Can statins prevent or help treat Alzheimer's disease?

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Review

Can Statins Prevent or Help Treat Alzheimer's Disease?

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Abstract. Evidence accumulating from biological and epidemiological studies suggests that high levels of serum cholesterol may promote the pathological processes that lead to Alzheimer's disease (AD). Lowering cholesterol in experimental animal models slows the expression of Alzheimer's pathology. These findings raise the possibility that treating humans with cholesterol lowering medications might reduce the risk of developing AD or help treat it. The statins (lovastatin, pravastatin, simvastatin, and others) are powerful cholesterol lowering agents of proven benefit in vascular disease. Several clinical studies comparing the occurrence of AD between users and non-users of statins suggested that risk of AD was substantially reduced among the users. However, because these studies were not randomized trials, they provided insufficient evidence to recommend statin therapy. Cochrane reviews are based on the best available information about healthcare interventions and they focus primarily on randomized controlled trials (RCTs). On the issue of prevention, two randomized trials have been carried out and neither showed any reduction in occurrence of AD in patients treated with statins compared to those given placebo. Statins cannot therefore be recommended for the prevention of AD. Regarding treatment of AD, the large RCTs which have assessed this outcome have not published their results. Initial analysis from the studies available indicate statins have no benefit on the outcome measure ADAS-Cog but have a significant beneficial effect on MMSE as an outcome. We need to await full results from the RCTs before we can be certain. In addition statins were not detrimental to cognition in either systematic review.

Keywords: Alzheimer's disease, cholesterol, cognitive impairment, dementia, statins

This is a version of a Cochrane Review, which is available in the Cochrane Library. Cochrane systematic reviews are regularly updated to include new research, and in response to feedback from readers. If you wish to comment on this or other Cochrane reviews of dementia, interventions for dementia, please send your comments to Sue Marcus.

The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of review authors, and not necessarily shared by the Cochrane Collaboration.

INTRODUCTION

Epidemiological studies from the mid-1990s suggested an association between high cholesterol and increased risk of Alzheimer's disease (AD). It was then proposed that statins, due to their role in cholesterol reduction, may prevent the onset of AD or delay its progression. As a result Cochrane reviews were commissioned on the topics 'Statins for the prevention of dementia' and 'Statins for the treatment of dementia'. Based on the best available information about healthcare interventions, Cochrane reviews explore the evi-

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dence for and against the effectiveness and appropriateness of treatments. They are designed to facilitate the choices that doctors, patients, policy-makers, and others face in health care. A more detailed review 'Statins for the prevention of dementia' has been published and will be updated in the Cochrane Database of Systematic Reviews [1] while 'Statins for the treatment of dementia' is awaiting publication [2].

Because Cochrane reviews address questions about the effects of health care, they focus primarily on randomized trials. Randomization is the only way to prevent systematic differences between baseline characteristics of participants in different intervention groups in terms of both known and unknown confounders. For clinical interventions, deciding who receives an intervention and who does not is influenced by many factors, including prognostic factors. Empirical evidence suggests that, on average, non-randomized studies produce effect estimates that indicate more extreme benefits of the effects of health care than randomized trials.

In carrying out a Cochrane review, one performs a thorough search and systematic review of evidence available. If appropriate the numerical results of all, or perhaps some, of the studies are combined to produce a meta-analysis. Potential advantages of meta-analyses include an increase in power, an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. Such a meta-analysis yields an overall statistic (together with its confidence interval) that summarizes the effectiveness of the experimental intervention compared with a control intervention.

BACKGROUND: CHOLESTEROL AND ALZHEIMER'S DISEASE

In AD, amyloid-β peptide (Aβ) accumulation is thought to trigger the pathological changes that ultimately lead to cognitive dysfunction [3]. Aβ is derived from amyloid-β protein precursor (AβPP) by the sequential proteolytic activities of β- and γ-secretase in the amyloidogenic pathway [4]. Aβ genesis may be precluded if AβPP is cleaved by α-secretase and then γ-secretase forming a non-amyloidogenic fragment [5]. Aβ occurs in two different forms, Aβ_{40} and Aβ_{42}, varying in the length at the C terminus. It is the longer Aβ_{42} that aggregates more avidly. Cerebral Aβ generation in vitro [6,7] and in vivo is cholesterol dependent [8–10]. Cell biology investigations indicat-

ed that lipid rafts might be the link between cholesterol and amyloidogenic processing of AβPP. Both β- and γ-secretases are active in lipid rafts and it appears that AβPP processing within these lipid rafts by secretases determines the levels of Aβ production [11, 12]. Isoprenylation also appears to play a role targeting proteins to plasma membranes, possibly specifically to membrane lipid microdomains and may be implicated in the progression of AD [13]. This experimental evidence strengthens the putative association between cholesterol and AD.

