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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Statins and Cognitive Function: an Updated Review

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Abstract Ischemic heart disease remains the leading cause of death in the USA. Statins have substantially contributed to the decline in mortality due to heart disease. Historically, statins are hypothesized to be neuroprotective and beneficial in dementia, but recent reports have suggested an association with transient cognitive decline. We have critically appraised the relationship between statins and cognitive function in this review. Most of the data are observational and reported a protective effect of statins on dementia and Alzheimer's disease in patients with normal cognition at baseline. Few studies, including two randomized control trials, were unable to find a statistically significant decrease in the risk or improvement in patients with established dementia or decline in cognitive function with statin use. As more randomized control trials are required to definitively settle this, cardiovascular benefits of statins must be weighed against the risks of cognitive decline on an individual basis.

Keywords Statin use · Cognitive function · Dementia · Alzheimer's disease

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Introduction

Statins are competitive inhibitors of the enzyme HMG Co-A reductase, which is the rate-controlling step of cholesterol synthesis (Fig. 1). This leads to an increase in the number of LDL receptors expressed on hepatocytes, which extracts more LDL from the blood [1]. There is a concomitant decrease in triglyceride levels in blood and a small increase in HDL cholesterol as well [2]. By inhibiting HMG Co-A reductase, they inhibit the synthesis of isoprenoids and the prenylation of proteins. Studies have shown that statins also have various pleiotropic actions by decreasing the prenylation of Rho and Rab proteins. Prenylated Rho proteins activate an enzyme that plays a role in vascular biology and atherosclerotic plaque formation. Hence, statins also decrease oxidative stress and vascular inflammation and possibly increase the stability of atherosclerotic plaques. Similarly, a lower quantity of prenylated Rab proteins decreases the formation of amyloid-beta (ABeta) proteins, which have been implicated in the formation of the amyloid plaques in Alzheimer's disease [2].

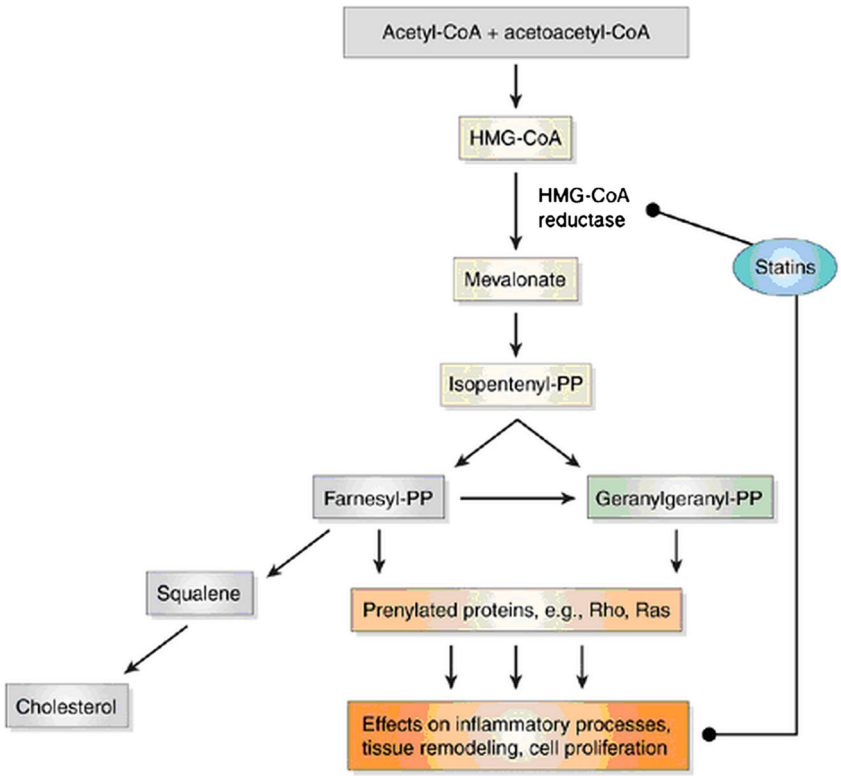

Fig. 1 Schematic illustration of the cholesterol biosynthetic pathway. Sites of action of HMG-CoA reductase inhibitors (statins) are indicated, PP pyrophosphate (reproduced with permission from: Bettina Haslinger-Löffler. Multiple effects of HMG-CoA reductase inhibitors (statins) besides their lipid-lowering function. Kidney Int. 2008;74(5):553–55, 2008) [42]

