

Review Article

Hypercholesterolaemia and vascular dementia

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Vascular dementia (VaD) is the second commonest cause of dementia. Stroke is the leading cause of disability in adults in developed countries, the second major cause of dementia and the third commonest cause of death. Traditional vascular risk factors – diabetes, hypercholesterolaemia, hypertension and smoking – are implicated as risk factors for VaD. The associations between cholesterol and small vessel disease (SVD), stroke, cognitive impairment and subsequent dementia are complex and as yet not fully understood. Similarly, the effects of lipids and lipid-lowering therapy on preventing or treating dementia remain unclear; the few trials that have assessed lipid-lowering therapy for preventing (two trials) or treating (four trials) dementia found no evidence to support the use of lipid-lowering therapy for these indications. It is appropriate to treat those patients with vascular risk factors that meet criteria for lipid-lowering therapy for the primary and secondary prevention of cardiovascular and cerebrovascular events, and in line with current guidelines. Managing the individual patient in a holistic manner according to his or her own vascular risk profile is recommended. Although the paucity of randomized controlled evidence makes for challenging clinical decision making, it provides multiple opportunities for on-going and future research, as discussed here.

Introduction

Dementia is a progressive and largely irreversible clinical syndrome comprising global impairment of mental function, which manifests as difficulties in memory, language, activities of daily living, and psychosocial and psychiatric disturbance [1,2]. As of 2015, there were an estimated 46.8 million people living with dementia worldwide; this number is predicted to double every 20 years, and reach 131.5 million in 2050 [3].

The three most common dementia subtypes are Alzheimer's disease (AD), vascular dementia (VaD) and mixed dementia (combined AD and VaD pathology) [2]. AD is the most common accounting for 60 to 70% of all cases, with a prevalence of approximately 1% in those aged 60–64 years, increasing to 40% in those aged 85 years or older [4]. VaD accounts for a further 17–25% of cases, [2,4] with an estimated prevalence of 1.6% and 1.7% in Europe [5] and China [6] respectively. In reality, many people have mixed AD/VaD disease.

Stroke is the leading cause of disability in adults in developed countries, the second major cause of dementia and the third commonest cause of death [7]. Post-stroke dementia is a major cause of dependency in stroke survivors and encompasses all dementias after stroke, regardless of aetiology [8]. Traditional vascular risk factors – diabetes, hypercholesterolaemia, hypertension and smoking – are implicated as risk factors for VaD [9–11], but are also important in AD with an estimated one third of AD due to modifiable vascular risk factors [12]. In light of increasing life expectancy, there is an urgent need to find therapies to prevent and treat both cognitive impairment and dementia.

Here, we review the associations between hypercholesterolaemia and VaD, intracerebral haemorrhage (ICH) and post-stroke dementia, the effects of statin therapy on stroke, cognitive impairment and dementia, and on-going and future research opportunities.

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Aetiology of vascular dementia

The aetiology of VaD comprises small and large vessel disease. Cerebral small vessel disease (SVD) is the commonest cause of VaD responsible for 350,000 cases of dementia per year in the U.K. It is characterized by damage to deep grey and white matter as a result of injury to perforating arterioles and capillaries, although the significance of venular damage is unclear [13]. Histologically, plasma constituents and inflammatory cells infiltrate arteriolar walls and perivascular tissue with resultant damage labelled as arteriosclerosis, fibrinoid necrosis and lipohyalinosis [14]. Such endothelial dysfunction leads to breakdown of the blood–brain barrier (BBB). In addition, perivascular inflammation is a common pathological feature [15]; blood markers of endothelial activation and inflammation are raised in lacunar stroke [16]; and cerebral vasoreactivity is impaired [17]. This combination of endothelial dysfunction and inflammation leads to arteriolar wall thickening, limiting the ability of arterioles to dilate when required [17]. Brain tissue supplied by stiff and thickened arterioles may be at increased risk of ischaemia and damaged arteriolar walls may be more likely to precipitate secondary thrombosis [14]. These pathological changes manifest as imaging abnormalities that can be detected on magnetic resonance imaging (MRI): lacunar or subcortical infarctions; lacunes; microbleeds; and white matter hyperintensities (WMH) [18,19]. SVD can present clinically in a number of ways: lacunar ischaemic stroke (IS); vascular cognitive impairment and VaD; ICH; depression; or gait and/or bladder dysfunction [14]. However, most imaging features of SVD develop silently and when numerous lacunes, microbleeds and/or WMH are present there is an increased risk of cognitive impairment, dementia and stroke [20–22]. In contrast, other causes of stroke such as large vessel disease – extracranial or intracranial – and cardioembolic disease [e.g. atrial fibrillation (AF), recent myocardial infarction (MI)] have differing pathological mechanisms to SVD; atherosclerosis and enhanced platelet function in large artery stroke and pro-coagulant activity in cardioembolic disease [22].

