Statins for the treatment of dementia

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Statins for the treatment of dementia (Review)

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TABLE OF CONTENTS

[Intervention Review]

Statins for the treatment of dementia

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ABSTRACT

Background

The use of statin therapy in established Alzheimer's disease (AD) or vascular dementia (VaD) is a relatively unexplored area. In AD ß-amyloid protein (Aß) is deposited in the form of extracellular plaques and previous studies have determined Aß generation is cholesterol dependent. Hypercholesterolaemia has also been implicated in the pathogenesis of VaD. Due to the role of statins in cholesterol reduction it is biologically plausible they may be efficacious in the treatment of AD and dementia.

Objectives

To assess the clinical efficacy and tolerability of statins in the treatment of dementia.

Search strategy

We searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, as well as many trials registries and grey literature sources (27 October 2008).

Selection criteria

Double-blind, randomized controlled trials of statins given for at least six months in people with a diagnosis of dementia.

Data collection and analysis

Two independent authors extracted and assessed data independently against the inclusion criteria. Data were pooled where appropriate and entered into a meta-analysis.

Main results

Three studies were identified (748 participants, age range 50-90 years). All patients had a diagnosis of probable or possible AD according to standard criteria and most patients were established on a cholinesterase inhibitor. Treatment in ADCLT 2005 consisted of 80mg atorvastatin compared to placebo for 52 weeks, serum low density lipoprotein (LDL) cholesterol was reduced by 54% in the atorvastatin group. Treatment in Simons 2002 consisted of 40mg simvastatin compared to placebo for 26 weeks, serum LDL cholesterol was reduced by 52% in the simvastatin group. Treatment in LEADe 2010 consisted of 80mg atorvastatin compared to placebo for 72 weeks, LDL cholesterol was reduced by 50.2% by month 3 and remained constant through month 18. Change in Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-Cog) from baseline was a primary outcome in 3 studies; when data were pooled there was considerable heterogeneity so the random effects model was used, statins did not provide any beneficial effect in this cognitive measure

[mean difference -1.12, 95% CI -3.99, 1.75, p = 0.44]. All studies provided change in Mini Mental State Examination (MMSE) from baseline; again random effects model was used due to considerable heterogeneity: there was no significant benefit from statins in this cognitive measure when the data were pooled [mean difference -1.53, 95% CI -3.28, 0.21, p = 0.08]. There was some evidence that patients on statins in ADCLT 2005 maintained better cognitive function if serum cholesterol was high at baseline, MMSE was higher at baseline or if they had an apolipoprotein E4 allele present. This would need to be confirmed in larger studies however. Treatment related adverse effects were available from two studies, LEADe 2010 and Simons 2002; when data were pooled there was no significant difference between statins and placebo [odds ratio 2.45, 95% CI 0.69, 8.62, p = 0.16]. There was no significant difference in global function, behaviour or activities of daily living in the statin and placebo groups. One large randomised controlled trial (RCT) (CLASP 2008) has not yet published its results. There were no studies identified assessing role of statins in treatment of VaD. There was no evidence that statins were detrimental to cognition.

Authors' conclusions

There is insufficient evidence to recommend statins for the treatment of dementia. Analysis from the studies available, including one large RCT, indicate statins have no benefit on the outcome measures ADAS-Cog or MMSE. We need to await full results from CLASP 2008 before we can be certain. This Cochrane review will be updated as these results become available.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence to recommend statins for the treatment of Alzheimer's disease or dementia.

High levels of serum cholesterol are thought to contribute to the pathology of Alzheimer's disease and vascular dementia. The statin family of medications (lovastatin, pravastatin, simvastatin and others) are powerful cholesterol lowering medications and are first line treatments for reducing cholesterol in patients with, or at risk of cardiovascular disease. There has been much interest in their possible role in treatment of dementia and several trials have been carried out in order to assess this outcome. We identified three studies involving 748 participants, age range 50-90 years. From these trials, including one large one, there is insufficient evidence that statins help in the treatment of dementia. One large scale trial has yet to publish their results. When this study is reported we will have greater evidence regarding role of statins in the treatment of dementia.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patients: Patients with dementia
Setting: Community
Intervention: Statin medication
Comparison: Placebo

Outcomes	Absolute Difference in Means (95% CI)	Number of participants (Studies)	Quality of Evidence	Comments
Change in ADAS-Cog	0.18 (-0.69,1.05)	704 (3)	High	
Change in MMSE	-0.50 (-0.92,-0.08)	721 (3)	High	
Change in CGIC	-0.02 (-0.14, 0.10)	660 (2)	High	
Change in NPI	-0.94 (-2.07,0.19)	577 (2)	High	

BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50 to 60% of all cases. Cerebrovascular disease is the second most common cause responsible for 25 to 30% of cases and resulting in vascular dementia (VaD). AD and VaD also frequently co-occur leading to mixed dementia. In total, dementia is thought to affect approximately 7% of the population older than 65 years of age and 30% of people older than 80. Other studies have quoted that 10% of people aged > 65 years are affected, rising to nearly 50% of all persons aged > 85 years (Evans 1989; von Strauss 1999). Dementia is already a major public health problem and is set to become even more so due to the anticipated increase in life expectancy. In 2001 more than 24 million people worldwide had dementia, this is expected to double every 20 years up to 81 million in 2040 (Ferri 2005).

There is accumulating evidence that cholesterol may be implicated in the pathogenesis of dementia (AD and VaD) and this has led investigators to assess the possible role of lipid lowering agents in treatment of dementia. Many questions remain unanswered, however. This review aims to collate best evidence available regarding use of statins in the treatment of dementia.

Cholesterol and AD

A possible role for cholesterol in AD was based on observations of AD neuropathology among relatively young individuals with no history of dementia but with coronary heart disease (Sparks 1990). A central event in the development of AD is thought to be abnormal processing of the cell membrane-associated amyloid precursor protein (APP) followed by deposition of toxic β-amyloid (Aβ) protein in the form of amyloid plaques in the extracellular space of the neocortex (Selkoe 2001). APP is a protein containing 770 amino acids. Aβ peptide is generated by the sequential cleavage of APP by beta and gamma secretase in the amyloidogenic pathway. Aβ genesis may be precluded if APP is instead cleaved first by alpha secretase within the Aβ domain, and then by gamma secretase, forming a non-amyloidogenic fragment (Cole 2007). The nonamyloidogenic pathway appears to be neuroprotective compared to the neurodegenerative, amyloidogenic pathway (Vetrivel 2006). Aβ occurs in two different forms, Aβ40 and Aβ42, varying in the length at the C terminus. It is the longer Aβ42 that aggregates more avidly. Early work discovered elevated cholesterol levels led to greatly reduced levels of nonamyloidogenic APP alpha in vitro (Bodovitz 1996). Perhaps more importantly, subsequent studies suggested that cerebral Aβ generation

in vitro (Simons 1998; Mizuno 1999) and in vivo (Burns 2003; Sparks 1994; Refolo 2000) is cholesterol dependent. Cell biology investigations indicated that specialised cellular membrane microdomains rich in cholesterol and sphingolipids, termed lipid rafts, might be the link between cholesterol and amyloidogenic processing of APP. Both beta and gamma secretases are active in lipid rafts and it appears that APP processing within these lipid rafts by secretases determines the levels of Aβ production (Ehehalt 2003; Vetrivel 2004).

The ApoE $\epsilon 4$ allele is associated with sporadic AD. Meta-analysis has shown that the ApoE $\epsilon 4$ allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes (Farrer 1997). It acts mainly by modifying age of onset, with each copy of the allele lowering the age at onset by almost 10 years (Corder 1993). This is significant in the context of cholesterol metabolism as ApoE acts as a cholesterol transporter in the brain. It has been shown to bind directly to the Aβ peptide and influence its fibrillogenesis and clearance in vitro (Strittmatter 1993) and in vivo (Naslund 1995; Wisniewski 1995). ApoE has also been shown to be critically important for the formation of fibrillar Aβ in brain parenchyma in vivo (Holtzman 2000). Two recent genome-wide association studies reported a significant association of AD with a locus within the clusterin (CLU) gene (Harold 2009; Lambert 2009). Functionally clusterin has similarities to APOE as both are major brain apolipoproteins and act as cholesterol transporters in the central nervous system. Both are also present in amyloid plaques and interact with Aß, and regulating the conversion of Aß into insoluble forms, cooperating to suppress Aß deposition and modifying Aß clearance at the blood brain barrier (BBB) (van Es 2009). The amyloid cascade hypothesis states that an imbalance between production of and clearance of Aβ in the brain is the initiating event in the pathogenesis of AD, ultimately leading to neuronal degeneration and dementia (Hardy 2002) and thus theoretically links cholesterol metabolism to the development of AD.

Central and peripheral cholesterol pools are separate, however, and almost all cholesterol in the brain is synthesized locally and is not transferred into plasma because of the BBB (Dietschy 2001). How serum cholesterol affects brain cholesterol has been a major question to date. Brain cholesterol content does not seem to be affected by high serum low density lipoprotein (LDL) or low serum high density lipoprotein (HDL) levels, perhaps as a result of the stability of cholesterol in myelin but it has not been established whether intramembranous lipid domains or intracellular cholesterol content are affected (Lane 2005). Studies in animal models have shown that diet-induced hypercholesterolaemia increases Aβ and ApoE concentrations in temporal and frontal cortices, but not in the cerebellum, and that these regional increases parallel the amyloid pathology observed in the AD brain (Wu 2003). Side chain oxidised cholesterol metabolites such as hydroxy-cholesterols do cross the BBB. In the steady state in the adult brain, cholesterol clearance is facilitated by the formation and excretion of 24-hydroxycholesterol (Lutjohann 2000). This is the major pathway for efflux of brain cholesterol and is crucial for maintenance of brain cholesterol homeostasis (Reiss 2004). 27-Hydroxycholesterol is also found in the brain and may also provide a link between hypercholesterolaemia and AD (Heverin 2005); the contribution of the 27-hydroxylase pathway to AD is an area in need of further exploration.

Several epidemiological studies have shown an association between high serum cholesterol levels and an increased susceptibility to AD (Jarvik 1995; Kivipelto 2002; Notkola 1998). The Notkola study was a long-term prospective study that found elevated total serum cholesterol level was a risk factor for AD, independent of the ApoE $\epsilon 4$ allele; however, the association between AD and the ApoE $\epsilon 4$ allele became weaker after adjustment for serum total cholesterol. The authors concluded that some of the effect of the ApoE $\epsilon 4$ allele on the risk of AD might be mediated through elevated levels of total serum cholesterol. The Kivipelto study was again a prospective population-based study that showed elevated midlife total cholesterol level was a risk factor for AD and was independent from risk from the ApoE $\epsilon 4$ allele and high midlife systolic blood pressure. The Jarvik study was a case-control study which again showed a positive association between serum cholesterol and risk of AD.

There may also be converging pathogenic mechanisms between cerebrovascular and Aβ plaque pathology - cerebrovascular pathology with ischaemia resulting in upregulation of APP expression followed by Aβ deposition (Jendroska 1995). However, coexisting pathology may occur independently of the disease process and increase the probability of exhibiting dementia in otherwise asymptomatic patients (Riekse 2004).

Cholesterol and VaD

VaD is the second most common form of dementia. It is characterised by both large and small vessel lesions. Subcortical ischaemic vascular disease caused by damage to tiny blood vessels that lie deep in the brain is now thought to be more prevalent than multi-infarct dementia caused by large vessel lesions and stroke (Ballard 2000; Esiri 1997).

Sclerosis of small cerebral arteries and arterioles is considered to be responsible for the diffuse periventricular white matter abnormalities involved in the pathogenesis of subcortical VaD (Ryglewicz 2002). Risk factors for VaD are similar to risk factors for all types of vascular disease, namely hypertension, diabetes, smoking and hypercholesterolaemia (Ott 1998; Posner 2002; Stewart 1999). These factors are also important in the pathogenesis of AD (Decarli 2004); furthermore the effects of vascular and AD pathologies are additive and in most population samples these disorders appear together (Snowdon 1997).

Plasma lipids could be associated with the risk of VaD through several mechanisms. High levels of LDL cholesterol and low levels of HDL cholesterol are established risk factors for coronary heart dis-

ease (Moroney 1999) and carotid artery atherosclerosis (Sharrett 1994). These may lead to cognitive impairment through cerebral hypoperfusion or embolism (Breteler 1994). LDL cholesterol may interact with APOE to cause small vessel disease, and low levels of antioxidants known to occur in brains of VaD patients' may lead to a higher susceptibility to oxidative stress and a higher grade of LDL cholesterol oxidation (Dantoine 2002; Paragh 2002).

A previous cross-sectional analysis showed that the prevalence of VaD decreased with higher levels of HDL cholesterol and increased with higher levels of non-HDL cholesterol. Treatment with lipid lowering agents was not associated with the risk of prevalent VaD, however. Incidence of VaD was also calculated, again risk of VaD rose with increasing non-HDL level but treatment with lipid lowering agents did not lower risk of incident VaD (Reitz 2004). Other studies have found an association of VaD with decreased levels of HDL cholesterol (Kuriyama 1994; Muckle 1985; Zuliani 2001). The role of LDL cholesterol remains controversial, with some studies finding an association between increased LDL cholesterol and risk of VaD (Klich-Raczka 2002; Moroney 1999; Paragh 2002) and other studies reporting a negative association (van Exel 2002; Yoshitake 1995).