Statins are among the most commonly prescribed medications for treating hyperlipidemia and also for primary and secondary prevention of major adverse cardiovascular events in specific subgroup populations. Myopathy is the most well-characterized adverse effect of statins known to date. Cerivastatin was withdrawn in 2001 after 32 deaths were reported because of rhabdomyolysis, most of them being older individuals undergoing concurrent therapy for hypercholesterolemia with gemfibrozil [3]. Historically, the other common adverse effect is hepatotoxicity. While sustained transaminasemia may occur in 1 %, incidence of true hepatotoxicity is exceedingly low [4]. The JUPITER trial [5] and a subsequent meta-analysis [6] reported an increase in the rate of physician-reported diabetes and in the median value of HbA_1C levels. However, there has been increasing controversy regarding the use of statins and cognitive function decline after the FDA released label changes in 2012 [7]. As per the FDA report, statin use was associated with ill-defined memory loss and confusion, which were reversible after medication discontinuation and not restricted to a particular age group. Also, it was noted that statin use was not associated with fixed or progressive dementias such as Alzheimer disease. There have been much media attention and several recent meta-analysis and reports commenting on the use of statins and cognitive function, one of them showing no significant short-term cognitive dysfunction and also long-term beneficial role of statins when used in patients with no baseline cognitive impairment [8••]. Hence, we decided to systematically review and analyze the literature and evidence behind the effect of statins on dementia, Alzheimer's disease (AD), and cognitive function in this article.

Effect on Dementia

There is controversy regarding the effect of statins on dementia of different causes. There is an association of high levels of LDL cholesterol with Alzheimer's disease and dementia, and hence, in theory, a reduction in these levels using statins should have a protective effect on cognitive function. In addition to lowering the blood levels of LDL cholesterol, statins are believed to exert a protective effect through anti-inflammatory mechanisms and oxidative stress reduction. Data available through epidemiological, observational, in vitro, and in vivo investigational studies show a protective effect of statins on dementia as predicted [9, 10].

Case Reports

In an analysis of 60 case reports obtained from searching the MedWatch drug surveillance system of the Food and Drug Administration between November 1997 and February 2002, researchers noted that 50 % of the patients reported cognitive

changes within 2 months of statin use and 14 out of 25 patients noted an improvement once the drug was discontinued [9].

Case Control Studies

A protective effect of statins can be inferred from two case control studies performed nearly two decades ago. The first one is a case control study, which used data from the UK-based General Practice database. All cases with a diagnosis of dementia were matched to four controls each, after adjusting for age, sex, practice, and index date of case. The study demonstrated a decreased risk of dementia in statin users above the age of 50 irrespective of their cholesterol levels or the use of other lipid-lowering agents. However, selection bias, ICD code errors, and no laboratory values including lipid panel were major limitations [11]. The second case control study compared 492 patients with dementia greater than 65 years of age with 823 controls without any evidence of cognitive impairment, selected from the Canadian Study of Health and Aging. A decrease in the risk of dementia in patients less than 80 years of age and, more specifically, the risk of Alzheimer's dementia was noted with use of lipid-lowering agents [12]. Another case control study looked at 845 individuals with mean age 80.5 years of low socio-economic status and found a decreased association of dementia with lipid-lowering mediations. Although this trend was seen specifically with statins, the association was not statistically significant for statins [13].

Retrospective Cohort Studies

A subgroup analysis of 2978 adults above the age of 65 years from the Cardiovascular Health Cognition Study, an ancillary study of the Cardiovascular Health Study, who were free from dementia at baseline as determined by magnetic resonance imaging and modified MMSE results, concluded that current statin use did not decrease the risk of incident dementia, but former use of statins was associated with an increased risk of dementia. However, the limitations of the study were most patients enrolled were over 75 years of age and were using statins only for a median duration of 5 years. It is likely that greater duration of use is required for a protective effect to be seen. It is also possible that discontinuation of statin use is an indicator of declining health which in turn is associated with a higher risk of dementia [14].

