender. Disease markers of interest include the amyloid burden, CSF β-amyloid load, and the apoE4 allele status. Cognitive effects of statins in mild cognitive impairment versus mild to moderate dementia may be very different and deserves study as does the possibility that statins may sometimes cause cognitive side effects in susceptible individuals.

Disclosure

The authors report no conflicts of interest.

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