Several factors are implicated in the development of post-stroke dementia. These can be split into demographic and clinical characteristics, stroke characteristics and neuroimaging findings (Table 1) [8]. Attempting to determine the degree of cognitive impairment that can be attributed to either stroke, concurrent AD or SVD remains difficult. The proportion of patients with post-stroke dementia presumed to have AD varies widely from 19% to 61% [23]. Of those with post-stroke dementia approximately one third have medial temporal atrophy, [24] and 15–30% have a diagnosis of dementia that predates their stroke [24,25]. These two factors may increase the likelihood of AD in this group of patients, but this is speculative at present [26].

Intracerebral haemorrhage and vascular dementia

Although ICH accounts for only 15% of strokes, it is associated with high rates of stroke-related death and disability [27,28]. Re-bleeding, IS and cognitive impairment and dementia – all frequent events following ICH – are endpoints that may be mediated by underlying SVD, which is probably the aetiology responsible for these secondary clinical outcomes and ICH [14,29]. Indeed, compared with general elderly controls those with ICH have an increased frequency of both neuroimaging and genetic markers of SVD [30–32].

Despite dementia being common after ICH, its risk factors are poorly understood. One recent study sought to establish whether different factors were associated with early (≤ 6 months) or delayed (> 6 months) dementia following ICH [33]. Dementia diagnosis was based on International Classification of Diseases-9 (ICD-9) codes established from electronic medical records and/or modified Telephone Interview for Cognitive Status (TICS-m) scores < 20 . The sensitivity and specificity of dementia diagnoses established from ICD-9 codes and TICS-m compared with face-to-face assessment by a neurologist (available in 70.7% of the cohort) were 90% and 94% respectively. Of the 738 people with ICH recruited, 279 (37.8%) developed dementia during the median follow-up of 47.4 months; 140 patients developed dementia within 6 months, with the remaining 139 being diagnosed more than 6 months post-ICH. Risk factors for early and delayed dementia after ICH varied significantly [33]. ICH volume, lobar location and presence of ≥ 1 copy of apolipoprotein E (APOE) $\epsilon 2$ were associated with early dementia but not delayed dementia. The APOE $\epsilon 2$ variant has been reported to be associated with larger haematoma volumes and/or expansion and therefore poor functional outcome at 90 days [34,35]. Conversely, educational level, pre-morbid mood disturbance, imaging markers of SVD [white matter disease on computed tomography (CT) and cerebral microbleeds (CMB)] and presence of ≥ 1 copy of APOE $\epsilon 4$ were associated with delayed but not early dementia [33].

Biffi et al. [33] report a high incidence of dementia (5.8% per year), which could be an overestimation, perhaps through the use of TICS-m rather than in-person assessment, although the concordance between telephone and in-person assessments was high. Despite this, it is clear that cognitive impairment or dementia following ICH is under-recognized. In summary, ICH characteristics were associated with early and not late dementia after ICH, and markers associated with both SVD and late-onset AD were associated with delayed onset dementia [33]. Further

Table 1 Predictors of post-stroke dementia [8,26]

ACA, anterior cerebral artery; CCF, congestive cardiac failure; PCA, posterior cerebral artery.

Clinical/demographic predictors

Increasing age
Low education level
Pre-stroke dependency
Pre-stroke cognitive decline without dementia
Hypertension
DM
AF
MI
Epileptic seizures
Sepsis
Cardiac arrhythmias
CCF

Stroke predictors

Severe neurological deficit at stroke onset
Stroke recurrence
Supratentorial stroke
Left hemisphere stroke
ACA and PCA territorial infarcts
Strategic infarcts:
 Left angular gyrus
 Inferomedial temporal
 Mesial frontal
 Anterior and dorsomedial thalamus
 Left capsular genu
 Caudate nucleus
Multiple infarcts
Increased volume of stroke lesion [195]
Early post-stroke complications [196]
 Seizure
 Delirium
 Hypoxia
 Hypotension

Neuroimaging predictors

Silent infarcts
Global cerebral atrophy
Medial temporal lobe atrophy
White matter changes

studies are required to elucidate the contribution of AD to cognitive impairment following ICH. Although this cohort provides evidence of separate risk factors for early and late dementia after ICH, these results need to be verified. An important question to address in those with delayed dementia following ICH is whether cognitive impairment is secondary to the ICH, or are the bleed and cognitive impairment both sequelae of the same underlying disease process [36]?

Lipid effects on vascular dementia

There are a variety of pathological mechanisms involved in the development of VaD, and lipids have a vital role in many of these processes. Both high levels of low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol are known risk factors for carotid atherosclerosis and coronary artery disease [37,38], which may result in cognitive impairment secondary to cerebral hypoperfusion or embolism [39]. HDL cholesterol

may be involved in the removal of excess cholesterol from the brain mediated by APOE and heparin sulphate proteoglycans in the subendothelial space of cerebral microvessels [40]. In addition, HDL particles reverse the inhibitory action of oxidized LDL particles on endothelium-dependent arterial relaxation [41] and also inhibit cytokine-induced expression of endothelial cell adhesion molecules [42]; both of which may be potential mechanisms in the development of VaD.