Wolozin et al. analyzed over 700,000 patients on simvastatin and 50,000 patients on atorvastatin (all ≥65 years of age) using the US Veterans Affairs database. Incident dementia was determined based on the ICD9 code for senile dementia of the Alzheimer's type in the patient records. A significant decrease in the risk of incident dementia was observed in patients using simvastatin even after adjusting for age, other risk factors for dementia including hypertension, cardiovascular disease, and diabetes and Charlson index (a composite measure of the co-morbid illnesses). However, only a significant decrease in incident dementia was seen in the atorvastatin group after adjusting only for age. There was also a significant decrease in the incidence of Parkinson's disease with simvastatin. A major limitation of this study was the lack of objective assessment of cognitive function including diagnostic imaging, laboratory results, or cognitive function tests [15].

Parikh et al. conducted a retrospective longitudinal study examining the effects of diabetes and other risk factors on dementia in 377,838 US veterans aged above 65 years with a diagnosis of diabetes. The study found an increased risk of dementia with increase in the duration of diabetes and decreased dementia risk in diabetic patients using statins. Limitations of the study were no information on severity of diabetes and biomarkers such as HbA1c and also lack of adjustment for confounders such as BMI [16]. This is in contrary to the recent FDA warning about statin use and risk of diabetes as observed from other longitudinal studies [7]. The study also noted an increase dementia risk with age, African American race, and geography and higher risk in the mid-west and south which is predominantly African American, lower socio-economic class with higher prevalence of chronic diseases such as hypertension, diabetes, and coronary artery disease.

Prospective Cohort Studies

Data from the prospective BLSA (Baltimore Longitudinal Study of Ageing) showed a decrease in incidence of dementia among statin ever users compared to never users. This study compared the incidence of dementia and minimal cognitive impairment (MCI) in 1604 and 1345 participants above 50 years of age, respectively, over a median period of 25 years. It also analyzed the effect of time-dependent statin use on primary outcomes. There was a two to threefold decrease in the risk of dementia in statin-ever users compared to never users. It also showed a decrease in risk of dementia when analyzed in a time-dependent manner. Interestingly, all patients who developed dementia had higher total cholesterol levels at their first visit and certain range of HDL to total cholesterol ratio decreased the risk of MCI. However, increased dementia risk with decrease in total cholesterol levels was observed in men. The authors concluded that the effect of statins on cognitive function and specifically dementia is complex and multi-factorial and that the protective effect of statins is likely through mechanisms other than lowering of serum cholesterol [17].

Interestingly, a study from the original cohort of the Framingham Heart study also noted an association between lower

total serum cholesterol levels and worsening cognitive function which emphasizes that cognitive function is independent of cholesterol levels [18]. More recently, a prospective cohort study by Ancelin et al. assessed the effects of lipid-lowering agents on cognitive function in community-dwelling elderly patents above the age of 65 years over a 7-year period. This study had adjusted for more confounding factors than any of the other studies reviewed above including APoE and CETP genotyping. Baseline cognitive function was assessed comprehensively using tests such as the MMSE and TMT (trail-making test). A three-step approach was used to diagnose patients with dementia, screening interview by psychologists, brain imaging using MRI and CT scan, and second exam by a neurologist. A neutral committee of neurologists further evaluated suspected dementia using the DSM-IV criteria and a diagnosis of Alzheimer's was made as per the standardized criteria. They did not find a significant association between statins and cognitive decline but fibrates caused a decline in visual memory in elderly women with high levels of LDL cholesterol. The authors concluded that there might be an increased risk for cognitive decline in elderly women with high LDL cholesterol but that association between fibrate use and cognitive decline was only coincidental as fibrates are typically prescribed to patients with very high LDL levels resistant to statins. Few limitations were patients lost to follow-up and indication to use fibrates over statins in selected patients [19].

Randomized Control Trials

The PROSPER trial was an RCT which analyzed data from adults aged between 70 and 82 years with pre-existing vascular disease or risk factors for vascular disease including diabetes, smoking and hypertension. A significant decrease in risk of coronary heart disease as well as a decrease in the risk for TIA but no difference in the risk of stroke or cognitive function was seen with the use of pravastatin [20]. Similarly, in the MRC/BHF Heart Protection Study, a randomized placebo-controlled trial comparing the effects of simvastatin 40 mg daily vs. placebo over a 5-year period in 20,536 adults aged 40 to 80 years with a history of coronary artery disease, other occlusive arterial disease or diabetes, a mortality benefit was observed with statin use as a result of a reduced risk of death from coronary artery disease as well as other vascular deaths. But, no significant effect on cognitive function was noted when the two groups were compared using the TICS-m questionnaire (Telephone Interview for Cognitive Status) [10]. The greatest strength of this trial was the power it achieved by acquiring and analyzing the data of a set of 20,536 subjects. Thus, both these RCTs have not demonstrated a significant association between statin use and cognitive decline. This could be attributed to two reasons: the trials were not designed to assess cognitive function as the primary outcome and the subjects studied could have developed dementia/Alzheimer's disease prior to the start of the trial, especially given their advanced age. These studies did not use any form of brain imaging such as MRI or CT scans to screen and hence could have missed evidence of vascular disease. A meta-analysis of 10 studies showed a statistically significant decreased risk for dementia (RR 0.87, CI 0.82, 0.92) [21••]. It is to be noted that these studies examined the effect of statins on cognition over a longer duration of time ranging from 2 to more than 15 years.