The apolipoprotein E (ApoE) ε4 allele was the only established genetic risk factor for AD until recently and is involved in cholesterol metabolism. This is significant as ApoE acts as a cholesterol transporter in the brain, and it has been shown to bind directly to the Aβ peptide and influence its fibrillogenesis and clearance in vitro [14] and in vivo [15,16]. ApoE has also been shown to be critically important for the formation of fibrillar Aβ in brain parenchyma in vivo [17]. The ε4 allele is also associated with higher plasma concentrations of total and low density lipoprotein (LDL) cholesterol as well as a higher risk of atherosclerosis, making inheritance of this allele a major susceptibility factor for both sporadic and late-onset AD [18]. Interestingly two recent genome-wide association studies reported significant association for rs11136000 located in the clusterin (CLU) gene [19,20]. Functionally clusterin has similarities to APOE as both are major brain apolipoproteins, both are present in amyloid plaques, interact with Aβ, and regulate the conversion of Aβ into insoluble forms. Both cooperate in suppressing Aβ deposition as well as in modifying Aβ clearance at the blood brain barrier (BBB) [21]. The Harold et al. study [19] also found a genome wide significant association for rs3851179 in the phosphatidylinositol-binding clathrin assembly protein gene (PICALM) while the Lambert et al. study [20] reported a genome wide significance for a linkage disequilibrium block within boundaries of the complement component (3b/4b) receptor 1 (CR1) gene. PICALM is involved in clathrin-mediated endocytosis (CME): cell culture experiments have shown that AβPP is retrieved from the cell surface by CME and that aberrant processing via CME results in altered Aβ levels. CR1 may be involved in Aβ clearance via the complement system. Lines of evidence, therefore, suggest protein products from these genes may play a role in Aβ clearance from the brain [21].

Brain cholesterol homeostasis is regulated through de novo synthesis with little or no transfer from the peripheral circulation due to impermeability of the BBB

to plasma lipoproteins [22]. It is therefore difficult to understand how hypercholesterolemia affects the brain and causes neuropathology characteristic of AD. It has been suggested that during the neurodegenerative process an increased amount of cholesterol is removed from the brain [23]. The mechanism of transport is unclear but may be mediated by either ApoE or enzymatic oxidation by 24S-hydroxycholesterol (SHC) [24,25]. In humans SHC is predominantly produced in the brain and is a key element in cholesterol homeostasis. A continuous flux of this substance occurs across the BBB. SHC has been proposed to be a biochemical marker of neurodegenerative processes as higher plasma levels are seen in patients with early AD and vascular dementia (VaD), while lower levels are observed in patients with severe disease [26].

High density lipoprotein cholesterol (HDL-C) has been described as a negative risk factor for the development of cognitive impairment. It can prevent aggregation and polymerization of $A\beta$ and has anti-inflammatory properties [27,28].

Several epidemiological studies have shown an association between high serum cholesterol levels and an increased susceptibility to AD [29–31]. In contrast the Framingham Heart Study reported a significant positive linear association between total cholesterol and cognitive measures [32].

There is also a close relationship between AD and cardiovascular disease with coronary heart disease and hypertension being significant risk factors for AD [30, 33]. These vascular-related AD risk factors have an established association with cerebral hypoperfusion.

STATINS

Statins are a class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the rate-limiting enzyme in the cascade of cellular cholesterol biosynthesis. Statins reduce formation and entry of LDL cholesterol into the circulation and upregulate LDL receptor activity lowering LDL cholesterol and triglycerides and increasing HDL cholesterol. Previous studies in cell culture and animals have demonstrated that treatment with cholesterol lowering drugs reduces the production of $A\beta$ [6, 34,35]. It was therefore hypothesized that reduction of $A\beta$ levels by statins may have neuroprotective effects in patients with AD [36,37]. Further work demonstrated an association between antecedent statin use and

neurofibrillary tangle burden at autopsy with risk for typical AD pathology reduced in statin users [38].