Oxidative stress and lipid oxidation in particular have a pivotal role in the development of VaD [43]; lipid peroxidation may influence neuronal membrane permeability, affecting cellular function and damaging membrane-bound receptors and enzymes [44]. The brain may be particularly susceptible to oxidative lipid damage due to its high content of polyunsaturated fatty acids [44]. Paraonase 1 is an A-esterase with peroxidase-like activity present on the surface of HDL, which decreases peroxidation of LDL. Levels of paraonase 1 decrease with increasing age and in those with cardiovascular disease (CVD); they have also been found to be reduced in patients with VaD [45]. Further evidence for the role of oxidative stress comes from the demonstration of low levels of plasma antioxidants in patients with AD and VaD compared with controls; vitamins A, C and E, uric acid and carotenoids were all significantly lower than controls [46]. However, in the same cohort there was no difference in plasma malondialdehyde, a biomarker of lipid peroxidation, between controls and those with either AD or VaD [46]. Low plasma vitamin E levels have also been seen in patients with VaD in comparison with controls, although in a published cohort levels in people with AD were similar to controls [47]. Low levels of antioxidants may render individuals more susceptible to oxidative stress and thus reduced antioxidant defences may have an important role in the development of VaD.

Apolipoprotein B (ApoB) is the main surface protein found on pro-atherogenic lipoproteins: LDL; very-low density lipoprotein (VLDL); intermediate density lipoprotein (IDL); and lipoprotein (a) [48]. One particle of pro-atherogenic lipoprotein contains one molecule of ApoB [49], thus ApoB provides a surrogate measure of the number of circulating pro-atherogenic lipoprotein particles. As such, ApoB may be more strongly related to cardiovascular risk than cholesterol contained within the lipoproteins. However, epidemiological data are inconclusive and therefore discrepancy exists between current guidelines on the significance of ApoB to cardiovascular risk [50–52]. Data on ApoB and SVD or dementia are scanty. A Swedish twin study ($n=60$) found that higher ApoB at baseline predicted dementia at least 3 years later, although any cause of dementia was included in this small study [53]. A pooled analysis of two Finnish prospective population-based cohort studies ($n=13,275$) found that baseline ApoB was not associated with incident AD or dementia 10 years later [54]. At present, the role of ApoB in the development of SVD or VaD is unclear.

Whilst several studies have reported no association between LDL cholesterol and MRI markers of SVD [55–57], one cohort ($n=1,919$) noted a significant relationship between reducing LDL cholesterol and WMH progression [58]. Further, in 1,135 acute IS patients hypercholesterolaemia, hypertriglyceridaemia or use of lipid-lowering medication was associated with decreased WMH severity [59]. Unfortunately, the authors were unable to assess the contribution of statin therapy to the association seen, which may have confounded their findings. Although a smaller cohort ($n=112$) found no association between midlife total cholesterol and WMH two decades later, lipid-lowering therapy decreased the risk of WMH being present in later life [60]. Lower midlife HDL cholesterol was associated with increased WMH volumes in later life in 148 monozygotic male twins [61]. The somewhat contradictory findings regarding the associations between cholesterol and WMH are also noted in regard to lacunes. A cross-sectional analysis of MRI data ($n=1,827$) found that smaller lacunes (≤ 7 mm) were associated with diabetes mellitus (DM) and larger lacunes (8–20 mm) were associated with LDL cholesterol [62]. The authors propose that these differences support the theory that differing pathologies result in small and large lacunes, namely lipohyalinosis and microatheroma respectively [62]. Within the Leukoaraiosis and Disability study ($n=396$) lower HDL cholesterol was associated with new lacunes on MRI over 3 years, whilst high LDL cholesterol was protective against formation of new lacunes [55]. In contrast, the Rotterdam Scan Study ($n=668$) found no association between total HDL cholesterol and incident lacunar infarcts over 3 years, but did note an association between carotid atherosclerosis and incident lacunar infarcts [57]. Although the data are unclear, there may be a suggestion that LDL cholesterol is not as damaging to small arteries as it is to larger vessels.

Epidemiological data from two French cohorts ($n=2,608$) found that increasing triglyceride levels, but not LDL or HDL cholesterol, were associated with larger WMH volume and lacunes on MRI; an effect that was maintained after adjusting for inflammatory markers and vascular risk factors, and in those taking and not taking lipid-lowering therapy [63]. There are several proposed mechanisms to explain this association. Firstly, triglyceride levels have been associated with breakdown of the BBB, contributing to the formation of lacunes [55] and WMH [64]. Secondly, triglyceride levels are associated with markers of inflammation [65], which in turn have been reported to be associated with MRI features of SVD [66,67]. Thirdly, APOE plays a pivotal role in lipid metabolism and polymorphisms $\epsilon 2$ and $\epsilon 4$ have been found to be associated with MRI markers of SVD [68]. Finally, triglyceride levels adversely affect the compliance of small arteries [69], which may potentially contribute to chronic white matter hypoperfusion [70].