Effect on Alzheimer's Disease

There is a significant overlap of studies between dementia of all causes and AD as AD is the most common cause of dementia. The Mirage study was a family-based case control study of 895 subjects with AD and 1483 controls over a period of 6 years. It aimed to analyze the impact of race and the APOE genotype on the association between statins and AD. Cognitive function was assessed using standardized, validated questionnaires including age, sex, race, awareness of heart disease, stroke, diabetes, smoking, and APOE genotype. The results showed a statistically significant reduction in the risk of AD among statins users, not affected by race or APO-E genotype [22]. A cross-sectional study by Wolozin et al. determined the prevalence of AD among patients using statins and other medications for hypertension and cardiovascular disease. A 60–73 % decrease in prevalence of AD was seen with patients on statin compared with the others not on statin [23].

A longitudinal, observational study of 3069 patients over 75 years of age enrolled in the GEMS (Gingko Evaluation of Memory Study) demonstrated a decrease in dementia risk of all causes including Alzheimer's with statin use. The effect was significant even in patients with statin treatment initiated during the study. No benefit was seen in patients with MCI at baseline. Greater benefit was observed with lipophilic statins compared to lipophobic [24]. Alzheimer's Disease anti- inflammatory Prevention Trial (ADAPT) demonstrated a 67 % decrease in the risk of incident AD with statin use even after adjusting for gender, age and APOE genotype [25].

Unlike the observational studies, RCTs have not shown much benefit with the use of statins. Two RCTs concluded statins have no protective effect on patients already diagnosed with Alzheimer's. The LEADe study is a placebo-controlled RCT of patients with mild or moderate AD divided in two groups receiving high-dose atorvastatin (80 mg) and placebo drug for 72 weeks followed by 8-week withdrawal of atorvastatin. The study found no improvement in cognitive or global function in the atorvastatin group compared to placebo [26]. Similarly, a recent double-blind placebo controlled trial comparing the effects of simvastatin with placebo in patients with

AD concluded that simvastatin did not help slow the cognitive decline in patients with Alzheimer's disease after more than 18 months [27•].

MCI or Cognitive Impairment Without Dementia

Statins were hypothesized to have an adverse effect on cognition as initial reports described sleep disturbances, which led to the hypothesis that statins may affect (daytime) cognitive performance [28, 29]. As mentioned above, the MRC/Heart Protection study found no significant change in cognitive function with the use of statins [10]. Beydoun et al. studied the association of statin use with dementia and mild cognitive function using data from the Baltimore Longitudinal Study. A statistically significant decrease in risk for mild cognitive impairment was found in statin ever users compared to never users. A HDL-to-TC ratio of 0.19 to 0.24 was protective against MCI as compared to a ratio to 0.19 of 0.00. Also, total cholesterol level between 211 and 238 was protective against MCI as compared to 56.3 and 186.2. The decreased risk of developing MCI with higher levels of total cholesterol at the first visit might indicate that a certain level of cholesterol is needed for the neurons [17]. A number of cohort studies found a decrease in the risk of MCI with the use of statins. ADAPT trial (Alzheimer's Dementia Anti-inflammatory Prevention Trial) observed a decrease in the incidence of MCI with the use of LLA similar to AD. There was no significant difference between statins and other LLA in terms of cognitive function [25].