Statins are classified according to their solubility in lipids or water (lipophilic and hydrophilic respectively). Lipophilic statins (lovastatin, simvastatin, cervistatin) cross the BBB and penetrate cell membranes more effectively and may be more efficient theoretically in the treatment of dementia than the hydrophilic statins (atorvastatin, pravastatin, fluvastatin). In contrast, however, reducing cholesterol synthesis below a critical level can induce neuronal death [39] and may paradoxically make treatment with hydrophilic statins more appropriate [40].

Statins also have pleiotrophic effects. They can improve the endothelial function of atherosclerotic vessels by decreasing endothelial 1 and angiotensin II type 1 receptor and increasing nitric oxide [41]. Statins also have antithrombotic and anti-inflammatory effects [42]. They may also have the ability to reduce apoptosis and cellular death [43]. Many of these cholesterol-independent effects reflect statins' ability to block the synthesis of important isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules [44].

It is also possible that reduced cholesterol synthesis and concentration in the central nervous system (CNS) caused by treatment with statins may cause neurocognitive deficits. Statins lower circulating levels of vitamin E and ubiquinone (Coenzyme Q10) and may affect the synthesis of polyunsaturated fatty acids that are integral to neuronal membranes [45,46]. Researchers have speculated that low concentrations of components of lipoprotein particles may produce subtle impairments of mental processes [47].

STATIN THERAPY AND PREVENTION OF DEMENTIA

The evidence for the potential benefit of statins in the management of AD has largely come from epidemiological studies. Two clinical reports had described an association between statin therapy and a reduction in the occurrence of AD by as much as 70% [37,48]. At that stage, there were no randomized clinical trials assessing use of statins and reduced risk of AD. Further epidemiological studies followed; cross-sectional studies mostly demonstrated an association between statin use and reduced occurrence of AD [49–51]. Rodriguez and colleagues demonstrated reduced incidence of AD with lipid lowering agent (LLA) use [52]. Evidence

from prospective studies has been less clear and inconsistent with some studies showing reduced incidence of AD with statin use [53–57] and others showing no benefit [58–61]. Interestingly Reitz and collaborators demonstrated that a protective effect was seen if their data were analyzed (incorrectly) as a cross-sectional study but not as a (correctly) cohort study [42]. Li and coworkers demonstrated likewise [58]. This serves to demonstrate that earlier reports of reduced risk of dementia with use of statins may have been spurious and due to problems with design. The Rotterdam study subsequently performed proportional hazard ratios thereby addressing this concern and found a significantly reduced risk of incident AD with statin use [57].

In general, epidemiological studies are subject to important limitations such as confounding and issues with representation. Cross-sectional studies are subject to indication bias which occurs when a drug is prescribed for a reason that itself is associated with an outcome of interest. Of note from the Wolozin study [37], while the data were being collected (1996–1998) physicians may have prescribed statins to patients who were 'more highly educated, attentive, inquisitive and concerned about their future health' [62] than persons at lower risk of dementia. This may also explain why an effect was seen for pravastatin and lovastatin but not simvastatin, sales of which lagged behind the former two. Indication bias often is the explanation for observational studies reporting a positive effect of a drug on a condition. Prospective randomized, double-blind placebo-controlled trials are then required to establish treatment effects.

Two large clinical trials have been published. The Medical Research Council/British Heart Foundation Heart Protection Study (HPS 2002) was a placebo-controlled randomized clinical trial primarily assessing the ability of simvastatin to reduce the development of vascular disease in 20,536 high-risk individuals including 5806 aged 70 to 80 years at baseline [63]. Participants were followed up for five years. Prevention of cognitive decline was a tertiary outcome. The modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants at final follow-up, either face-to-face in the clinic or over the telephone. There was no data on cognition at baseline apart from excluding patients with dementia. LDL-cholesterol was reduced by an average of 1.0 mmol/l in the simvastatin group compared to the placebo group. Despite significantly reduced rates of myocardial infarction, stroke, and revascularization, there was no significant difference between treatment groups in the per-centages of patients classified as cognitively impaired either overall or in subgroups with respect to their age at study entry or their previous history of cerebrovascular disease. Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 in each group).