Cholesterol lowering medications, such as statins, are used to prevent first and recurrent vascular events including MI and IS [71,72]. Reducing stroke occurrence by lowering cholesterol may, as a consequence, reduce the incidence of post-stroke dementia. The Finnish Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study found that midlife total cholesterol predicted cognitive impairment 21 years later, an effect that was attenuated following adjustment for statin usage [73]. Similarly, raised midlife cholesterol was associated with an increased risk of developing VaD over a 30-year period in a study based on medical records [74]. In contrast, results from cohorts involving those in later-life vary with some finding higher levels of cholesterol to be associated weakly with a higher risk [37], and others finding a relationship with a lower risk [75] of VaD. These inconsistencies probably represent the timing of cholesterol measurement in relation to age and clinical onset of dementia. Indeed, pravastatin in older people at risk of CVD had no effect on multiple cognitive outcomes when compared with placebo [76].

Lipid effects on Alzheimer's disease

Whilst both coronary heart disease and hypertension are independent risk factors for AD [77,78], the association between cholesterol and AD is less clear. There are conflicting epidemiological data; some report an association between raised serum cholesterol levels and an increased risk of developing AD [74,77,79–81], whereas other studies have shown no effect [82–88] or a negative association [37,75]. These incongruous findings are likely to be due to differing study design, participant age at enrolment (mid- compared with later-life), timing of cholesterol measurement in terms of age and dementia onset and length of follow-up. APOE is an important protein involved in cerebral cholesterol transport and influences aggregation and clearance of amyloid- β peptide [89–91]. The amyloid cascade hypothesis suggests that an imbalance between production and clearance of amyloid- β is the first step in AD pathogenesis, culminating in neuronal degeneration and dementia [92]. This provides a theoretical link between cholesterol metabolism and pathogenesis of AD. Presence of the APOE ϵ 4 allele increases the risk of AD by 3 and 15 times in heterozygotes and homozygotes respectively [93]. The ϵ 4 allele is associated with a higher risk of atherosclerosis and higher plasma levels of total and LDL cholesterol [94]. In addition, several other genes involved in cholesterol metabolism have been associated with AD including adenosine triphosphate (ATP)-binding cassette subfamily A member 7 (ABCA7) [95], clusterin [96] and sortilin-related receptor (SORL1) [97].

The majority of cerebral cholesterol is produced locally and is not transported into plasma due to the BBB [98]. Cerebral cholesterol levels are not altered by high LDL or low HDL cholesterol plasma levels, but whether intramembranous lipid domains or intracellular cholesterol content are affected remains unclear [99]. Cholesterol removal from the brain is mediated by 24-hydroxycholesterol [100], which is crucial for cerebral cholesterol homeostasis [101]. Diet-induced hypercholesterolaemia in animal models has been associated with increased amyloid- β and APOE levels in temporal and frontal cortical regions, in line with the geographical amyloid-related pathological changes seen in AD [102].

Ischaemia has been noted to cause up-regulation of amyloid precursor protein expression with resultant amyloid- β deposition in human brains [103]. Furthermore, co-existent cerebrovascular and amyloid- β plaque pathology may increase the chance of clinically apparent dementia occurring [104].

Epidemiology of lipids and intracerebral haemorrhage

The association between higher total and LDL cholesterol levels and increased IS risk is seen in most observational studies [105–116]. Similarly, most observational data report an association between lower total and LDL cholesterol levels and increased ICH risk (Table 2) [106,117–121]. A meta-analysis of 23 prospective studies involving 1,430,141 patients found an association between lower total cholesterol and increased rates of ICH; dose–response analysis revealed a relative risk (RR) of ICH per 1 mmol/l increment of total cholesterol of 0.85 (95% confidence interval [CI] 0.80–0.91) [122]. The nature of this association remains poorly understood. Of note, low levels of LDL cholesterol have been identified in patients with haematological cancers [123] and liver disease [124], who have a higher risk of ICH.

Studies assessing triglycerides and stroke risk have shown similar results to total cholesterol (Table 2): for each 0.1 mmol/l increase in baseline triglycerides, there was an associated RR of IS of 1.05 (95% CI 1.03–1.07) [125]; triglyceride levels were also inversely associated with ICH [120,121].

Statins

Statins are 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. This enzyme is involved in cholesterol synthesis and by inhibiting its activity statins reduce formation and release of LDL cholesterol, up-regulate

Table 2 Lipids and ICH

CV, cardiovascular.