Yaffe et al. studied the effect of statin use and cognitive function using MMSE scores in 1037 post-menopausal women with known CHD over 4 years. A significant cognitive decline was noted in women with higher total and LDL cholesterol levels. Women using statins had higher MMSE scores independent of serum cholesterol levels. No similar benefit was seen when cholesterol levels were lowered using other LLAs, which validates the hypothesis of other protective mechanisms due to statin use other than their lipid lowering action [30]. A cohort of 1789 Mexican American adults noted a similar decrease in incidence of both dementia and CIND (cognitive impairment without dementia) with the use of statins over 5 years [31]. Carlsson et al. studied the association of non-HDL cholesterol and statin use with cognitive decline in a cohort of 65 to 97 years. Statin use was associated with lower odds of cognitive decline but was not statistically significant after adjusting for confounders such as vascular disease and lifestyle [32]. Rockwood et al. examined the association of statin use with CIND from the Canadian study of Health and Ageing cohort. There was a 60 % reduction in the odds of developing CIND in subjects less than 80 years of age on a statin but not more than 80. Results were significant even after adjusting for various indication bias [12].

REGARDS trial is one of the few studies where statins have shown to have a detrimental effect on cognitive function. It was a cross-sectional study assessing cognitive decline in subjects greater than 45 years of age with an equal distribution of whites and blacks as well as men and women. A six-item screener, derived from the MMSE, was used to assess cognitive decline and subjects were followed up every 6 months. The study analyzed the association between cognitive functions and statin use including type of statin. Morisky scale was used to measure medication compliance. A trend towards higher cognitive decline was seen in statin users specifically in patients using lipophilic statins. However, these results were not statistically significant after adjusting for confounders such as age, diabetes, and level of education. Limitations were unknown baseline cognitive function prior to statin therapy and no information on the dose and duration of statin use [33].

Three RCTs individually examining 59 to 283 subjects over 21 days to 6 months reported poorer cognitive performance among statin-treated compared to placebo-treated groups [34–36]. The first RCT to describe an adverse cognitive effect of statin therapy randomized 59 healthy, normocholesterolemic men with no history of cardiovascular disease to lovastatin 40 mg, pravastatin 40 mg, or placebo [34]. The lovastatin group manifested small but statistically significant decrements of performance scores from baseline to 21 days in three of five tests [central response time ($p<0.05$), peripheral response time ($p<0.01$), reaction time ($p<0.01$)]. No significant differences between baseline and on-treatment scores were observed in subjects administered placebo or pravastatin. Interpretation of these findings is limited by differing baseline scores among the three groups despite randomization. A second RCT evaluated 209 healthy hypercholesterolemic patients randomized to daily lovastatin 20 mg or placebo [35]. Cognitive testing was conducted at baseline and after 6 months using a battery of 17 neuropsychological tests across 5 cognitive domains (attention, psychomotor speeds, mental flexibility, working memory, and memory recall). Consistent with the effects of practice on test performance, the placebo group demonstrated statistically significant improvement from baseline to 6 months in all 5 cognitive domains ($p<0.05$). On the other hand, lovastatin-treated patients improved only on tests of memory recall ($p=0.03$). Statistically significant differences in change in cognitive function from baseline to 6 months favoring the placebo group were observed in 2 of the 5 cognitive domains [attention ($p=0.005$), psychomotor speed ($p=0.004$)] and 4 of the 17 individual neuropsychological tests (all $p<0.05$). In the setting of these modest differences, the authors reported that lovastatin did not "substantially alter cognitive function" and concluded that the clinical importance of these findings remained "uncertain." A follow-up RCT conducted by the same group examined 283 hypercholesterolemic patients randomized to simvastatin

10 mg, simvastatin 40 mg, or placebo [36]. Neuropsychological evaluation employed 12 tests at study onset and after 6 months of daily medication. Ten of these cognitive performance tests had been previously incorporated into the battery of 17 tests used in the aforementioned RCT. In the primary analysis, the active treatment groups were collapsed and compared to placebo. Of the four tests that had previously exhibited significantly poorer changes in cognitive function in the statin-treated group, two tests again showed significant differences favoring placebo [recurrent words (p=0.04), maze completion (p=0.02)]. However, as noted by the authors, differences in baseline scores confound interpretation of the recurrent words test (percentage of words identified correctly as either new or repeated when words are read).

Global Cognitive Performance in Cognitively Intact Patients

The most commonly used measure of global cognitive function is the MMSE. The PROSPER trial comparing pravastatin to placebo found no change in global cognitive performance as measured by the MMSE [20]. Sparks et al. noticed no difference in MMSE scores between statin-users and non-user although a decrease in risk of incidence of AD was seen [25]. Arvanitakis et al. studied global cognitive function with statins in 929 Catholic clergy free of dementia using a composite measure for of MMSE scores and different neuropsychological tests assessing episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. No difference was found in global cognitive function with the use of statins [37]. A study comparing cognitive performance in four domains including global cognitive performance in statin user and non-users above 65 years of age did not find any difference after a median period of statin use for 2 years [38].