Stroke is also a major risk factor for VaD. Debate continues as to whether increased cholesterol levels are a risk factor for stroke. Recent clinical trials indicate that statins significantly decrease stroke risk in vascular patients including patients with stroke (CTTC 2005; SPARCL 2006). The meta-analysis carried out by the The Cholesterol Treatment Trialists' Collaborators including 90,056 patients found that the use of statins caused a significant 17% proportional reduction in the incidence of first ever-stroke of any type per 1 mmol/l LDL cholesterol reduction. In the secondary prevention of stroke, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that treatment with atorvastatin reduced the risk of recurrent cerebrovascular events in patients with recent stroke or transient ischaemic attack but no history of heart disease. By reducing the risk of stroke, statins may also act to reduce the incidence of post-stroke dementia.

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 thereby reduce the formation and entry of LDL cholesterol into the circulation and upregulate LDL receptor activity, lowering LDL cholesterol and triglycerides and increasing HDL cholesterol. Several studies in cell culture and animals have demonstrated that treatment with cholesterol lowering drugs reduces the production of Aβ (Fassbender 2001; Refolo 2001; Simons 1998). It was therefore hypothesised that reduction of Aβ levels by statins may have neuroprotective effects in patients with AD (Simons 2001; Wolozin 2001). However, one study of transgenic mice found that levels of Aβ in the brains of simvastatin treated mice did not differ from those of untreated mice. Simvastatin treatment did lead to the reversal of learning and memory deficits and the authors hypothesized the benefit of simvastatin may have been due to modulation of signaling pathways in memory formation (Li 2006). Further work, however, then demonstrated an association between antecedent statin use and neurofibrillary tangle burden at autopsy with risk for typical AD pathology reduced in statin users (Li 2007). The effects of statins on AD neuropathology are therefore not totally understood. Their possible role in the treatment of VaD includes secondary prevention of stroke and other pleiotrophic effects as detailed below.

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 (Michikawa 1998) and may paradoxically make treatment with hydrophilic statins more appropriate (Sparks 2006).

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 (Wassmann 2001). Low nitric oxide levels lead to impaired endothelial function, platelet aggregation and enhanced leucocyte adhesion to the endothelium. Statins also have antithrombotic effects as they decrease plasminogen activator levels and have anti-inflammatory effects as they decrease adhesion molecules (Reitz 2004). They may also have the ability to reduce apoptosis and cellular death (Ruocco 2002). 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 signalling molecules (Liao 2002).

It is also possible that reduced cholesterol synthesis and concentration in the CNS caused by treatment with statins may cause neurocognitive deficits. Several investigators have therefore questioned the potential detrimental effects of lowering cholesterol on cognition (King 2003; Muldoon 2000; Wagstaff 2003; Zhang 2004). It has been shown that large doses of statins can produce substantial neurotoxicity in dogs (Berry 1988; Walsh 1996). 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 (Palomaki 1997; Rise 1997). Researchers have speculated that low concentrations of one or more components of lipoprotein particles circulating in the bloodstream may produce subtle but measurable impairments of mental processes by influencing the supply of fat-soluble micronutrients, specifically, vitamin E, β-carotene and vitamin A (Muldoon 1997). On balance, however, potential benefits from statins appear to outweigh potential detrimental effects and adverse effects from statins will be assessed in this review.

Statins are widely available and prescribed for treatment of dyslipi-

demia and secondary prevention of cardiovascular and cerebrovascular disease. Their cost is relatively low and some have come off patent so are prescribed generically.

Statin treatment in dementia

The use of statin therapy in established AD or VaD is a relatively unexplored area. There have been a number of studies on the role of statins in the prevention of dementia but these are the focus of another Cochrane review (McGuinness 2009). Further trials have followed patients with AD and dementia; these are the focus of this review and are presented in the results section.

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 (Winblad 2007).

An observational study in patients with AD followed for 34.8 months showed that patients treated with lipid lowering agents had a slower decline on the MMSE than patients with untreated dyslipaemia or normolipaemic patients. The study concluded that lipid lowering agents (including fibrates and statins) may slow cognitive decline in patients with AD and may have a neuroprotective effect but this finding needs to be confirmed by randomized placebo-controlled trials (Masse 2005).

Other lipid lowering agents (fibrates, niacin/nicotinic acid, anion-exchange resins) (LLAs) have been assessed with statins in several dementia studies. Fibrates are the main class in use other than statins. Rockwood et al. published a population based survey from the Canadian Study of Health and Aging (CSHA) demonstrating use of statins and other LLAs on reduced risk of AD in subjects younger than 80 years old (Rockwood 2002). In contrast the UK GP Research Database study showed that only statins reduced the risk of dementia, other LLAs did not (Jick 2000). In a further study in patients with AD all LLAs including statins were associated with a slower annual cognitive decline but there was no significant difference between statins and other LLAs and there was lack of statistical power to compare statins to fibrates (Masse 2005).

Fibrates do not inhibit cholesterol biosynthesis, they stimulate β-oxidation of fatty acids and act mainly by decreasing serum triglycerides. They are only used first line in those with hypertriglyceridaemia and can be used in combination with statins in those not responding to single therapy. They also have anti-inflammatory effects as they inhibit the production of different pro-inflammatory molecules (Pahan 2006). In this review however we are primarily interested in role of statins in the treatment of dementia.

This review aims to collate the best available evidence regarding use of statins in AD and VaD.

Statins have been proven to significantly decrease coronary events in the primary and secondary prevention of coronary heart disease. The question is whether they have a significant therapeutic effect in dementia. Any intervention shown to slow the progression of dementia would have huge worldwide economic benefit.

OBJECTIVES

Primary objective

To evaluate the efficacy and safety of statins in the treatment of AD and VaD.

Secondary objective

To evaluate if the efficacy of statins in the treatment of AD and VaD depends on cholesterol level, APOE genotype or cognitive level.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized double-blind placebo controlled trials in which a statin was given for at least six months. Six months was chosen as this was felt to be the minimum length of time required to be on treatment to allow a disease-modifying effect and before any cognitive benefit could be attained.

Trials comparing two different statins without a placebo were excluded.

Types of participants

Patients with a diagnosis of probable or possible Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke-the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria or acceptable equivalent.

Patients with a diagnosis of probable or possible vascular dementia according to National Institute of Neurological Disorders and Stroke-Association International pour le Recherché at l'Enseignement en Neurosciences (NINDS-AIREN) criteria or acceptable equivalent.

Trials with DSM 3, 3R or 4 dementia will be included but analysed separately from those with causal diagnoses for dementia.

Types of interventions

Any type of statin (hydrophilic and lipophilic) given in appropriate dose compared to placebo.

Types of outcome measures

Primary outcomes

Change in MMSE, ADAS-cog or other accepted cognitive measure.

Secondary outcomes

- Incidence and severity of adverse effects from RCTs
- Change in cognitive status accounting for prior cholesterol level, APOE genotype and cognitive level
- Patient perceived quality of life
- Change in Activities of Daily Living (ADLs)
- Change in behaviour

Search methods for identification of studies

See Cochrane Dementia and Cognitive Improvement Group methods used in reviews.

On 27 October 2008, searches were run in the Dementia and Cognitive Improvement Group Specialized Register, *The Cochrane Library,* MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS as well as in many trials databases and grey literature sources. The following search terms were used in combination with terms used for Alzheimer's disease and dementia: statin* OR lipophilic OR hydrophilic OR lovastatin OR simvastatin OR cervistatin OR atorvastatin OR rosuvastatin OR provastatin OR fluvastatin OR hydroxymethylglutaryl-CoA Reductase Inhibitors.

For the detailed search strategy, see Table 1.

Table 1. Search strategy

Database/source	Search strategy	Notes
Specialized Register	statin* OR lipophilic OR hydrophilic	
The Cochrane Library	1. statin*.tiabkw. 2. hydroxymethylglutaryl-CoA Reductase Inhibitors/ (all subheadings) 3. 1 OR 2 4. Alzheimer-disease/ all subheadings 5.exp dementia-vascular/ all subheadings 6.creutzfeldt-jakob-syndrome/ all subheadings 7.kluver-bucy-syndrome/ all subheadings 8.lewy-body-disease/ all subheadings 9.pick-disease-of-the-brain/ all subheadings 10.Huntington-disease/ all subheadings 11.delirium/ all subheading 12.wernicke-encephalopathy/ all subheadings 13.(dement$ OR Alzheimer$).tiab. 14.(lewy$ AND bod$).tiab. 15.((cognit$ OR memor$ OR mental) and (decline$ OR impair$ OR los$ OR deteriorate$)).tiab. 16.(chronic AND cerebrovascular).tiab. 17.((organic brain syndrome) OR (organic brain disease)).tiab. 18.((cerebr$ AND deteriorate$) OR (cerebr$ AND insufficien$)).tiab. 19.((pick$ and disease) or (creutzfeldt or JCD or CJD) or huntington$ or binswanger$ or korsako$).tiab. 20. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 21. 20 AND 4	

Table 1. Search strategy (*Continued*)

	22. limit 21 to (randomized controlled trial).pt.	
Medline (Ovid SP)	1.(statin$ OR lipophilic OR hydrophilic).mp. 2.(lovastatin OR simvastatin OR cervistatin OR atorvastatin OR rosuvastatin OR provastatin OR fluvastatin).mp. 3.Hydroxymethylglutaryl-CoA Reductase Inhibitors/ all subheadings 4.Alzheimer-disease/ all subheadings 5.exp dementia-vascular/ all subheadings 6.creutzfeldt-jakob-syndrome/ all subheadings 7.kluver-bucy-syndrome/ all subheadings 8.lewy-body-disease/ all subheadings 9.pick-disease-of-the-brain/ all subheadings 10.Huntington-disease/ all subheadings 11.delirium/ all subheading 12.wernicke-encephalopathy/ all subheadings 13.(dement$ OR Alzheimer$).mp. 14.(lewy$ AND bod$).mp. 15.((cognit$ OR memor$ OR mental) and (decline$ OR impair$ OR los$ OR deteriorate$)).mp. 16.(chronic AND cerebrovascular).mp. 17.((organic brain syndrome) OR (organic brain disease)).mp. 18.((cerebr$ AND deteriorate$) OR (cerebr$ AND insufficien$)).mp. 19.((pick$ and disease) or (creutzfeldt or JCD or CJD) or huntington$ or binswanger$ or korsako$).mp. 20.1 OR 2 OR 3 21.4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 22.20 AND 21 23.randomized controlled trial.pt. 24.controlled clinical trial.pt. 25.randomized.ab. 26.placebo.ab. 27.drug therapy.fs. 28.randomly.ab. 29.trial.ab. 30.groups.ab. 31.23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 32.humans.sh. 33.31 AND 32 34.22 AND 33	

Table 1. Search strategy (*Continued*)

Embase (Ovid SP)	1.(statin$ OR lipophilic OR hydrophilic).mp. 2.(lovastatin OR simvastatin OR cervistatin OR atorvastatin OR rosuvastatin OR provastatin OR fluvastatin).mp. 3.Hydroxymethylglutaryl-CoA Reductase Inhibitors/ all subheadings 4.Alzheimer-disease/ all subheadings 5.exp dementia-vascular/ all subheadings 6.creutzfeldt-jakob-syndrome/ all subheadings 7.kluver-bucy-syndrome/ all subheadings 8.lewy-body/ all subheadings 9.pick-presenile-dementia/ all subheadings 10.Huntington-chorea/ all subheadings 11.delirium/ all subheading 12.wernicke-encephalopathy/ all subheadings 13.(dement$ OR Alzheimer$).mp. 14.(lewy$ AND bod$).mp. 15.((cognit$ OR memor$ OR mental) and (decline$ OR impair$ OR los$ OR deteriorate$)).mp. 16.(chronic AND cerebrovascular).mp. 17.((organic brain syndrome) OR (organic brain disease)).mp. 18.((cerebr$ AND deteriorate$) OR (cerebr$ AND insufficien$)).mp. 19.((pick$ and disease) or (creutzfeldt or JCD or CJD) or huntington$ or binswanger$ or korsako$).mp. 20.1 OR 2 OR 3 21.4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 22.20 AND 21 23.randomized controlled trial.pt. 24.controlled clinical trial.pt. 25.randomized.ab. 26.placebo.ab. 27.drug therapy.fs. 28.randomly.ab. 29.trial.ab. 30.groups.ab. 31.23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 32.humans.sh. 33.31 AND 32 34.22 AND 33	
Cinahl (Ovid SP)	1.(statin$ OR lipophilic OR hydrophilic).mp. 2.(lovastatin OR simvastatin OR cervistatin OR atorvastatin OR rosuvastatin OR provastatin OR flu-	

Table 1. Search strategy (*Continued*)

	vastatin).mp. 3.Hydroxymethylglutaryl-CoA Reductase Inhibitors/ all subheadings 4.Alzheimer-disease/ all subheadings 5.exp dementia-vascular/ all subheadings 6.creutzfeldt-jakob-syndrome/ all subheadings 7.kluver-bucy-syndrome/ all subheadings 8.lewy-body-disease/ all subheadings 9.pick-disease-of-the-brain/ all subheadings 10.Huntington-disease/ all subheadings 11.delirium/ all subheading 12.wernicke-encephalopathy/ all subheadings 13.(dement$ OR Alzheimer$).mp. 14.(lewy$ AND bod$).mp. 15.((cognit$ OR memor$ OR mental) and (decline$ OR impair$ OR los$ OR deteriorate$)).mp. 16.(chronic AND cerebrovascular).mp. 17.((organic brain syndrome) OR (organic brain disease)).mp. 18.((cerebr$ AND deteriorate$) OR (cerebr$ AND insufficien$)).mp. 19.((pick$ and disease) or (creutzfeldt or JCD or CJD) or huntington$ or binswanger$ or korsako$).mp. 20.1 OR 2 OR 3 21.4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 22.20 AND 21 23.randomized controlled trial.pt. 24.controlled clinical trial.pt. 25.randomized.ab. 26.placebo.ab. 27.drug therapy.fs. 28.randomly.ab. 29.trial.ab. 30.groups.ab. 31.23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 32.humans.sh. 33.31 AND 32 34.22 AND 33	
PsycINFO (Ovid SP)	1.(statin$ OR lipophilic OR hydrophilic).mp. 2.(lovastatin OR simvastatin OR cervistatin OR atorvastatin OR rosuvastatin OR provastatin OR fluvastatin).mp. 3.Hydroxymethylglutaryl-CoA Reductase Inhibitors/ all subheadings 4.Alzheimer-disease/ all subheadings	