Lipid	Study	n	Results	Comments
Total cholesterol	Multiple risk factor Intervention Trial [117]	350,977 men (U.S.A.)	Risk of death from ICH was three times higher in men with cholesterol <4.14 mmol/l, compared with high levels	Risk of death from ICH when cholesterol <4.14 mmol/l was overwhelmed by the positive association of higher cholesterol with death from IS and total CV disease
	Korean Medical Insurance Corporation Study [118]	114,793 men (Korea)	Low total cholesterol was not an independent risk factor for ICH	This cohort had a mean age of 45.4 years and were government employees with stable socioeconomic status, not necessarily representative of middle-aged Korean men
	Asia Pacific Cohort Studies Collaboration [106]	352,033 (Asia/Australasia)	Each 1 mmol/l increase in total cholesterol was associated with 20% decreased risk of fatal ICH	Each 1 mmol/l increase in total cholesterol was also associated with 35% increased risk of coronary death, 25% increased risk of IS
LDL cholesterol	Pooled analysis of the ARIC study and Cardiovascular Health Study [119]	21,680 (U.S.A.)	LDL cholesterol was inversely associated with ICH [RR of ICH for top quartile versus quartiles 1–3: 0.52 (95% CI 0.31–0.88)]	Total cholesterol and HDL cholesterol levels were not associated with ICH
Triglycerides	Pooled analysis of the ARIC study and Cardiovascular Health Study [119]	21,680 (U.S.A.)	Triglycerides were inversely associated with ICH [RR of ICH per log unit mg/dl: 0.56 (95% CI 0.37–0.84)]	Total cholesterol and HDL cholesterol levels were not associated with ICH
	Three City Study [120]	8,393 (France)	A low triglyceride level (≤ 0.94 mmol/l) was associated with an increased risk of ICH (HR 2.36, 95% CI 1.18–4.70)	A high triglyceride level (≥ 1.34 mmol/l) was associated with an increased risk of ischaemic events, coronary events and IS
	Rotterdam Study [121]	9,068 (Netherlands)	Triglycerides were inversely associated with ICH (HR for highest versus lowest quartile: 0.20 (95% CI 0.06–0.69))	A similar association was seen between triglycerides and CMBs in deep or infratentorial regions; no associations for LDL or HDL cholesterol were found

LDL receptor activity [126], with subsequent lowering of LDL cholesterol and triglycerides, and increase in HDL cholesterol [127]. In addition to their effects on lipids, statins increase the integrity of the BBB, improve endothelial cell function [128] and reduce platelet aggregation, smooth muscle cell proliferation and markers of inflammation [e.g. C-reactive protein (CRP)] [129,130]. Statins can be classified according to whether they are soluble in water (hydrophilic) or in lipids (lipophilic). Atorvastatin, fluvastatin, lovastatin and simvastatin are lipophilic statins and therefore cross the BBB and cell membranes with greater ease than their hydrophilic equivalents (pravastatin) [131].

Statin therapy protects against stroke in terms of both primary and secondary prevention. In the Heart Protection Study (HPS), involving 20,536 participants aged 70–80 years at high risk of vascular disease, simvastatin (40 mg daily) was associated with a 20% reduction in stroke risk compared with placebo [132]. Atorvastatin 80 mg versus 10 mg

daily was associated with a 25% reduction in stroke risk in the Treating to New Targets (TNT) study [133]. Two large meta-analyses have shown significant reductions in stroke risk for each 1 mmol/l reduction in LDL cholesterol with statin therapy; 21.1% [134] and 16% [135] RR reduction respectively.

In those with a history of cerebrovascular disease in HPS ($n=3,280$), simvastatin was associated with a 20% reduction in major cardiovascular events compared with placebo, but there was no reduction in stroke rate [132]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial ($n=4,742$) found that atorvastatin (80 mg) was associated with an RR reduction in recurrent stroke of 16% compared with placebo [136]. These results were seen in both subgroups with large artery stroke and lacunar stroke, and in those with transient ischaemic attack (TIA).

Statins in ICH

Epidemiological evidence described above suggests that there is an inverse association between lipids and ICH. Further studies assessing the relationship between statin usage and ICH have had conflicting results. The HPS showed a non-significant increased risk of ICH in those randomized to simvastatin compared with placebo [132], whilst those participants treated with atorvastatin in the SPARCL trial had an higher risk of ICH than those who received placebo [136]. Retrospective analysis using the Virtual International Stroke Trials Archive (VISTA) dataset ($n=8,535$) compared participants with prior statin usage and recently commenced statin within 3 days of acute IS with those without statin exposure. There was no association between statin use and early symptomatic ICH or any ICH, regardless of whether thrombolysis was administered or not. Indeed, there was a non-significant tendency to less death at 90 days in participants with prior statin usage (adjusted hazard ratio [HR] 0.84, 95% CI 0.70–1.00) and recently commenced statin therapy (adjusted HR 0.67, 95% CI 0.46–0.97) [137]. Meta-analysis of 31 trials revealed no increased risk of ICH in people taking statins (odds ratio [OR] 1.08, 95% CI 0.88–1.32) [138].