A cross-sectional study from Scotland compared the IQ scores of 478 subjects at age 11 and 80 using the Moray House Test, excluding any subjects with a diagnosis of dementia. The study examined the association of disease and several medication use in a sample from a unique national population of older people with known childhood IQ's using the same sensitive, validated cognitive measure nearly 70 years later. There was an absolute increase in IQ score for a subject at age 80 compared to IQ score at age 11 if they were statin users even after adjusting for confounders [39].

Global Cognitive Performance in Cognitively Impaired Patients

Most studies have not shown statins to improve cognitive function or slow the rate of cognitive decline in patients with dementia. A double-blind RCT assessed the effect of statins on cognitive decline in patients with AD. There was no significant difference between simvastatin and placebo group in the rate of change of AD Assessment Scale–cognitive portion (ADAS-cog) scores [27•]. Similarly, the LEADe trial showed no benefit of atorvastatin on cognition measured by ADAS-cog or on global function as measured by Alzheimer's Disease Cooperative Study Clinical Global Impression of Change [26]. However, Rosenberg et al. studied the change in cognitive function of 216 individuals from the Cache County Study with a diagnosis of incident AD as measured by change in Clinical Dementia Rating Sum of Boxes (CDR-Sum) each year. Statins and beta-blockers were both shown to have a protective effect. The protective effect of statins was significant even after adjusting for MMSE scores. This is one of the few cohort studies to demonstrate an actual protective effect of statins in patients with impaired cognitive function. The limitations of the study were the limited number of participants as well as the short duration of the study, both of which reduce the power of the study. Laboratory data and medication compliance were also unknown [40]. Elluj et al. studied the effects of commonly used drugs by patients with AD on deterioration of cognitive function. Use of sedatives and anti-psychotic drugs had a higher risk of deterioration of cognitive function while patients taking statins, drugs affecting the renin-angiotensin system and drugs approved for dementia had a lower risk of deterioration [41].

There are several limitations to the studies included. The accuracy of the diagnosis of dementia or impaired cognitive function is often subjective rather than objective. The tools used to measure cognitive abilities might miss subtle impairments in cognitive function. We believe that most of the studies did control appropriately for covariates such as gender, race, education, socioeconomic status, and co-existent medical conditions such as cardiovascular disease and hypertension. However, new factors have now been proposed to have an effect on cognitive ability and the risk of dementia including the concurrent use of other medications (such as anti-psychotic or anti-hypertensive medications) as well as more minor medical problems such as vitamin deficiencies, which need to be, included in future studies as well. There is evidence to support that statins decrease the risk for dementia and Alzheimer's disease and at least no harm if used in patients with no cognitive impairment at baseline. However, more randomized control trials are required to study this further and to comment on dose, duration, and type of statin—lipophilic or hydrophilic as well as other co-existing medical conditions in addition to cardiovascular disease, stroke and hypertension.

Conclusions

We present a comprehensive review of studies investigating the effects of statins on cognitive function. Statins could be

associated with a lower risk of dementia and AD through their anti-oxidant effect and effect on neurochemical markers as shown in animal models. However, this effect has not been consistently demonstrated in practice with studies showing varying results. Also, recent reports have been controversial and contradictory that statins might be associated with decline in short-term cognitive function. A number of case control and cohort studies have shown a decrease in the risk of dementia or Alzheimer's disease with the initiation of statin therapy. Yet, as we know, observational studies cannot determine causality and RCTs are required to confirm the association. RCTs on effect of statins and cognitive function have shown debatable and controversial results with three RCTs reporting poorer performance scores in a minority of cognitive tests among statin users. Hence, we conclude that there is a need for more randomized control trials and until then benefits of statins must be weighed against the risks of cognitive decline on an individual basis.

Compliance with Ethics Guidelines

Conflict of Interest Saurav Chatterjee, Parasuram Krishnamoorthy, Pragya Ranjan, Ahana Roy, Anasua Chakraborty, Manpreet Singh Sabharwal, Richard Ro, Vikram Agarwal, Partha Sardar, Jacqueline Danik, Jay S Giri, Emil M DeGoma, and Dharam J Kumbhani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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