Table 1. Search strategy (*Continued*)

	5.exp dementia-vascular/ all subheadings 6.creutzfeldt-jakob-syndrome/ all subheadings 7.kluver-bucy-syndrome/ all subheadings 8.lewy-body-disease/ all subheadings 9.pick-disease-of-the-brain/ all subheadings 10.Huntington-disease/ all subheadings 11.delirium/ all subheading 12.wernicke-encephalopathy/ all subheadings 13.(dement$ OR Alzheimer$).mp. 14.(lewy$ AND bod$).mp. 15.((cognit$ OR memor$ OR mental) and (decline$ OR impair$ OR los$ OR deteriorate$)).mp. 16.(chronic AND cerebrovascular).mp. 17.((organic brain syndrome) OR (organic brain disease)).mp. 18.((cerebr$ AND deteriorate$) OR (cerebr$ AND insufficien$)).mp. 19.((pick$ and disease) or (creutzfeldt or JCD or CJD) or huntington$ or binswanger$ or korsako$).mp. 20.1 OR 2 OR 3 21.4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 22.20 AND 21 23.randomized controlled trial.pt. 24.controlled clinical trial.pt. 25.randomized.ab. 26.placebo.ab. 27.drug therapy.fs. 28.randomly.ab. 29.trial.ab. 30.groups.ab. 31.23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 32.humans.sh. 33.31 AND 32 34.22 AND 33	
LILACS	(statin* OR lipophilic OR hydrophilic) AND (alzheimer$ OR dementia)	

Data collection and analysis

Selection of studies

The search and screening of publications was undertaken by two authors (BMcG, supported by JOH). The MeSH terms and search strategy were agreed upon and tested by both reviewers. The other authors (PP, DC and RB) acted as adjudicators and reviewed the process. Authors independently selected trials for relevance against the defined inclusion criteria. Those trials that did not fulfil the criteria were excluded from further analysis.

Quality assessment

The methodological quality of the included trials was assessed with particular emphasis on the concealment of treatment allocation. Trials were ranked using the Cochrane approach (Higgins 2008):
Grade A: Adequate concealment
This is where the report describes allocation of treatment by:
(i) some form of centralised randomized scheme, such as having to provide details of an enrolled participant to an office, or by phone to receive the treatment group allocation;
(ii) some form of randomisation scheme controlled by a pharmacy;
(iii) numbered or coded containers, such as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administered sequentially to enrolled participants;
(iv) an on-site or coded computer system, given that the allocations are in a locked, unreadable file that can be accessed only after inputting the characteristics of an enrolled participant; or
(v) if assignment envelopes were used, the report will at least specify that they are sequentially numbered, sealed, opaque envelopes;
(vi) other combinations of described elements of the process that provides assurance of adequate concealment.
Grade B: Uncertain
This is where the report describes allocation of treatment by:
(i) use of a 'list' or 'table' to allocate assignments;
(ii) use of 'envelopes' or 'sealed envelopes';
(iii) stating the study as 'randomized' without further detail.
Grade C: Inadequate concealment
This is where the report describes allocation of treatment by:
(i) alternation;
(ii) reference to case record numbers, dates of birth, day of the week, or any other approach;
(iii) any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers or assignments.
Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but less pronounced than inadequately concealed trials (Chalmers 1983; Schulz 1995). Thus, trials were included if they conformed to category A and those falling into categories B or C were excluded. Other aspects of trial quality were not assessed by a scoring system although details were noted of blinding, whether intention-to treat analyses were extractable from the published data, and the number of patients lost to follow up.

Inclusion criteria

Identified trials with the above quality assessment were included. Any disagreement in the independent selection was resolved with discussion.

Data extraction

Data were extracted from the published reports. The summary statistics required for each trial and each outcome for continuous data are the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation and the number of patients for each treatment group at each time point was extracted. We also extracted available data on demographics of patients (age, gender, diabetes, hypertension, current smoker, prior myocardial infarction/cerebrovascular accident, lipid values at baseline), statin regimen (type of statin, daily dosage, starting time, duration), follow-up duration.
For binary data the numbers in each treatment group and the numbers experiencing the outcome of interest were sought. The baseline assessment is defined as the latest available assessment prior to randomization, but no longer than two months prior. For each outcome measure, data were sought on every patient assessed. To allow an intention-to-treat analysis, the data were sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data were not available in the publications, "on-treatment" or the data of those who completed the trial were sought and indicated as such. Data from titration phases prior to the randomized phase were not used to assess safety or efficacy because patients are usually not randomized, nor are treatments concealed.
Publication bias is a potential problem when carrying out a review. We will investigate whether this review is subject to publication bias by preparing a funnel plot and examining for signs of asymmetry. If asymmetry is present likely reasons will be explored, these can include reasons other than publication bias and these will also be considered: selection biases, poor methodological quality of smaller studies, artefactual and chance. The trim and fill method will be carried out in the event of asymmetry to estimate the impact of possible publication bias.

Data analysis

Analysis: All types of statins (hydrophilic and lipophilic) used in the treatment of dementia.
The outcomes measured in clinical trials of dementia and cognitive impairment often arise from ordinal rating scales. Where the rating scales used in the trials have a reasonably large number of categories (more than 10), the data were treated as continuous outcomes arising from a normal distribution. Summary statistics (n, mean and standard deviation) were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. When change from baseline results was not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measure-

ments at baseline and assessment time was assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable in a meta-analysis.

The meta-analysis requires the combination of data from trials that may not have used the same rating scale to assess an outcome. The measure of the treatment difference for any outcome is the weighted mean difference where the pooled trials use the same rating scale or test, and the standardised mean difference, which is the absolute mean difference divided by the standard deviation, where different rating scales or tests are used. The duration of the trials varied from 24-72 weeks. A separate meta-analysis was conducted for each period. Some trials may contribute data to more than one time period if multiple assessments have been done. For binary outcomes, such as dead or alive, progression of dementia or not, mild or moderate dementia, the odds ratio was used to measure treatment effect. A weighted estimate of the treatment effect across trials was calculated. Overall estimates of the treatment difference are presented. In all cases the overall estimate from a fixed effect model is presented and a test for heterogeneity using a standard chi-square statistic performed. If there was significant heterogeneity a random effects model will be presented. Sensitivity analyses were undertaken to assess the robustness of the results to fixed effect versus random effects models and on the inclusion or exclusion of studies of poor quality. If the treatment effect in the sensitivity analysis were of similar magnitude and precision as that of the main analysis, a definite conclusion about the treatment effectiveness could be made, otherwise no definite conclusion will be made on the effectiveness of the treatment. The impact of heterogeneity on the meta-analysis was also assessed using I^2 as it is considered appropriate for small sample sizes. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

152 references were retrieved by the electronic searches. 5 were considered as potentially eligible after screening.

Included studies

3 randomized placebo-controlled trials were identified with 748 participants - ADCLT 2005, LEADe 2010 and Simons 2002. For full details see Characteristics of included studies. Ages for participation ranged from 50-90 years but mean ages in studies were 68-78 years representing older adults with dementia.

ADCLT 2005 included 63 patients with a diagnosis of probable or possible AD as outlined by NINCDS-ADRDA and DSM-IV criteria; individuals 51 years or older with mild to moderate impairment (MMSE score 12-28) were eligible. All but 6 individuals were taking cholinesterase inhibitors, 3 in the atorvastatin group and 3 in the placebo group. Mean age was 78.9±1.2 years in placebo group and 78.15±1.3 years in atorvastatin group.

LEADe 2010 included 614 patients with a diagnosis of probable AD according to DSM IV and NINCDS-ADRDA criteria and of mild to moderate severity, defined as a MMSE score of 13-25 at screening. Subjects were 53% female age range 50 to 90 years, mean age 74±8 years. Patients were receiving donepezil 10mg for at least 3 months before randomization and LDL-C was 2.5-3.5mmol/l for inclusion.

Simons 2002 was primarily a study investigating whether statins alter cholesterol metabolites and reduce Aβ levels in the CSF of AD patients. Cognition was assessed as a secondary outcome. 44 patients with probable AD as defined by NINCDS-ADRDA criteria and mild to moderate severity (MMSE scores 12-26) were recruited. 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 26-week study period. Mean age was 68.5±8 years in placebo group and 68.0±9 years in simvastatin group.

Participants were recruited primarily from the community.

ADCLT 2005 provided data on change in ADAS-Cog at 3 monthly intervals up to 1 year. Data were also provided on change in total cholesterol level, CGIC score, MMSE score, NPI total score and GPS total score between placebo and atorvastatin groups.

LEADe 2010 provided data on change in ADAS-Cog and ADCS-CGIC scores between atorvastatin and placebo groups. Following randomization these measures were performed at 3-month intervals through month 18. Secondary outcome measures were change in NPI, ADFACS, CDR-SB, MMSE and modified ADAS-Cog. Change in total, LDL and HDL cholesterol and triglycerides was provided.

Simons 2002 provided data on change in MMSE and ADAS-Cog score between simvastatin and placebo groups at 26 weeks.

Treatment in ADCLT 2005 consisted of atorvastatin 80mg daily or matching placebo. 63 individuals were considered evaluable by completing the three month visit, 32 individuals receiving atorvastatin and 31 individuals receiving placebo. 46 individuals completed the 1 year study, 25 receiving atorvastatin and 21 receiving placebo. Reasons for drop-out were not provided. Atorvastatin treatment produced significant decreases in total cholesterol (40%), LDL-C (54%), and VLDL-C (30%) relative to placebo. ApoE genotyping was carried out on study participants. 60% of the placebo group and 62.5% of the atorvastatin group had $\geq$1 E4 allele. Change in performance among subjects with screening

cholesterol levels ≥200mg/dL was compared with performance change in subjects with levels <200mg/dL. Mean change in ADAS-Cog performance at 6 months was established for atorvastatin and placebo treated individuals grouped according to their ApoE genotype. Within and between group comparisons according to presence of apolipoprotein E4 allele were performed, followed by comparisons based on dose of the apolipoprotein E4 allele.

Treatment in LEADe 2010 consisted of 80mg of atorvastatin daily or matching placebo for 72 weeks. 640 patients were randomized with a modified intention to treat population of 297 in the atorvastatin group and 317 in the placebo group. Mean prior donepezil treatment was 409±407 days. Results concerning APOE genotype were available for 511 patients, observed ApoE4 frequency was 60%. Atorvastatin treatment produced significant decreases in total cholesterol, LDL-C (50.2%) and triglycerides but no significant change in HDL-C. Reasons for drop-outs were given.

In Simons 2002 treatment consisted of simvastatin 40mg daily for 4 weeks and 80mg daily for the following 22 weeks. Disease duration was 2.8±1.3 years in the placebo group and 2.6±1.4 years in the simvastatin group. Serum LDL-C showed few changes in the placebo group but was reduced by 52% on average in the simvastatin group. Reasons for drop-outs were given. ApoE genotyping was not carried out.

Total adverse events were reported by LEADe 2010 and Simons 2002.

Excluded studies

Two studies were excluded from the analysis (Gutterman 2002, Winblad 2007). For full details see Characteristics of excluded studies. Gutterman 2002 used data pooled from trials of patients treated with galantamine 24mg/day or placebo for 5 to 6 months in randomized, double-blind placebo controlled trials. This was a post-hoc analysis and so did not fulfil criteria for inclusion nor did it have adequate power to examine the effects of statins. Using last observation carried forward, mean ADAS-Cog change from baseline was measured. Of 1,311 patients 8.8% were taking statins. In the placebo, galantamine, statin and galantamine + statin groups there were 598, 598, 60 and 55 patients respectively. While galantamine use was associated with a significant change in mean ADAS-Cog from baseline (p<0.001), statin use (p=0.195) or the interaction of galantamine with statins (p=0.372) were not. The conclusion was the use of statins did not lead to significant improvement of cognitive function among AD patients either alone or in combination with galantamine.

Winblad 2007 was also a post-hoc analysis conducted on data pooled from three double-blind, placebo-controlled, clinical trials of galantamine in patients with AD. There were 4 treatment groups: statin plus galantamine (n=42), statin alone (n=50), galantamine alone (n=614) and neither galantamine nor statin (n=619). While galantamine was associated with a significant beneficial effect on cognitive status (p<0.001) there was no association seen with use of statins (p=0.083). There was no significant effect on cognition with use of statins and galantamine together (p=0.183).

Studies Awaiting Publication: CLASP 2008 was identified by the search strategy through the search of trial databases as a large randomised controlled trial fulfilling the inclusion criteria. Results from CLASP 2008 have not been published. The study authors were contacted but no response was received. Approximately 405 participants from 45 US sites were recruited. Primary outcomes were change in ADAS-Cog and CGIC. When the results of this study are known we will gain further information regarding statin therapy for the treatment of dementia and the Cochrane review will be updated.