Statins in VaD

Trials of statins assessing outcomes relevant to cognition, dementia and SVD are lacking. Several observational studies have observed an association between statin use and dementia. These have been systematically reviewed by several groups of authors. All found significant heterogeneity between studies and reported the biases and confounding factors commonly associated with observational research, making conclusive results and implications for practice difficult to establish and disseminate [139–141]. The key confounders can be summarized as follows. First, inclusion of those with advanced dementia or very elderly people, who carry multiple vascular risk factors and are therefore at risk of vascular disease. Second, different markers of dementia were used including a variety of cognitive tests and diagnostic definitions. Third, different statin types were assessed including lipophilic and hydrophilic subtypes. Fourth, the duration of treatment and timing of assessment in relation to the former varied considerably. Fifth, patients from lower socioeconomic class are less likely to be prescribed statins. Last, the pathophysiology of VaD is heterogeneous with significant overlap with AD [142].

Two randomized controlled trials (RCTs) of statins have reported outcomes relating to cognition. The aforementioned HPS showed that simvastatin had no effect on cognitive decline, evaluated using TICS-m, compared with control [132]. A less potent statin (pravastatin) was assessed in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study and exerted no effect on cognitive function, measured by mini-mental state examination (MMSE), after 4 years of treatment ($n=5,804$) in those aged 70–82 years at baseline [76]. A subsequent meta-analysis, under the auspices of the Cochrane Collaboration, of these two trials did not alter the neutral effects seen within the trials individually (Table 3) [4]. Similarly, assessment of pravastatin and simvastatin on WMH progression in the PROSPER ($n=535$) and Regression of Cerebral Artery Stenosis (ROCAS) ($n=227$) studies respectively found neutral effects [143,144]. In summary, evidence to date suggests that statins given in later life have no effect on preventing cognitive decline or dementia [4,26]. The American Heart Association guideline suggests that treatment of hypercholesterolaemia for prevention of dementia has uncertain usefulness [26].

The Prevention Of Decline in Cognition After Stroke Trial (PODCAST) [145] randomized patients without dementia who were 3 to 7 months after stroke to intensive (systolic <125 mmHg) versus guideline (systolic <140 mmHg) blood pressure lowering. In addition, participants with IS were randomized to intensive (<1.3 mmol/l) versus guideline (<3 mmol/l) lipid-lowering therapy. Lipid-lowering therapy was suggested to investigators as follows: guideline to simvastatin 10–40 mg, pravastatin 10–40 mg or fluvastatin 10–80 mg; intensive to atorvastatin >20 mg or rosuvastatin at any dose. Eighty-three participants were recruited and followed-up for a median of 24 months. Although total and LDL-cholesterol were reduced with intensive versus guideline lipid-lowering therapy, there was no difference in the Addenbrooke's Cognitive Examination-Revised (ACE-R, primary outcome) between

Table 3 Summary of systematic reviews with meta-analyses for lipid-lowering therapies

MD, mean difference; SMD, standardized mean difference.

Intervention	Population	Trials	Patients	Stroke RR/OR (95% CI)	Cognitive impairment MD/OR (95% CI)	ICH
Statins for dementia prevention [4]	Normal cognition	1	20,536		OR 1.0 (0.61, 1.65)	
		1	5,804		MD MMSE 0.06 (−0.04, 0.16)	
Statins for dementia treatment [131]	Probable or possible AD	4	1,110		ADAS-Cog MD −0.26 (−1.05, 0.52)	
		4	1,127		MMSE MD −0.32 (−0.71, 0.06)	
Statins [164]	Normal cognition	14	27,643		SMD 0.01 (−0.01, 0.03)	
	AD	4	935		SMD −0.05 (−0.19, 0.10)	
Statins [138]	ICH	31	182,803	OR 0.84 (0.78, 0.91)		OR 1.08 (0.88, 1.32)
Statins [155]	AD	3	546		MMSE MD 1.14 (−0.20, 2.47)	
Niacin [166]	CVD	11	9,959	OR 0.88 (0.50, 1.54)		
Diet [177]	CVD	7	60,554	OR 0.92 (0.69, 1.23)		
Fibrates [177]	CVD	12	28,144	OR 0.98 (0.86, 1.12)		
Fibrates [168]	CVD	18	45,058	RR 1.03 (0.91, 1.16)		
PCSK-9 inhibitors [176]	Hyperlipidaemia	2	4,465	RR 1.43 (0.45, 4.57)		

groups during treatment. However, intensive lipid-lowering was associated with improvements in several secondary outcomes including cognition (ACE-R at 6 months, trail making A), death or dependency (modified Rankin Scale; mRS) and quality of life (Euro-QoL visual analogue scale). Unfortunately, PODCAST grossly under-recruited compared with an initial protocol target of 600 participants [146], and was therefore underpowered for all outcomes. In a *post hoc* global analysis of multiple outcomes (using the Wei–Lachin test [147]), intensive lipid lowering improved on-treatment global cognition (Figure 1) and on-treatment global outcome (Figure 2), findings that warrant further investigation.