The PROSPER trial was a randomized controlled trial in which 5804 participants aged 70 to 82 years were assigned to 40 mg pravastatin or placebo per day, all participants had a history of, or risk factors for, vascular disease [64]. PROSPER 2002 results included difference between last-on-treatment and second baseline values for a number of cognitive tests: number of correct letter digit codes, number of words remembered in the picture word learning test, time needed to complete the Stroop test, Mini-Mental Status Examination (MMSE) score. The first baseline measure was used as a practice measurement to reduce possible learning effects. Mean MMSE score at entry was 28/30 points in both groups. These participants were considered to be of reasonable risk of developing dementia over the average 3.2 years of follow-up. Despite a 34% reduction in LDL cholesterol and a significant reduction in the primary endpoint of composite coronary death, non-fatal myocardial infarction, and fatal or nonfatal stroke, there was no significant effect on cognitive function either way.

Data could not be combined from the two studies as they measured different cognitive outcomes at different time periods.

Neither of the studies, however, can proclaim to have included a systematic clinical cognitive assessment although the PROSPER 2002 data is more informative in cognitive terms compared to the HPS 2002 study. Decline in cognition is also very low in both studies and this may relate to careful control of cardiovascular risk factors. This parallels the absence of decline in two vascular dementia clinical trials and the control of cardiovascular risk factors is common in both [65,66].

One follow-up study from PROSPER 2002 showed no association between ApoE4 genotype and rate of cognitive decline in statin users compared to placebo [67].

From the RCTs, therefore, there is good evidence that statins given in late life to individuals at risk of vascular disease have no effect in preventing dementia. The two trials identified were large scale and included patients at high risk of vascular disease. The fact they had similar findings was reassuring. As neither the lipophilic statin simvastatin (HPS 2002) nor the hydrophilic statin pravastatin (PROSPER) had a signif-

Study or Subgroup	Placebo Mean	SD	Total	Statin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
ADCLT 2005	-3.7	6.7	21	0.5	5.9	25	12.4%	-4.20 [-7.88, -0.52]	
LEADe 2008	3.3	10	320	2.77	9	320	77.2%	0.53 [-0.94, 2.00]	
Simons 2002	3.4	7	20	4.1	6.5	24	10.4%	-0.70 [-4.72, 3.32]	
Total (95% CI)			361			369	100.0%	-0.18 [-1.48, 1.11]	

Heterogeneity: Chi² = 5.53, df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 0.28 (P = 0.78)

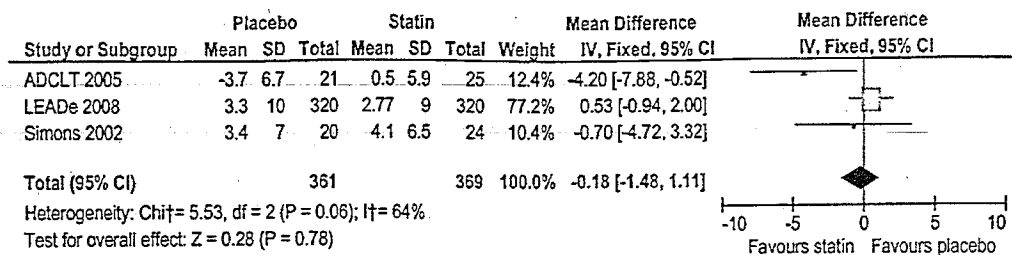Favours statin   Favours placebo

Fig. 1. Forest plot of comparison. Cognitive change from baseline – change in ADAS-Cog. (Colours are visible in the electronic version of the article at www.iospress.nl.)

icant effect in prevention of dementia, neither can be recommended on the basis of their ability to cross the BBB. Of note, there was also no evidence that statins were detrimental to cognition.

STATIN THERAPY AND TREATMENT OF DEMENTIA

Again due to the possible link between elevated cholesterol and dementia studies have also been carried out on the role of statins in the treatment of established dementia. A post-hoc analysis on data pooled from three double-blind placebo-controlled clinical trials of galantamine in AD showed no significant change in cognitive status in association with the use of statins [68]. An observational study in patients with AD followed for 34.8 months showed that patients treated with LLAs had a slower decline on the MMSE than patients with untreated dyslipaemia or normolipaemic patients [69].