Risk of bias in included studies

For full details see Risk of Bias tables

Allocation

In ADCLT 2005 randomization was performed in blocks of 10 using the Excel spreadsheet random-number generator, this appeared adequate. In LEADe 2010 1:1 randomization was carried out, the medication was assembled for each patient based on a randomization code prepared by Clinical Data Operations of Pfizer Inc.This appeared satisfactory. In Simons 2002 a randomization list was computer generated, two copies were prepared: one was used by the packaging department of the study medication or placebo and the other was kept in a locked location until the study was completed. This appeared satisfactory.

Blinding

In ADCLT 2005 all investigators were blinded to both treatment group and cholesterol profiles after randomization as active treatment was expected to reduce circulating cholesterol levels. Medications were supplied in bulk by the pharmaceutical company and were coded at pharmacy. This appeared adequate.

In LEADe 2010 it is stated in the published article there was 'blinding of both the investigator and the subject' and in conference proceedings 'trial data remained blinded, and the authors, steering committee, and the sponsor had no information relating to study outcomes'. This appeared adequate.

In Simons 2002 adequate blinding appears to have been carried out. 'All personnel directly involved in the conduct of the study remained unaware of the treatment groups until all patients had completed the trial and all data had been retrieved'. Blood results were monitored by a physician not involved in the study, this guaranteed that all investigators were kept blinded.

Incomplete outcome data

In ADCLT 2005 flow of subjects through the year long study was provided, from 63 evaluable subjects 46 attended for final assessment. Reasons for not attending were not given.
In LEADe 2010 incomplete data were addressed.
In Simons 2002 incomplete data were addressed comprehensively.

Selective reporting

There was no evidence of this.

Other potential sources of bias

None identified

Effects of interventions

See: **Summary of findings for the main comparison** Statins Compared to Placebo for the Treatment of Dementia

Primary Outcomes:

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 -0.69,1.05, p=0.68] (Analysis 1.1). There was also considerable heterogeneity when the studies were combined (chi²=6.08, p=0.05, I²=67%). The random effects model, which usually gives more weight to small studies, was therefore used to re-pool the data; the combined results were not significant [mean difference -1.12, 95%CI -3.99, 1.75, p=0.44] (Analysis 1.2). As the Simons 2002 study ran for 26 weeks, data from ADCLT 2005 at 24 weeks and from LEADe 2010 at 26 weeks were combined and again there was no significant difference in ADAS-Cog between the statin and placebo groups [mean difference 0.02, 95% CI -1.05, 1.10] (Analysis 1.3). Change in ADAS-Cog and Modified ADAS-Cog (13-item, 85-point scale) Mohs 1997) from LEADe 2010 has been provided in the tables from the various time points. At no time was a beneficial effect on ADAS-Cog or Modified ADAS-Cog seen with statin treatment.
Change in MMSE was available from the three studies also. When data were combined in a meta-analysis there was a significant but small difference between the statin and placebo groups favouring the statin group [mean difference -0.50, 95% CI -0.92,-0.08, p= 0.02] (Analysis 2.1). There was significant heterogeneity when the studies were combined (chi²=11.66, p<0.01, I²=83%) so again the random effects model was used. There was no significant difference between statins and placebo [mean difference -1.53, 95% CI -3.28, 0.21, p=0.08] (Analysis 2.2). Data were also compared at 24 weeks for ADCLT 2005 and LEADe 2010; there was no significant difference between the statin and placebo groups [mean difference -0.37, 95% CI -0.80, 0.07, p=0.10] (Analysis 2.3). Change in MMSE at different time points has been provided from LEADe 2010; at no time was a beneficial effect from statin therapy seen.
Change in ADCS-CGIC assessing clinical global impression of change was given in two studies: ADCLT 2005 and LEADe 2010. When data from these two trials were combined in a meta-analysis using generic inverse variance there was no significant difference between the statin and placebo groups [mean difference -0.02, 95% CI -0.14,0.10, p=0.74] (Analysis 3.1).

Secondary Outcomes:

Side Effects: These were elicited from blood tests and from speaking to patients and caregivers. LEADe 2010 stated incidence of persistent elevated liver enzymes (3X upper limit of normal on 2 consecutive measures 4 to 10 days apart) in the atorvastatin group was low at 2.6% and 0% in the placebo group. There were 60 (19.1%) atorvastatin-treated and 69 (21.2%) placebo-treated patients who experienced serious adverse events (SAEs), 6 of which in the atorvastatin group and 1 in the placebo group considered treatment related by the investigator or sponsor. The SAEs considered treatment related in the atorvastatin group were hepatitis, acute renal failure/rhabdomyolysis/pancreatitis, abdominal pain/ nausea/chest discomfort, transaminases elevation, liver disorder and gastrointestinal haemorrhage. In Simons 2002 2 patients in the simvastatin group experienced adverse events: 1 patient had muscle pain without elevation of creatine kinase, 1 patient was withdrawn because creatine kinase was elevated. No adverse effects were reported in the placebo group. Data from LEADe 2010 and Simons 2002 were combined and no significant difference between statin and placebo groups was seen (Analysis 6.1).
Change in cognitive status accounting for prior cholesterol, ApoE genotype and cognitive level: Data provided in ADCLT 2005: Among subjects treated with atorvastatin, those who had improved on the ADAS-Cog at 6 months had baseline MMSE scores 2 points higher than those who continued to deteriorate (21.93±0.85 compared to 19.83±1.10, p<0.06). Those who improved on the ADAS-Cog also had higher baseline cholesterol levels than those who deteriorated. [Mean change in ADAS-Cog -2.14±1.20 atorvastatin + cholesterol >200mg/dl; 0.11±0.68 atorvastatin + cholesterol <200mg/dl]. A significant difference was seen in ADAS-Cog performance at 6 months between the atorvastatin and placebo groups in individuals with an apolipoprotein E-4 allele (p=0.012) but not between the groups comprised of subjects without an apolipoprotein E4 allele (p=0.967). NB There were very small numbers in all groups.
Quality of Life: In LEADe 2010 there was no significant difference between the atorvastatin and placebo groups in Caregiver Burden Questionnaire and Patient Health Resources Utilization.
Behaviour: ADCLT 2005 and LEADe 2010 provided data on Neuropsychiatric Inventory Caregiver Distress Scale (NPI) (information obtained from the caregiver). Data from these two studies were combined at 6 months (Analysis 4.1) and 12 months (Analysis 4.2). There was no significant benefit from statins seen [mean difference at 12 months -0.94, 95% CI -2.07,0.19, p=0.10;

mean difference at 6 months -0.72 95% CI -1.61, 0.16]. As there was considerable heterogeneity data at 12 months were analysed using a random effects model, no significant difference between the groups was seen [mean difference -2.07, 95% CI -5.73, 1.59] (Analysis 4.3). ADCLT 2005 provided change in Geriatric Depression Scale (GDS) (information obtained from the patient). Atorvastatin provided significant benefit on the GDS ($p<0.04$); there was deterioration in the placebo group and improvement in the atorvastatin group.

Activities of Daily Living:In ADCLT 2005 differences in performance on the caregiver rated Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) between the treatment and placebo groups did not reach significance ($p>0.23$). In LEADe 2010 there was no benefit from atorvastatin compared to placebo in the ADFACS, a measure of function (Analysis 5.4).

DISCUSSION

Summary of main results

Three studies were identified: Simons 2002, ADCLT 2005 and LEADe 2010. Mean change in ADAS-Cog from baseline was an outcome in the three trials and there was no significant difference between the statin and the placebo groups.

Change in MMSE from baseline was reported in all studies also. There was no significant difference between the statin and placebo groups when the random effects model was used due to heterogeneity.

Clinical Global Impression of Change did not differ between the two groups in the two studies that recorded this measure, ADCLT 2005 and LEADe 2010.

The statins were well tolerated and incidence of side effects was low. The statin group did not have a significantly higher rate of adverse effects requiring discontinuation of treatment when the data were combined.

There was some evidence from ADCLT 2005 that greater cognitive effect from atorvastatin was seen in patients with higher cholesterol at baseline, higher MMSE at baseline and those with an apolipoprotein E4 allele present.

There was no difference in activities of daily living or quality of life between the two treatment groups.There was no convincing evidence that statins provided a benefit in behaviour.

The three trials included patients with AD only. There were no trials identified that assessed effect of statins in the treatment of VaD.

It was not possible to assess if lipophilic statins or hydrophilic statins were more efficacious due to the small number of studies. There was no evidence that statins were detrimental to cognition.

Overall completeness and applicability of evidence

The LEADe 2010 study was the largest with 640 patients in total so results from this are likely to be more robust. Cognition was a primary outcome (ADAS-Cog) along with global function (ADCS-CGIC). Secondary outcomes included NPI, modified ADAS-Cog, MMSE, CDR-SB and ADFACS. Exploratory measures included a Caregiver Questionnaire and a Patient Health Resources Utilization questionnaire.

In Simons 2002 the primary outcome was effect of statins on cholesterol metabolites and Aβ levels in the CSF of 44 patients with AD. Cognitive performance was a secondary outcome and was assessed at the beginning and end of the 26 week study. Only 37 patients completed the study so the impact of this study is likely to be small.

In ADCLT 2005 primary outcomes were change in cognitive function (ADAS-Cog) and clinical efficacy (CGIC). Secondary outcomes were change in MMSE, NPI, ADCS-ADL and GDS so results were applicable. The study was small also however with data available from 63 subjects in total.

Quality of the evidence

All studies had adequate sequence generation and blinding. In ADCLT 2005 there was unclear allocation concealment and drop out data.

Potential biases in the review process

Results from CLASP 2008 have not been published yet. The study authors were contacted but no response was received.

Agreements and disagreements with other studies or reviews

A previous systematic review assessed prevention and treatment of dementia or AD by statins Zhou 2007. This was published before the LEADe 2010 results were available. Two studies were identified Simons 2002 and ADCLT 2005 as identified in this review and there was no statistically significant difference in ADAS-Cog between the statin and placebo groups when the trials were pooled. This is in agreement with this review.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend statins for the treatment of Alzheimer's disease or dementia. In LEADe 2010, the

first large scale RCT evaluating statins as a treatment for mild to moderate AD, the regimen of atorvastatin plus donepezil was not associated with significant benefit on clinical outcome measures over 72 weeks. When data from this trial were pooled with two smaller scale studies (Simons 2002 and ADCLT 2005) there was no benefit from statins seen with the primary outcome measure ADAS-Cog or in MMSE.

From ADCLT 2005 there was some evidence that atorvastatin treatment was more beneficial at six months in AD patients with higher MMSE at baseline, those with an apolipoprotein E4 allele and higher cholesterol levels at baseline. This would need to be confirmed in larger scale studies.

Implications for research

We await full results of the CLASP 2008 study. As this is a further large scale RCT it will provide further evidence as to whether statins are beneficial in the treatment of AD and dementia. Results from LEADe 2010 suggest statins have no clinical benefit in treatment of AD over 72 weeks so it would not be advisable to embark upon further large scale RCTs until full results are known. At this stage this Cochrane review will be updated to allow inclusion of results from CLASP 2008.

If considering additional studies it would be beneficial to further assess impact of treatment at an earlier stage of the disease process, effect of Apolipoprotein E4 allele and effect of baseline cholesterol level as results from ADCLT 2005 suggest these factors may have an impact on efficacy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADCLT 2005

Methods	Randomized controlled trial
Participants	63 participants (32 intervention, 31 control) with probable or possible AD (NINCDS/ADRDA and DSM-IV guidelines), 9th grade education or equivalent, speak English fluently and of good general health as evidenced by physical, neurological and clinical laboratory examination. Age≥51 years, mean 78.9±1.2 years in placebo group, 78.15±1.3 years in atorvastatin group. MMSE 12-28, score≤4 on the modified Hachinski scale and ≤20 on the Geriatric Depression Scale (GDS). Individuals were allowed to continue stable dose use of cholinesterase inhibitor and medications treating non-excluded medical conditions. Patients recruited from a single site in USA. Duration of study:1 year Mean total cholesterol at entry was 208.00±6.41 mg/dL [5.39±0.17mmol/l] in the placebo group and 207.97±5.98 mg/dL [5.39±0.15mmol/l] in the atorvastatin group, mean LDL cholesterol 122.22±6.19 mg/dL[3.16±0.16mmol/l] and 124.47±5.92 mg/dL[3.22±0.15mmol/l], mean VLDL cholesterol 26.65±2.26 mg/dL and 27.84±2.13 mg/dL in the placebo and atorvastatin groups respectively.(To convert total cholesterol to mmol/l, multiply by 0.0259; LDL cholesterol to mmol/l, multiply by 0.02586).
Interventions	Intervention: Atorvastatin 80mg daily Control: Matching placebo
Outcomes	Primary outcomes: change in ADAS-Cog and Clinical Global Impression of Change scale (CGIC) Secondary outcomes: change in MMSE, Neuropsychiatric Inventory Caregiver Distress Scale (NPI), GDS, Alzheimer's Disease Cooperative Study-Activities of Daily LIving Inventory (ADCS-ADL)
Notes	Subjects were excluded with a neurological or psychiatric disease other than AD, including suspected Parkinson's disease or dementia with Lewy bodies, significant systemic illness, organ failure, myocardial infarction, cardiac or thromboembolic vascular disease, major depression according to DSM-IV criteria, current anticholinergic use. Individuals with a history of head injury, significant liver disease and/or elevated transaminase levels, allergy to statin medication or screen cholesterol levels below 2.3mmol/l were also excluded. No study subject was using memantine or allowed to initiate cholinesterase inhibitor use after trial entrance and continue participation.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was performed in blocks of 10 (5 active medication and 5 placebo) using an Excel spreadsheet random number generator. The sequence was inspected to ensure there was no duplication of random sequences

ADCLT 2005 (*Continued*)

		and that there were 5 individuals assigned to each treatment group. Comment: Probably done
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	All investigators were blinded to both treatment groups and cholesterol profiles after randomization. Only the physician safety monitor, who was not involved in any other aspect of the trial, viewed quarterly cholesterol levels to ensure patient safety. Bottles of study medication were coded at pharmacy. Comment: probably done
Incomplete outcome data addressed? All outcomes	Unclear	Flow table provided detailing flow of subjects through the study. 29 active treatment and 27 placebo patients evaluated at visit 2, 26 active treatment and 22 placebo evaluated at visit 3 and 25 active treatment and 21 placebo patients evaluated at visit 4. Reasons for drop-out not given.