Data regarding statins as treatment for established dementia (either AD or VaD) are limited. Observational data from one study that followed patients with AD for 35 months suggested that people treated with lipid-lowering therapy had a slower decline in MMSE scores than those with untreated hyper- or normo-cholesterolaemia [148]. In the Ginkgo Evaluation of Memory Study, those without mild cognitive impairment at baseline who were on statins had a reduced risk of both AD (HR 0.57, 95% CI 0.39–0.85) and overall dementia (HR 0.79, 95% CI 0.65–0.96). In contrast, those with mild cognitive impairment at baseline on lipid-lowering therapy (including statins) had no evidence of cognitive benefit [149]. Further, a pooled analysis involving data from three RCTs of galantamine in AD found no change in cognition associated with the use of statins [150]. A recent Cochrane review found no RCTs that have assessed statins in the treatment of VaD, but identified four that assessed these medications (atorvastatin and simvastatin in two studies each) in AD (Table 3) [131]. These four studies [151–154] involved 1,154 participants aged 50–90 years with diagnoses of probable or possible AD. The authors found no change in the primary outcome of Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog) from baseline in those who received statins compared with those on placebo. Equally, there was no significant difference in MMSE scores from baseline between those randomized to statins compared with placebo [131]. These findings echo previous results prior to the

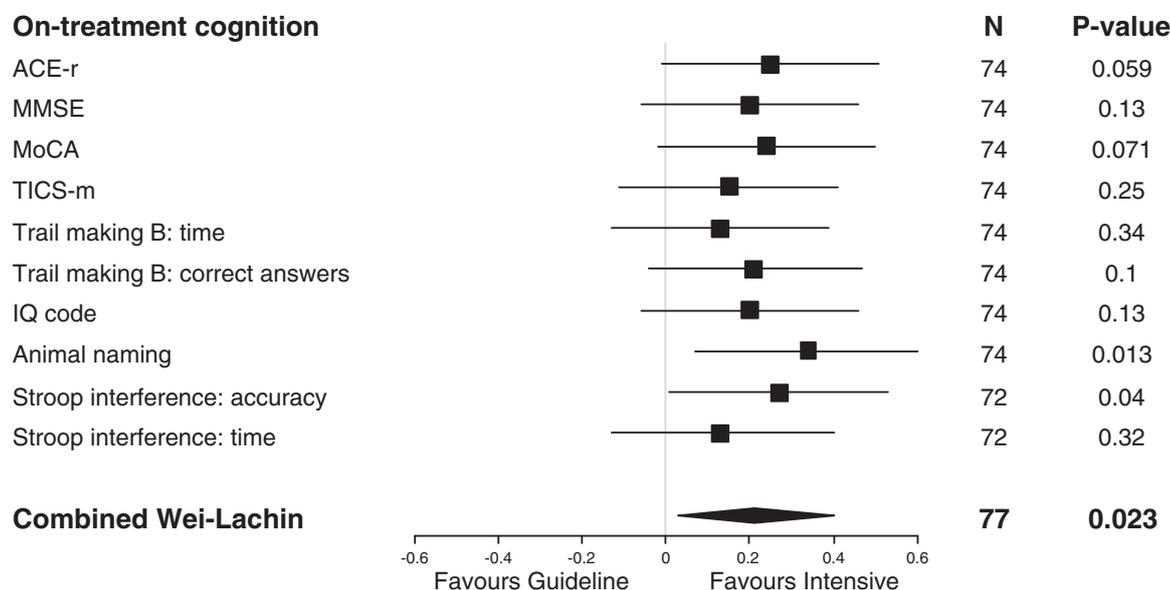


Figure 1. On-treatment global cognition: data from PODCAST

Analyses were performed using the multivariate directional Wilcoxon test. The effect sizes are the Mann–Whitney difference (and 95% CI) for each of the individual outcomes and for the combined outcome (using the Wei–Lachin procedure).