In carrying out the Cochrane review 'Statins for the treatment of dementia' randomized double-blind placebo-controlled trials were sought in order to provide best evidence. Three randomized placebo-controlled trials were identified that matched the inclusion criteria with 748 participants – ADCLT 2005 [70], LEADe 2008 [71,72], and Simons 2002 [73].

ADCLT 2005 included 63 patients with a diagnosis of probable or possible AD, individuals 51 years or older with mild-moderate impairment (MMSE score 12–28) were eligible. Treatment in ADCLT 2005 consisted of atorvastatin 80 mg daily or matching placebo. All but 6 individuals were taking cholinesterase inhibitors, 3 in each group. Mean age was 78.9 ± 1.2 years in placebo group and 78.15 ± 1.3 years in atorvastatin group.

LEADe 2008 included 641 patients with a diagnosis of probable AD mild-moderate severity, defined as

MMSE score of 13–25 at screening. Treatment in LEADe 2008 consisted of 80 mg atorvastatin daily or matching placebo for 72 weeks. Patients were receiving donepezil 10 mg for at least 3 months before randomization and LDL-C was 2.5–3.5 mmol/l for inclusion. Subjects were 53% female, age range 50 to 90 years, mean age 74 ± 8 years.

Simons 2002 was primarily a study investigating whether statins alter cholesterol metabolites and reduce $A\beta$ levels in the CSF of AD patients. Cognition was assessed as a secondary outcome. 44 patients with probable AD mild-moderate severity (MMSE scores 12–26) were recruited. Treatment consisted of simvastatin 40 mg daily for 4 weeks and 80 mg daily for the following 22 weeks. Patients were allowed to take donepezil or rivastigmine if the dose had been unchanged for 3 months prior to study entry and remained stable during the study period. Mean age was 68.5 ± 8 years in placebo group and 68.0 ± 9 years in simvastatin group.

The three studies assessed change in ADAS-Cog from baseline. The mean change and standard deviation were calculated from the available data and entered into a meta-analysis. When the three studies were combined, there was no significant difference in ADAS-Cog between the statin group and placebo group [mean difference −0.18, 95% CI −1.48, 1.11, $p = 0.78$] (Fig. 1).

Change in MMSE was available from two studies: ADCLT 2005 and Simons 2002. When data from these trials was combined in a meta-analysis there was a significant difference between the statin and placebo groups favoring the statin group [mean difference −2.25, 95% CI −3.42, −1.08, $p < 0.01$] (Fig. 2). These two studies were small, however, involving 107 patients in total. Of note in LEADe 2008, there was no benefit from atorvastatin in the MMSE outcome but data was not provided in the conference abstract to enable pooling in a meta-analysis.

Change in ADCS-CGIC assessing clinical global impression of change was given in two studies: ADCLT
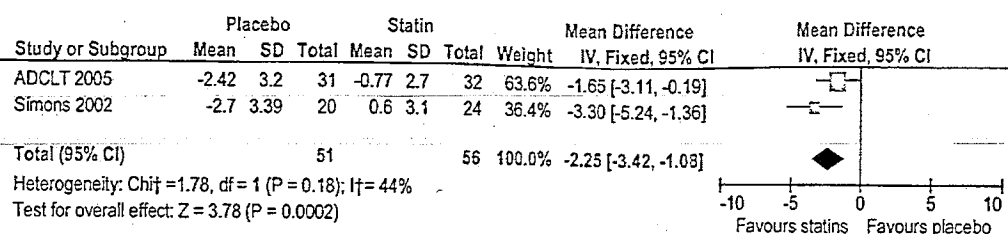
| Study or Subgroup | Placebo | | | Statin | | | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
	Mean	SD	Total	Mean	SD	Total			
ADCLT 2005	-2.42	3.2	31	-0.77	2.7	32	63.6%	-1.65 [-3.11, -0.19]	
Simons 2002	-2.7	3.39	20	0.6	3.1	24	36.4%	-3.30 [-5.24, -1.36]	
Total (95% CI)			51			56	100.0%	-2.25 [-3.42, -1.08]	

Heterogeneity: Chi² =1.78, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 3.78 (P = 0.0002)