LEADe 2010

Methods	Randomized, multicentre, parallel-group, placebo-controlled, double blind study with a double-blind randomized withdrawal phase.
Participants	640 patients with a diagnosis of probable AD (DSM IV and NINCDS-ADRDA criteria) and of mild to moderate severity (MMSE 13-25 at screening). Age 50-90 years, mean 74±8 years. A CT or MRI brain scan consistent with the diagnosis of probable AD and without other significant comorbid abnormalities was required within the previous 12 months. Subjects with diabetes mellitus who had stable blood sugars with diet or treatment with antidiabetic agents were permitted to enter the study if they had haemoglobin A1c levels of <10% and fasting serum glucose levels of <9.4 mmol/l and LDL-C values between 2.5mmol/l and 3.5 mmol/l. At entry all other subjects had to have LDL-C levels of 2.5 to 5.0mmol/l and must not have required treatment for dyslipidaemia with any lipid-lowering drug in the opinion of the investigator. Duration of study: 72 weeks trial period followed by 8 week atorvastatin withdrawal phase. Mean total cholesterol at study entry was 5.8±0.8 mmol/l in the groups combined, mean LDL-C was 3.7±0.7 mmol/l, mean HDL-C 1.6±0.5 mmol/l, mean VLDL-C 0.47±0.38 mmol/l and mean triglycerides 1.5±0.7 mmol/l. 53% women, 47% men. Patients recruited from Australia, Austria, Canada, Denmark, Germany, South Africa, Spain, Sweden, UK and USA. 96% white.
Interventions	Patients already receiving donepezil 10mg for at least 3 months before screening. Intervention group: Atorvastatin 80mg daily Control group: Matching placebo

Outcomes	Primary: Change in ADAS-Cog and ADCS-CGIC Secondary: Change in behaviour (NPI), general cognitive status (MMSE), overall dementia severity (Clinical Dementia Rating-Sum of Boxes [CDR-SB], activities of daily living (measured by AD Functional Assessment and Change Scale [ADFACS]. Additional analyses on effect of statin on cholesterol/lipid components (apolipoprotein B [apoB], apo E, serum total cholesterol, serum LDL-C, serum very low-density lipoprotein cholesterol [VLDL-C], triglycerides, and HDL-C Caregiver burden and Patient Healthcare Resource Ulitilation Questionnaire Rate of change in MRI whole brain and hippocampal volumes
Notes	Subjects were excluded if they were taking any medications that affect lipid metabolism or cholinesterase activity other than donepezil within 3 months of screening, or if they had known hypersensitivity to HMG-CoA reductase inhibitors. Subjects were also excluded if they were also experiencing any clinically significant or unstable medical condition including dermatologic, haematologic, pulmonary, cardiovascular, renal, hepatic, gastrointestinal, genitourinary, endocrine, or neurologic disease (other than AD). Subjects were discouraged from taking any putative cognitive enhancer e.g. gingko biloba, high dose vitamin E, nonsteroidal anti-inflammatory drugs), but in subjects who were taking them, the dose must have been stable 3 months before randomization and throughout the study. Subjects with medical conditions that could impact the bioavailability or metabolism of the study medication or affect the results of the study and those with a current primary psychiatric other than AD, and who within the previous 5 years met DSM IV criteria for drug or alcohol abuse were also excluded from the study.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	1:1 randomization carried out. Comment: probably done
Allocation concealment?	Yes	The medication was assembled for each patient based on a randomization code prepared by Clinical Data Operations of Pfizer Inc. Comment: probably done
Blinding? All outcomes	Yes	Blinding of investigator and subject stated. Comment: probably done
Incomplete outcome data addressed? All outcomes	Yes	Trial profile illustrated in a figure with reasons for not completing trial. 1088 selected for screening, 368 excluded-319 did not meet entry criteria, 21 no longer willing to participate, 19 other, 8 adverse event, 1 protocol violation. 640 underwent randomization: 326 assigned to placebo, 325 treated, 245 com-

		pleted (75.2%) 80 discontinued (24.5%). 314 assigned to atorvastatin, 314 treated, 207 completed (65.9%), 107 discontinued (34.1%). 317 on placebo analysed for efficacy by modified intention to treat, 325 analysed for safety. 297 on atorvastatin analyzed for efficacy by modified intention to treat, 314 analyzed for safety.

Simons 2002

Methods	Randomized, placebo-controlled double-blind trial
Participants	Patients eligible if they fulfilled a diagnosis of probable AD according to NINCDS-ADRDA criteria. MMSE score 12-26, then patients subgrouped into mild (MMSE 21-26) and moderate (MMSE 12-20) AD. Age 68.5±8 years in placebo group, 68.0±9 years in simvastatin group. All patients had a CT to rule out vascular encephalopathy as a cause of dementia. Patients were allowed to take donepezil or rivastigmine if the dose had been unchanged for the last 3 months before study entry and remained stable during the 26 week study period. 44 patients randomized. 47/53% F:M in placebo group; 63/37% F:M in intervention group. Duration of study: 26 weeks Patients recruited from Germany. Mean serum LDL cholesterol was 134±32 mg/dL in the placebo group and 137±42 mg/dL in the simvastatin group.
Interventions	Intervention: Up to 80mg simvastatin daily Control: Matching placebo
Outcomes	Those analysed in review: Change in MMSE and ADAS-Cog score Those not analysed in review: CSF Aβ40, Aβ42, lathosterol, cholesterol, 24S-hydroxycholesterol
Notes	Subjects were excluded if they had a Hachinski score above 3 and a continuous intake of anti-inflammatory drugs.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A randomization list was computer generated. Comment: probably done
Allocation concealment?	Yes	Two copies of the randomization list were prepared: one was used by the packaging department of the study medication or

Simons 2002 (*Continued*)

		placebo, the other was kept in a locked location until the study was completed. Comment: probably done
Blinding? All outcomes	Yes	All personnel directly involved in the conduct of the study remained unaware of the treatment groups until all patients had completed the trial and all data had been retrieved. Serum concentrations of total cholesterol, LDL-C, creatinine, creatine kinase, electrolytes, and liver transaminases were controlled monthly by a physician who was otherwise not involved in the study. Comment: probably done
Incomplete outcome data addressed? All outcomes	Yes	Trial profile illustrated in a figure with reasons for not completing trial. 3 withdrew consent from placebo group and 17 completed treatment. 1 withdrew consent from simvastatin group, 1 was deemed noncompliant because serum LDL-C level decreased to less than 10%, 1 withdrew due to muscle pain without elevation of creatine kinase, 1 patient was withdrawn as creatine kinase was elevated and 20 completed treatment.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gutterman 2002	Post-hoc analysis from randomized placebo-controlled clinical trials of galantamine in patients with AD. Not sufficiently powered.
Winblad 2007	Post-hoc analysis from randomized placebo-controlled clinical trials of galantamine in patients with AD. Not sufficiently powered.

Characteristics of studies awaiting assessment *[ordered by study ID]*

CLASP 2008

Methods	Multicenter, randomized, double-blind, placebo-controlled trial
Participants	406 participants randomized with mild to moderate probable AD.Lipid levels were required to be normal by NCEP guidelines 41% male. Study duration 18 months
Interventions	Simvastatin 20mg/day for 6 weeks, then 40 mg /day Control: matching placebo
Outcomes	Primary: Change in ADAS-Cog Secondary: ADCS-CGIC Other outcomes: MMSE, ADCS-ADL, Dependence Scale, NPI, Resource Use Inventory, and Quality of Life
Notes	Results not yet published

DATA AND ANALYSES

Comparison 1. Cognitive Change From Baseline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in ADAS-Cog from baseline	3	704	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.69, 1.05]
2 Change in ADAS-Cog from baseline (using random effect)	3	704	Mean Difference (IV, Random, 95% CI)	-1.12 [-3.99, 1.75]
3 Change in ADAS-Cog, 24-26 week data	3	661	Mean Difference (IV, Fixed, 95% CI)	0.02 [-1.05, 1.10]
4 Modified ADAS-Cog	1		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 Modified ADAS-Cog change from baseline at 3 months	1	612	Mean Difference (Fixed, 95% CI)	-0.15 [-0.99, 0.68]
4.2 Modified ADAS-Cog change from baseline at 6 months	1	571	Mean Difference (Fixed, 95% CI)	-0.23 [-1.27, 0.81]
4.3 Modified ADAS-Cog change from baseline at 9 months	1	533	Mean Difference (Fixed, 95% CI)	-0.66 [-1.73, 0.41]
4.4 Modified ADAS-Cog change from baseline at 12 months	1	514	Mean Difference (Fixed, 95% CI)	-0.41 [-1.76, 0.95]
4.5 Modified ADAS-Cog change from baseline at 18 months	1	437	Mean Difference (Fixed, 95% CI)	-0.76 [-2.40, 0.89]
4.6 Modified ADAS-Cog overall (0-18) months	1	614	Mean Difference (Fixed, 95% CI)	0.41 [-0.62, 1.44]
4.7 Modified ADAS-Cog (LOCF)	1	614	Mean Difference (Fixed, 95% CI)	-1.04 [-2.44, 0.37]
5 ADAS-Cog change from baseline over 18 months	1		Mean Difference (Fixed, 95% CI)	Subtotals only
5.1 ADAS Cog change from baseline at 3 months	1		Mean Difference (Fixed, 95% CI)	-0.18 [-0.92, 0.55]
5.2 ADAS-Cog Change from baseline at 6 months	1		Mean Difference (Fixed, 95% CI)	-0.42 [-1.34, 0.49]
5.3 ADAS-Cog Change from baseline at 9 months	1		Mean Difference (Fixed, 95% CI)	-0.89 [-1.83, 0.05]
5.4 ADAS-Cog Change from baseline at 12 months	1		Mean Difference (Fixed, 95% CI)	-0.51 [-1.71, 0.69]
5.5 ADAS-Cog Change from baseline at 15 months	1		Mean Difference (Fixed, 95% CI)	-0.35 [-1.64, 0.95]
5.6 ADAS-Cog Change from baseline at 18 months	1		Mean Difference (Fixed, 95% CI)	-0.84 [-2.33, 0.65]
6 ADAS-Cog Change from baseline (0 to 18) months	1	614	Mean Difference (Fixed, 95% CI)	-0.53 [-1.45, 0.38]

7 ADAS-Cog Change from baseline (0 to 18) months LOCF	1		Mean Difference (Fixed, 95% CI)	-1.11 [-2.37, 0.14]

Comparison 2. Change in MMSE from Baseline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in MMSE, 52 week data ADCLT	3	721	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.92, -0.08]
2 Change in MMSE 52 week data ADCLT (using random effects)	3	721	Mean Difference (IV, Random, 95% CI)	-1.53 [-3.28, 0.21]
3 Change in MMSE, 24 week data ADCLT and LEADe	3	678	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.80, 0.07]
4 MMSE change from baseline in LEADe	1		(Fixed, 95% CI)	1.29 [1.07, 1.56]
4.1 MMSE change from baseline at 3 months	1		(Fixed, 95% CI)	1.19 [0.78, 1.81]
4.2 MMSE change from baseline at 6 months	1		(Fixed, 95% CI)	1.18 [0.74, 1.87]
4.3 MMSE change from baseline at 9 months	1		(Fixed, 95% CI)	1.14 [0.68, 1.93]
4.4 MMSE change from baseline at 12 months	1		(Fixed, 95% CI)	1.48 [0.81, 2.69]
4.5 MMSE change from baseline at 15 months	1		(Fixed, 95% CI)	1.03 [0.54, 1.95]
4.6 MMSE change from baseline at 18 months	1		(Fixed, 95% CI)	1.69 [0.85, 3.35]
4.7 MMSE overall (0-18) months	1		(Fixed, 95% CI)	1.26 [0.80, 2.00]
4.8 MMSE LOCF	1		(Fixed, 95% CI)	1.97 [1.06, 3.65]

Comparison 3. Change in CGIC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in CGIC	2	660	Mean Difference (Fixed, 95% CI)	-0.02 [-0.14, 0.10]
2 CGIC at 3 months	1	603	Mean Difference (Fixed, 95% CI)	0.01 [-0.10, 0.12]
3 CGIC at 6 months	1	564	Mean Difference (Fixed, 95% CI)	0.03 [-0.11, 0.18]
4 CGIC at 9 months	1	527	Mean Difference (Fixed, 95% CI)	-0.02 [-0.18, 0.14]
5 CGIC at 12 months	1	505	Mean Difference (Fixed, 95% CI)	-0.03 [-0.20, 0.13]
6 CGIC at 15 months	1	486	Mean Difference (Fixed, 95% CI)	0.02 [-0.16, 0.20]
7 CGIC at 18 months	1	435	Mean Difference (Fixed, 95% CI)	0.12 [-0.07, 0.31]

8 CGIC LOCF	1	614	Mean Difference (Fixed, 95% CI)	0.16 [-0.01, 0.33]

Comparison 4. NPI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NPI change from baseline to 6 months	2	633	Mean Difference (IV, Fixed, 95% CI)	-0.72 [-1.61, 0.16]
2 NPI change from baseline to 1 year	2	577	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-2.07, 0.19]
3 NPI change from baseline to 1 year (using random effects)	2	577	Mean Difference (IV, Random, 95% CI)	-2.07 [-5.73, 1.59]
4 NPI change from baseline over 18 months	1		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 NPI change from baseline at 3 months	1		Mean Difference (Fixed, 95% CI)	-0.18 [-0.92, 0.55]
4.2 NPI change from baseline at 6 months	1		Mean Difference (Fixed, 95% CI)	-0.42 [-1.34, 0.49]
4.3 NPI change from baseline at 9 months	1		Mean Difference (Fixed, 95% CI)	-0.89 [-1.83, 0.05]
4.4 NPI change from baseline at 12 months	1		Mean Difference (Fixed, 95% CI)	-0.51 [-1.71, 0.69]
4.5 NPI change from baseline at 15 months	1		Mean Difference (Fixed, 95% CI)	-0.35 [-1.64, 0.95]
4.6 NPI change from baseline at 18 months	1		Mean Difference (Fixed, 95% CI)	-0.84 [-2.33, 0.65]
4.7 NPI overall (0-18) months	1		Mean Difference (Fixed, 95% CI)	-0.53 [-1.45, 0.38]
4.8 NPI changes from baseline to 18 months (LOCF)	1		Mean Difference (Fixed, 95% CI)	-1.11 [-2.37, 0.14]

Comparison 5. ADFACS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADFACS change from baseline at 6 months	1	596	Mean Difference (Fixed, 95% CI)	0.45 [-0.36, 1.26]
2 ADFACS change from baseline at 12 months	1	512	Mean Difference (Fixed, 95% CI)	0.4 [-0.74, 1.54]
3 ADFACS change from baseline at 18 months	1	470	Mean Difference (Fixed, 95% CI)	0.45 [-0.99, 1.89]
4 ADFACS over all (0-18) months	1	614	Mean Difference (Fixed, 95% CI)	0.43 [-0.55, 1.42]
5 ADFACS LOCF	1	614	Mean Difference (Fixed, 95% CI)	0.04 [-1.24, 1.32]

Comparison 6. Incidence of adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment related adverse effects requiring discontinuation of treatment	2	683	Odds Ratio (M-H, Fixed, 95% CI)	2.45 [0.69, 8.62]

Analysis 1.1. Comparison 1 Cognitive Change From Baseline, Outcome 1 Change in ADAS-Cog from baseline.

Review: Statins for the treatment of dementia

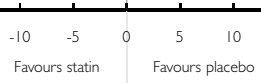
Comparison: 1 Cognitive Change From Baseline

Outcome: 1 Change in ADAS-Cog from baseline

Study or subgroup	Placebo N	Mean(SD)	Statin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	21	-3.7 (6.7)	25	0.5 (5.9)		5.6 %	-4.20 [-7.88, -0.52]
LEADe 2010	317	3.3 (5.7)	297	2.8 (5.9)		89.7 %	0.50 [-0.42, 1.42]
Simons 2002	20	3.4 (7)	24	4.1 (6.5)		4.7 %	-0.70 [-4.72, 3.32]
Total (95% CI)	**358**		**346**			**100.0 %**	**0.18 [-0.69, 1.05]**

Heterogeneity: Chi^2 = 6.08, df = 2 (P = 0.05); I^2 =67%

Test for overall effect: Z = 0.41 (P = 0.68)



Analysis 1.2. Comparison 1 Cognitive Change From Baseline, Outcome 2 Change in ADAS-Cog from baseline (using random effect).

Review: Statins for the treatment of dementia

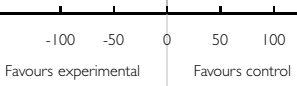
Comparison: 1 Cognitive Change From Baseline

Outcome: 2 Change in ADAS-Cog from baseline (using random effect)

Study or subgroup	Placebo N	Mean(SD)	Statin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
ADCLT 2005	21	-3.7 (6.7)	25	0.5 (5.9)		28.2 %	-4.20 [-7.88, -0.52]
LEADe 2010	317	3.3 (10)	297	2.77 (9)		46.0 %	0.53 [-0.97, 2.03]
Simons 2002	20	3.4 (7)	24	4.1 (6.5)		25.9 %	-0.70 [-4.72, 3.32]
Total (95% CI)	**358**		**346**			**100.0 %**	**-1.12 [-3.99, 1.75]**

Heterogeneity: $Tau^2 = 4.08$; $Chi^2 = 5.50$, df = 2 (P = 0.06); $I^2 = 64\%$

Test for overall effect: Z = 0.77 (P = 0.44)



Analysis 1.3. Comparison 1 Cognitive Change From Baseline, Outcome 3 Change in ADAS-Cog, 24-26 week data.

Review: Statins for the treatment of dementia

Comparison: 1 Cognitive Change From Baseline

Outcome: 3 Change in ADAS-Cog, 24-26 week data

Study or subgroup	Placebo N	Mean(SD)	Statin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	21	-2.2 (7.5)	25	1.8 (5.9)		7.3 %	-4.00 [-7.95, -0.05]
LEADe 2010	308	0.79 (8.5)	263	0.36 (5.5)		85.6 %	0.43 [-0.73, 1.59]
Simons 2002	20	3.4 (7)	24	4.1 (6.5)		7.1 %	-0.70 [-4.72, 3.32]
Total (95% CI)	**349**		**312**			**100.0 %**	**0.02 [-1.05, 1.10]**

Heterogeneity: $Chi^2 = 4.57$, df = 2 (P = 0.10); $I^2 = 56\%$

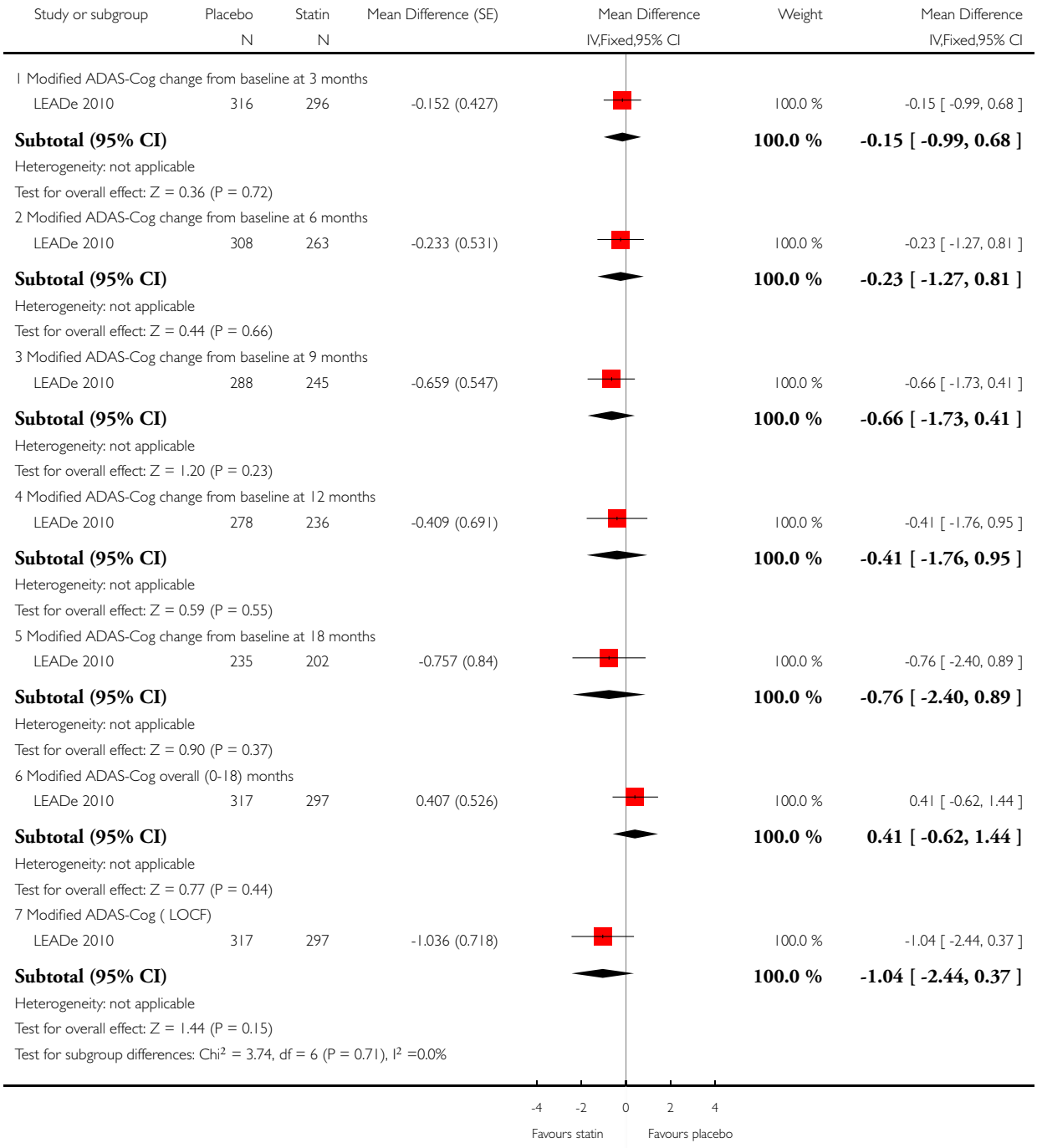
Test for overall effect: Z = 0.04 (P = 0.96)

Analysis 1.4. Comparison 1 Cognitive Change From Baseline, Outcome 4 Modified ADAS-Cog.

Review: Statins for the treatment of dementia

Comparison: 1 Cognitive Change From Baseline

Outcome: 4 Modified ADAS-Cog

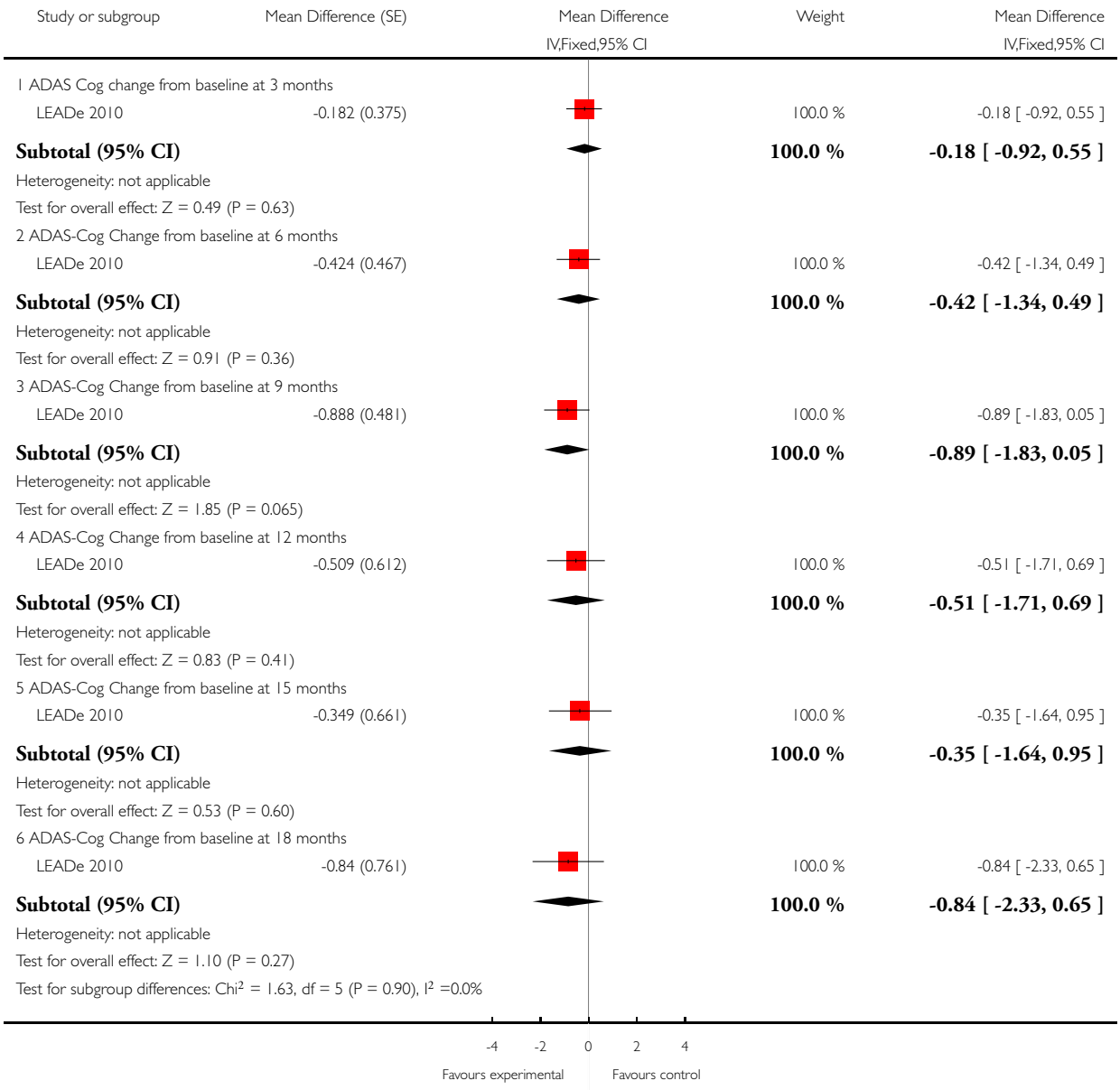


Analysis 1.5. Comparison 1 Cognitive Change From Baseline, Outcome 5 ADAS-Cog change from baseline over 18 months.