Favours statins　　Favours placebo

Fig. 2. Forest plot of comparison. Change in MMSE from baseline. (Colours are visible in the electronic version of the article at www.iospress.nl.)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
ADCLT 2005	-0.4	1.81	64.3%	-0.40 [-3.95, 3.15]	
LEADe 2008	-0.02	2.43	35.7%	-0.02 [-4.78, 4.74]	
Total (95% CI)			100.0%	-0.26 [-3.11, 2.58]	

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
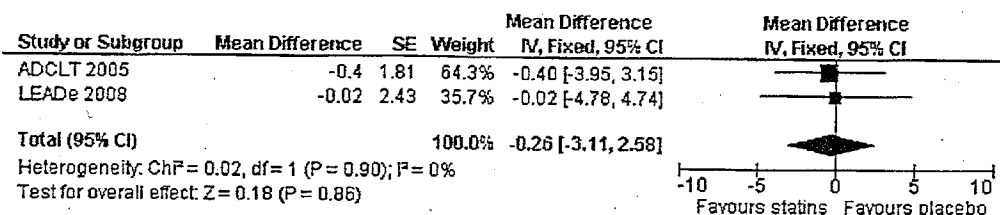
Favours statins　　Favours placebo

Fig. 3. Forest plot of comparison. Change in CGIC. (Colours are visible in the electronic version of the article at www.iospress.nl.)

2005 and LEADe 2008. When data from these two trials was combined in a meta-analysis using generic inverse variance, there was no significant difference between the statin and placebo groups [mean difference −0.26, 95% CI −3.11, 2.58, p = 0.86] (Fig. 3).

The statins were well tolerated and incidence of side effects was low. Again of note, there was no evidence that statins were detrimental to cognition.

There was some evidence from ADCLT 2005 that greater cognitive effect from atorvastatin was seen in patients with higher cholesterol and MMSE at baseline, and those with an ApoE4 allele present. This would need to be confirmed in larger scale studies.

It was not possible to assess if lipophilic statins were more efficacious due to the small number of studies.

The Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease (CLASP) was also a multi-centre randomized double-blind, placebo-controlled trial of simvastatin to slow the progression of AD. Recruitment has also finished in this study and the results are yet to be published [74].

CONCLUSIONS

There is insufficient evidence to recommend statins for the prevention or treatment of dementia. Although it is biologically plausible that statins may be efficacious in the prevention and treatment of AD results from RCTs have been disappointing.

A recent editorial by Sparks 2009 [75] concluded statin therapy exerts a beneficial effect at some point between normal cognitive performance and profound dementia based upon results from observational studies. While this may be true it has not been borne out by more rigorous RCTs. As stated previously, indication bias is a large factor in observational studies and other limitations in these trials include short periods of observation, short periods of statin use, lack of classification of dementia type, not controlling for vascular risk factors and lack of monitoring of compliance. From best evidence available from the RCTs there still remain unanswered questions both in terms of dementia prevention and treatment. Regarding prevention questions exist such as:

Whether there is a relationship between the occurrence of disease and the level of cholesterol – as one's cholesterol rises does the risk of disease rise in some graded fashion?

Whether lowering of cholesterol levels judged normal in the developed parts of the world might influence the onset of disease.

Whether persons with a family history of AD might preferentially benefit from therapy compared to those without a family history.

Whether therapy started in middle life has an advantage over therapy started in the 60s or early 70s.

For patients with an elevated cholesterol level, the decision to treat is made much easier because statins reduce the incidence of cardiovascular disease. The challenge comes from patients with normal cholesterol. From the identified studies, there is no convincing evidence to support their use for dementia prevention in

populations at low vascular risk. Those individuals, who request therapy, must be advised of the risk of drug treatment versus an unproven but biologically plausible benefit of treatment.

Regarding treatment of dementia, we await full results of the LEADe 2008 and CLASP 2008 studies. As these are large scale RCTs, they will most likely provide best evidence as to whether statins are beneficial in the treatment of AD and dementia. Preliminary results from LEADe 2008 suggest statins have no beneficial effect in treatment of AD so it would not be advisable to embark upon further large scale RCTs until full results are known.

If considering additional studies, it would be beneficial to further assess impact of treatment at an earlier stage of the disease process, effect of ApoE4 allele and effect of baseline cholesterol level as results from AD-CLT 2005 suggest these factors may have an impact on efficacy.

DISCLOSURE STATEMENTS

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=263).

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