Review: Statins for the treatment of dementia

Comparison: 1 Cognitive Change From Baseline

Outcome: 5 ADAS-Cog change from baseline over 18 months



Analysis 1.6. Comparison 1 Cognitive Change From Baseline, Outcome 6 ADAS-Cog Change from baseline (0 to 18) months.

Review: Statins for the treatment of dementia

Comparison: 1 Cognitive Change From Baseline

Outcome: 6 ADAS-Cog Change from baseline (0 to 18) months

Study or subgroup	Placebo N	Statin N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	317	297	-0.532 (0.467)		100.0 %	-0.53 [-1.45, 0.38]
Total (95% CI)					**100.0 %**	**-0.53 [-1.45, 0.38]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						

Analysis 1.7. Comparison 1 Cognitive Change From Baseline, Outcome 7 ADAS-Cog Change from baseline (0 to 18) months LOCF.

Review: Statins for the treatment of dementia

Comparison: 1 Cognitive Change From Baseline

Outcome: 7 ADAS-Cog Change from baseline (0 to 18) months LOCF

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	-1.112 (0.64)		100.0 %	-1.11 [-2.37, 0.14]
Total (95% CI)			**100.0 %**	**-1.11 [-2.37, 0.14]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.74 (P = 0.082)				

Analysis 2.1. Comparison 2 Change in MMSE from Baseline, Outcome 1 Change in MMSE, 52 week data ADCLT.

Review: Statins for the treatment of dementia

Comparison: 2 Change in MMSE from Baseline

Outcome: 1 Change in MMSE, 52 week data ADCLT

Study or subgroup	Placebo N	Mean(SD)	Statin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	31	-2.42 (3.2)	32	-0.77 (2.7)		8.3 %	-1.65 [-3.11, -0.19]
LEADe 2010	317	-1.11 (2.8)	297	-0.87 (2.9)		87.0 %	-0.24 [-0.69, 0.21]
Simons 2002	20	-2.7 (3.4)	24	0.6 (3.1)		4.7 %	-3.30 [-5.24, -1.36]
Total (95% CI)	**368**		**353**			**100.0 %**	**-0.50 [-0.92, -0.08]**

Heterogeneity: Chi² = 11.66, df = 2 (P = 0.003); I² =83%

Test for overall effect: Z = 2.33 (P = 0.020)

Analysis 2.2. Comparison 2 Change in MMSE from Baseline, Outcome 2 Change in MMSE 52 week data ADCLT (using random effects).

Review: Statins for the treatment of dementia

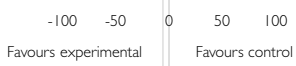
Comparison: 2 Change in MMSE from Baseline

Outcome: 2 Change in MMSE 52 week data ADCLT (using random effects)

Study or subgroup	Placebo N	Mean(SD)	Statin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
ADCLT 2005	31	-2.42 (3.2)	32	-0.77 (2.7)		32.1 %	-1.65 [-3.11, -0.19]
LEADe 2010	317	-1.11 (2.8)	297	-0.87 (2.9)		40.4 %	-0.24 [-0.69, 0.21]
Simons 2002	20	-2.7 (3.4)	24	0.6 (3.1)		27.5 %	-3.30 [-5.24, -1.36]
Total (95% CI)	**368**		**353**			**100.0 %**	**-1.53 [-3.28, 0.21]**

Heterogeneity: Tau² = 1.91; Chi² = 11.66, df = 2 (P = 0.003); I² =83%

Test for overall effect: Z = 1.72 (P = 0.085)



Analysis 2.3. Comparison 2 Change in MMSE from Baseline, Outcome 3 Change in MMSE, 24 week data ADCLT and LEADe.

Review: Statins for the treatment of dementia

Comparison: 2 Change in MMSE from Baseline

Outcome: 3 Change in MMSE, 24 week data ADCLT and LEADe

Study or subgroup	Placebo N	Mean(SD)	Statin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	31	-1.18 (2.99)	32	0.11 (2.7)		9.4 %	-1.29 [-2.70, 0.12]
LEADe 2010	308	-0.449 (2.85)	263	-0.285 (2.81)		85.7 %	-0.16 [-0.63, 0.30]
Simons 2002	20	-2.7 (3.39)	24	-0.6 (3.1)		5.0 %	-2.10 [-4.04, -0.16]
Total (95% CI)	**359**		**319**			**100.0 %**	**-0.37 [-0.80, 0.07]**

Heterogeneity: Chi^2 = 5.46, df = 2 (P = 0.07); I^2 =63%

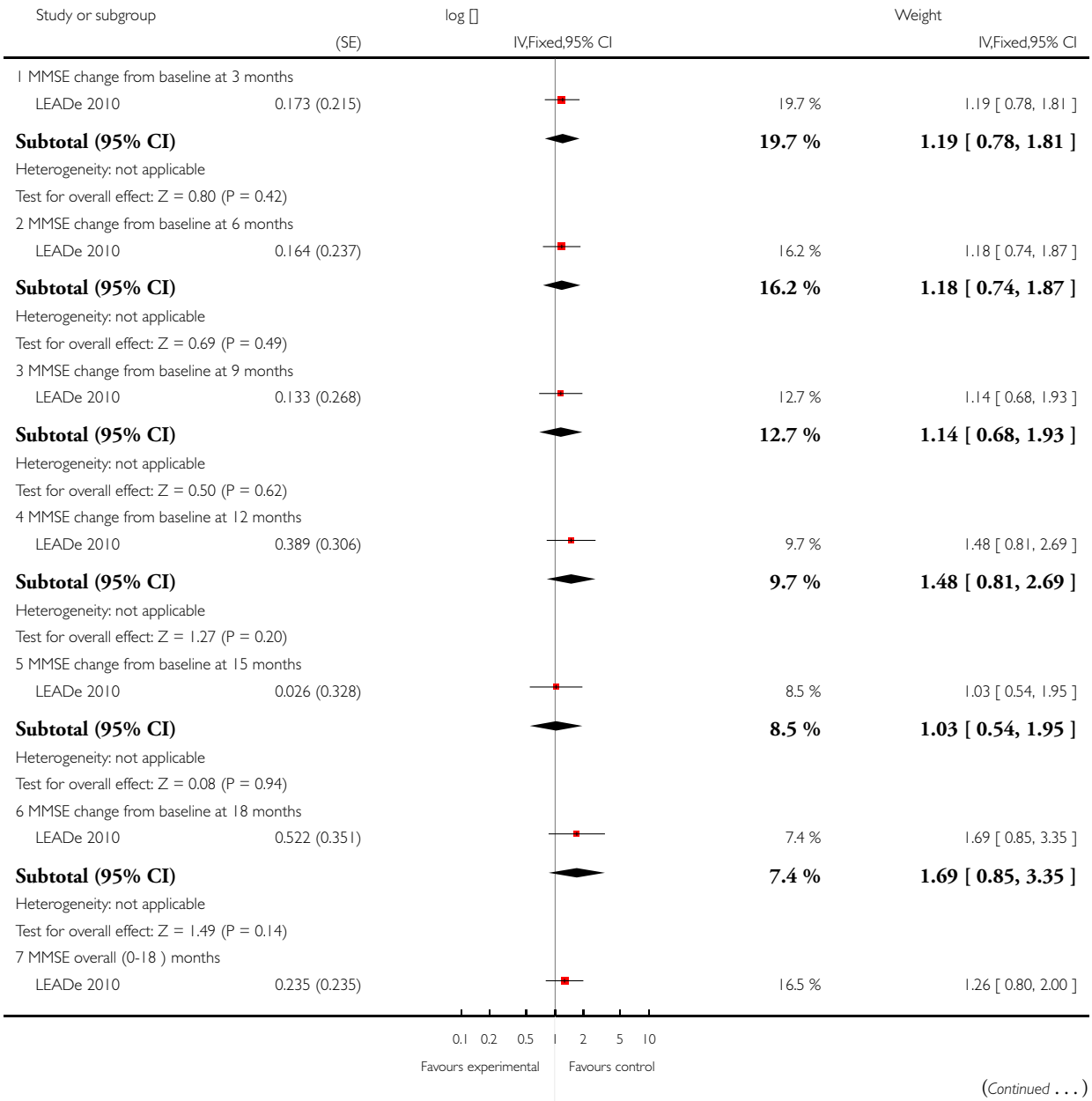
Test for overall effect: Z = 1.66 (P = 0.097)

Analysis 2.4. Comparison 2 Change in MMSE from Baseline, Outcome 4 MMSE change from baseline in LEADe.

Review: Statins for the treatment of dementia

Comparison: 2 Change in MMSE from Baseline

Outcome: 4 MMSE change from baseline in LEADe



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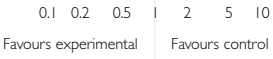
Study or subgroup	log [] (SE)	IV,Fixed,95% CI	Weight	IV,Fixed,95% CI
Subtotal (95% CI)			**16.5 %**	**1.26 [0.80, 2.00]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
8 MMSE LOCF				
LEADe 2010	0.677 (0.315)		9.2 %	1.97 [1.06, 3.65]
Subtotal (95% CI)			**9.2 %**	**1.97 [1.06, 3.65]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.15 (P = 0.032)				
Total (95% CI)			**100.0 %**	**1.29 [1.07, 1.56]**
Heterogeneity: Chi^2 = 3.56, df = 7 (P = 0.83); I^2 =0.0%				
Test for overall effect: Z = 2.70 (P = 0.0070)				
Test for subgroup differences: Chi^2 = 3.56, df = 7 (P = 0.83), I^2 =0.0%				



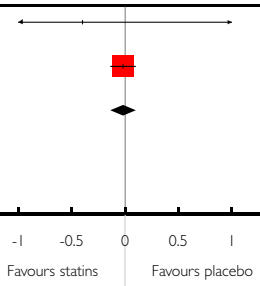
Analysis 3.1. Comparison 3 Change in CGIC, Outcome 1 Change in CGIC.

Review: Statins for the treatment of dementia

Comparison: 3 Change in CGIC

Outcome: 1 Change in CGIC

Study or subgroup	Placebo N	Experimental N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	21	25	-0.4 (1.81)		0.1 %	-0.40 [-3.95, 3.15]
LEADe 2010	317	297	-0.02 (0.061)		99.9 %	-0.02 [-0.14, 0.10]
Total (95% CI)					**100.0 %**	**-0.02 [-0.14, 0.10]**
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.83); I^2 =0.0%						
Test for overall effect: Z = 0.34 (P = 0.74)						



Analysis 3.2. Comparison 3 Change in CGIC, Outcome 2 CGIC at 3 months.

Review: Statins for the treatment of dementia

Comparison: 3 Change in CGIC

Outcome: 2 CGIC at 3 months

Study or subgroup	Placebo N	Statin N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	310	293	0.01 (0.058)		100.0 %	0.01 [-0.10, 0.12]
Total (95% CI)					**100.0 %**	**0.01 [-0.10, 0.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.17 (P = 0.86)

Analysis 3.3. Comparison 3 Change in CGIC, Outcome 3 CGIC at 6 months.

Review: Statins for the treatment of dementia

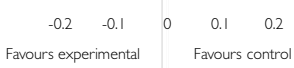
Comparison: 3 Change in CGIC

Outcome: 3 CGIC at 6 months

Study or subgroup	Placebo N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	306	258	0.032 (0.073)		100.0 %	0.03 [-0.11, 0.18]
Total (95% CI)					**100.0 %**	**0.03 [-0.11, 0.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)



Analysis 3.4. Comparison 3 Change in CGIC, Outcome 4 CGIC at 9 months.

Review: Statins for the treatment of dementia

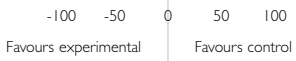
Comparison: 3 Change in CGIC

Outcome: 4 CGIC at 9 months

Study or subgroup	Placebo N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	283	244	-0.021 (0.081)		100.0 %	-0.02 [-0.18, 0.14]
Total (95% CI)					**100.0 %**	**-0.02 [-0.18, 0.14]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.26 (P = 0.80)



Analysis 3.5. Comparison 3 Change in CGIC, Outcome 5 CGIC at 12 months.

Review: Statins for the treatment of dementia

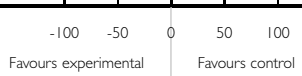
Comparison: 3 Change in CGIC

Outcome: 5 CGIC at 12 months

Study or subgroup	Placebo N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	272	233	-0.034 (0.083)		100.0 %	-0.03 [-0.20, 0.13]
Total (95% CI)					**100.0 %**	**-0.03 [-0.20, 0.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.41 (P = 0.68)



Analysis 3.6. Comparison 3 Change in CGIC, Outcome 6 CGIC at 15 months.

Review: Statins for the treatment of dementia

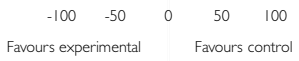
Comparison: 3 Change in CGIC

Outcome: 6 CGIC at 15 months

Study or subgroup	Placebo N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	264	222	0.019 (0.09)		100.0 %	0.02 [-0.16, 0.20]
Total (95% CI)					**100.0 %**	**0.02 [-0.16, 0.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.83)



Analysis 3.7. Comparison 3 Change in CGIC, Outcome 7 CGIC at 18 months.

Review: Statins for the treatment of dementia

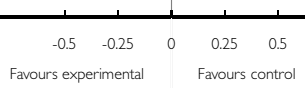
Comparison: 3 Change in CGIC

Outcome: 7 CGIC at 18 months

Study or subgroup	Placebo N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	234	201	0.122 (0.096)		100.0 %	0.12 [-0.07, 0.31]
Total (95% CI)					**100.0 %**	**0.12 [-0.07, 0.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.27 (P = 0.20)



Analysis 3.8. Comparison 3 Change in CGIC, Outcome 8 CGIC LOCF.

Review: Statins for the treatment of dementia

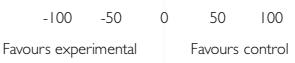
Comparison: 3 Change in CGIC

Outcome: 8 CGIC LOCF

Study or subgroup	Placebo N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	317	297	0.16 (0.086)		100.0 %	0.16 [-0.01, 0.33]
Total (95% CI)					**100.0 %**	**0.16 [-0.01, 0.33]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.86 (P = 0.063)



Analysis 4.1. Comparison 4 NPI, Outcome 1 NPI change from baseline to 6 months.

Review: Statins for the treatment of dementia

Comparison: 4 NPI

Outcome: 1 NPI change from baseline to 6 months

Study or subgroup	statin N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	31	2.19 (6.675)	31	6.94 (6.85)		6.9 %	-4.75 [-8.12, -1.38]
LEADe 2010	263	0.363 (5.55)	308	0.787 (5.59)		93.1 %	-0.42 [-1.34, 0.49]
Total (95% CI)	**294**		**339**			**100.0 %**	**-0.72 [-1.61, 0.16]**

Heterogeneity: Chi^2 = 5.90, df = 1 (P = 0.02); I^2 =83%

Test for overall effect: Z = 1.60 (P = 0.11)

Analysis 4.2. Comparison 4 NPI, Outcome 2 NPI change from baseline to 1 year.

Review: Statins for the treatment of dementia

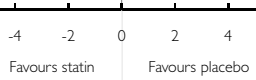
Comparison: 4 NPI

Outcome: 2 NPI change from baseline to 1 year

Study or subgroup	statin N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ADCLT 2005	32	2.69 (6.675)	31	6.99 (6.85)		11.4 %	-4.30 [-7.64, -0.96]
LEADe 2010	236	3.61 (6.897)	278	4.119 (6.952)		88.6 %	-0.51 [-1.71, 0.69]
Total (95% CI)	**268**		**309**			**100.0 %**	**-0.94 [-2.07, 0.19]**

Heterogeneity: Chi^2 = 4.38, df = 1 (P = 0.04); I^2 =77%

Test for overall effect: Z = 1.63 (P = 0.10)



Analysis 4.3. Comparison 4 NPI, Outcome 3 NPI change from baseline to 1 year (using random effects).

Review: Statins for the treatment of dementia

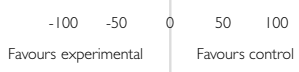
Comparison: 4 NPI

Outcome: 3 NPI change from baseline to 1 year (using random effects)

Study or subgroup	Statin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
ADCLT 2005	32	2.69 (6.68)	31	6.99 (6.85)		41.2 %	-4.30 [-7.64, -0.96]
LEADe 2010	236	3.61 (6.9)	278	4.12 (6.95)		58.8 %	-0.51 [-1.71, 0.69]
Total (95% CI)	**268**		**309**			**100.0 %**	**-2.07 [-5.73, 1.59]**

Heterogeneity: Tau^2 = 5.54; Chi^2 = 4.37, df = 1 (P = 0.04); I^2 =77%

Test for overall effect: Z = 1.11 (P = 0.27)

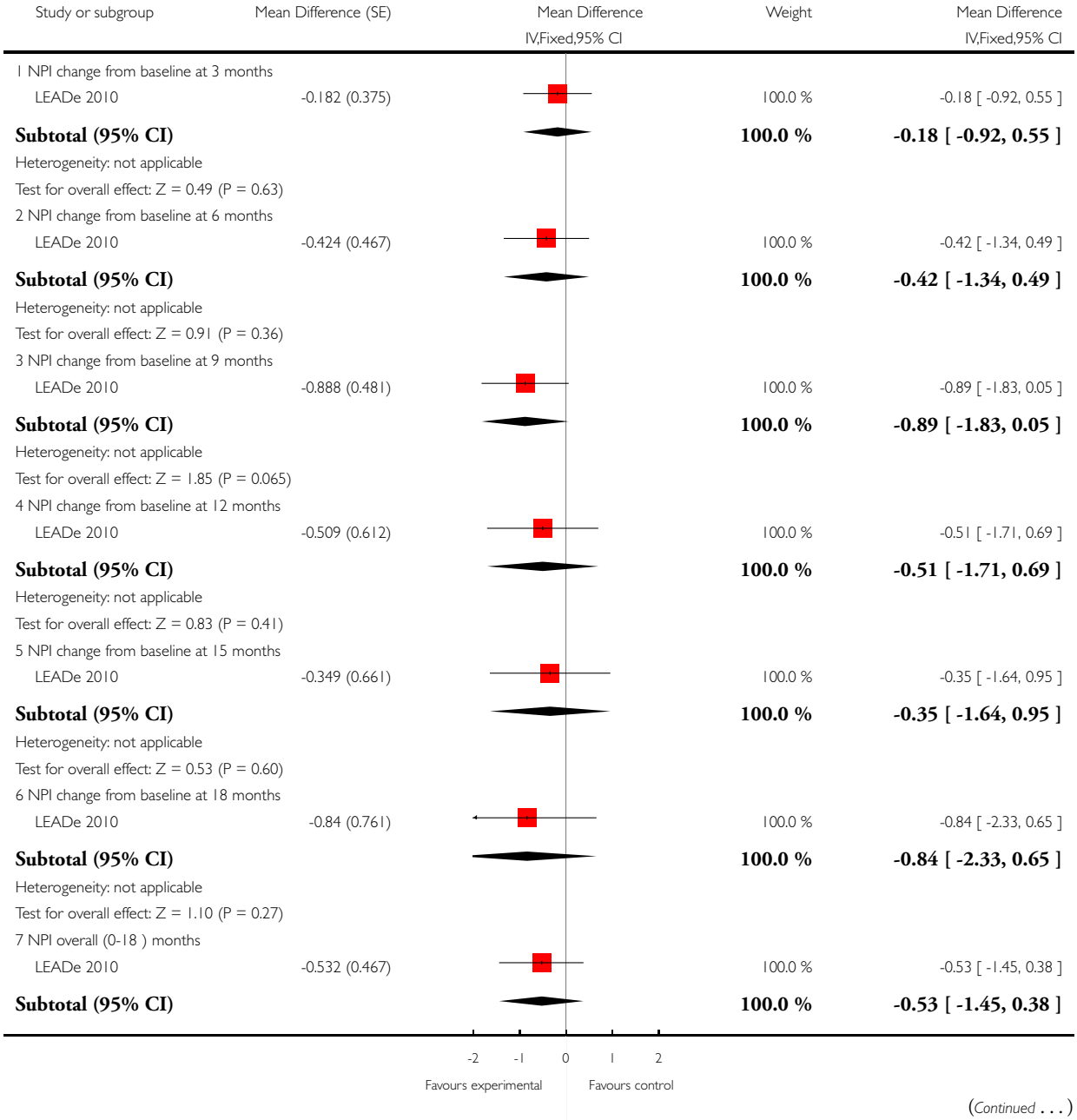


Analysis 4.4. Comparison 4 NPI, Outcome 4 NPI change from baseline over 18 months.

Review: Statins for the treatment of dementia

Comparison: 4 NPI

Outcome: 4 NPI change from baseline over 18 months



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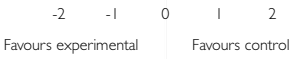
Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 1.14 (P = 0.25)				
8 NPI changes from baseline to 18 months (LOCF)				
LEADe 2010	-1.112 (0.64)		100.0 %	-1.11 [-2.37, 0.14]
Subtotal (95% CI)			**100.0 %**	**-1.11 [-2.37, 0.14]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.74 (P = 0.082)				
Test for subgroup differences: Chi^2 = 2.54, df = 7 (P = 0.92), I^2 =0.0%				



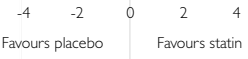
Analysis 5.1. Comparison 5 ADFACS, Outcome 1 ADFACS change from baseline at 6 months.

Review: Statins for the treatment of dementia

Comparison: 5 ADFACS

Outcome: 1 ADFACS change from baseline at 6 months

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	311	285	0.453 (0.413)		100.0 %	0.45 [-0.36, 1.26]
Total (95% CI)					**100.0 %**	**0.45 [-0.36, 1.26]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						



Analysis 5.2. Comparison 5 ADFACS, Outcome 2 ADFACS change from baseline at 12 months.

Review: Statins for the treatment of dementia

Comparison: 5 ADFACS

Outcome: 2 ADFACS change from baseline at 12 months

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	279	233	0.4 (0.581)		100.0 %	0.40 [-0.74, 1.54]
Total (95% CI)					**100.0 %**	**0.40 [-0.74, 1.54]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

Analysis 5.3. Comparison 5 ADFACS, Outcome 3 ADFACS change from baseline at 18 months.

Review: Statins for the treatment of dementia

Comparison: 5 ADFACS

Outcome: 3 ADFACS change from baseline at 18 months

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	256	214	0.446 (0.735)		100.0 %	0.45 [-0.99, 1.89]
Total (95% CI)					**100.0 %**	**0.45 [-0.99, 1.89]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.61 (P = 0.54)

Analysis 5.4. Comparison 5 ADFACS, Outcome 4 ADFACS over all (0-18) months.

Review: Statins for the treatment of dementia

Comparison: 5 ADFACS

Outcome: 4 ADFACS over all (0-18) months

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	317	297	0.433 (0.504)		100.0 %	0.43 [-0.55, 1.42]
Total (95% CI)					**100.0 %**	**0.43 [-0.55, 1.42]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.86 (P = 0.39)

Analysis 5.5. Comparison 5 ADFACS, Outcome 5 ADFACS LOCF.

Review: Statins for the treatment of dementia

Comparison: 5 ADFACS

Outcome: 5 ADFACS LOCF

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
LEADe 2010	317	297	0.043 (0.654)		100.0 %	0.04 [-1.24, 1.32]
Total (95% CI)					**100.0 %**	**0.04 [-1.24, 1.32]**

Heterogeneity: not applicable

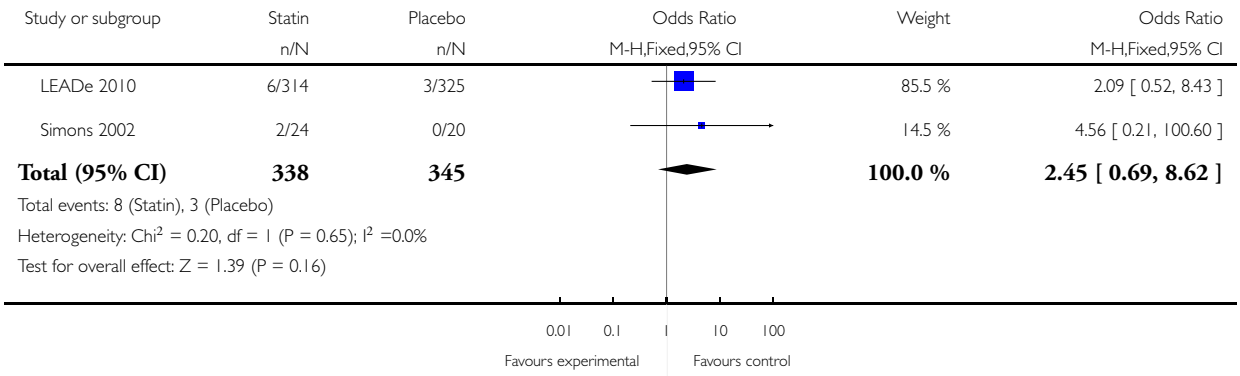
Test for overall effect: Z = 0.07 (P = 0.95)

Analysis 6.1. Comparison 6 Incidence of adverse effects, Outcome 1 Treatment related adverse effects requiring discontinuation of treatment.

Review: Statins for the treatment of dementia

Comparison: 6 Incidence of adverse effects

Outcome: 1 Treatment related adverse effects requiring discontinuation of treatment



HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 8, 2010

CONTRIBUTIONS OF AUTHORS

BMcG: All correspondence, drafting of Review versions, search for trials, obtaining copies of trial reports, selection of trials for inclusion/exclusion, extraction of data, entry of data, interpretation of data analyses.

JOH: All correspondence, drafting of Review versions, search for trials, obtaining copies of trial reports, selection of trials for inclusion/exclusion, extraction of data, entry of data, interpretation of data analyses.

RM: Statistical analysis, interpretation of data analyses.

DC: Drafting of reviews, interpretation of data analyses.

RB: Drafting of Review versions, interpretation of data analyses.

APP: All correspondence, drafting of Review versions, selection of trials for inclusion/exclusion, interpretation of data analyses.

DECLARATIONS OF INTEREST

Peter Passmore: Investigator in Leade study. Received grants from Pfizer, MSD, BMS and Novartis. Honoraria from Pfizer, MSD, Novartis and Astra Zeneca.