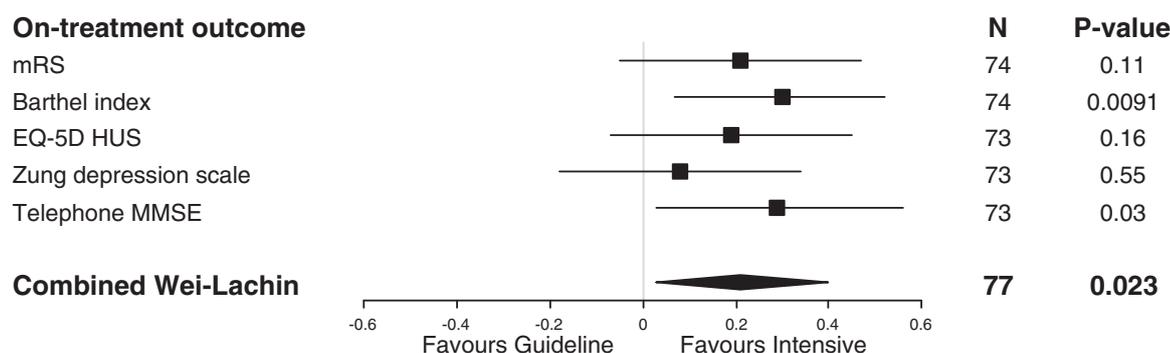


Figure 2. On-treatment global outcome: data from PODCAST

Analyses were performed using the multivariate directional Wilcoxon test. The effect sizes are the Mann–Whitney difference (and 95% CI) for each of the individual outcomes and for the combined outcome (using the Wei–Lachin procedure); EQ-5D HUS, Health utility status derived from Euro-quality of life five dimensions.

publication of Sano et al. [153] in which neither a treatment effect nor a difference between trials of atorvastatin and simvastatin was seen [155]. There is, therefore, no evidence to recommend the use of statin therapy for the treatment of AD or VaD. Despite this, a proportion of clinicians choose to prescribe statins for both primary and secondary prevention of vascular cognitive impairment [156].

Statin-induced cognitive impairment

There has been significant interest in the suggestion that statin treatment may negatively affect cognition. Randomized trials, case reports, observational studies and post-marketing surveillance have all reported data regarding cognitive impairment in people taking statins [149,157–161]. Symptoms of confusion, forgetfulness and memory loss have been reported within a few days of starting therapy, whilst others report symptom-onset years after commencing statins. Overall, the symptoms were not serious and reversed within a few weeks of ceasing statin therapy. Subsequently, at least three groups have systematically appraised the situation and found that there is no significant evidence to suggest that statins cause cognitive impairment [162–164]. For example, the meta-analysis by Ott et al. [164] involved 14

RCTs ($n=27,643$) and found that statins were not associated with cognitive impairment in either cognitively normal participants or people with AD (Table 3) [164].

Other lipid-lowering therapies and VaD

Alternative lipid-lowering agents are (at present) less efficacious at primary or secondary stroke prevention than statins [165]. Despite niacin increasing levels of HDL cholesterol, a systematic review and meta-regression including 11 studies with 9,959 patients showed no significant improvement in stroke risk (OR 0.88, 95% CI 0.50–1.54, Table 3) [166]. Similarly fibrates increase HDL cholesterol, but also lower triglyceride levels. In the Veterans Affairs-HDL Intervention Trial (VA-HIT), gemfibrozil reduced stroke risk by 31% in men with low HDL cholesterol and coronary artery disease [167]. Meta-analysis of 18 trials totalling >45,000 patients found that fibrates had no significant effect on stroke risk [168]. Observational data from Canada ($n=2,305$) suggested that use of statins and other lipid-lowering agents in those aged less than 80 years reduced the risk of overall dementia and, in particular, AD [169]. Alternative data from an U.K. general practice cohort found that individuals prescribed statins had a significantly reduced risk of developing dementia; an effect not demonstrated with other lipid-lowering treatments [170].

Ezetimibe reduces total cholesterol levels by inhibiting intestinal cholesterol absorption. When added to simvastatin (40 mg daily), ezetimibe (10 mg daily) significantly reduced stroke risk (HR 0.86, 95% CI 0.73–1.00, $p = 0.05$) compared with simvastatin monotherapy over a median follow-up of 6 years after acute coronary syndrome in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT, $n=18,144$) [171]. This reduced stroke risk was driven by a reduction in IS events (HR 0.79, 95% CI 0.67–0.94) between the two groups described. To date, no trials have specifically assessed ezetimibe in the prevention or treatment of dementia.

Proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors are parenterally administered, monoclonal antibodies that lower LDL cholesterol levels by preventing degradation of hepatic LDL receptors. When added to statins, PCSK-9 inhibitors reduce LDL cholesterol by 40–72% [172]. A meta-analysis of 24 studies including 10,159 participants found that PCSK-9 inhibitors were associated with reductions in all-cause mortality, cardiovascular mortality and the rate of MI compared with placebo [173]. The OSLER 1 and 2 studies ($n=4,465$) reported that the risk of major cardiovascular events (including stroke and TIA), over a median of 11 months follow-up, was reduced by 53% in those who received evolocumab [174], whilst in the ODYSSEY LONG TERM study ($n=2,341$) the rate of first major cardiovascular events (including IS), over a median follow-up of 18 months was lower (HR 0.52, 95% CI 0.31–0.90) with alirocumab compared with placebo [175]. A recent meta-analysis of these two trials sought to establish the effect of PCSK-9 inhibitors on stroke risk, but was limited due to the small number of strokes reported over relatively short follow-up periods: 5 ISs and 6 TIAs in OSLER, and 11 ISs in ODYSSEY LONG TERM [176]. There was no difference in stroke rates between PCSK-9 inhibitors and placebo (risk ratio 1.43, 95% CI 0.45–4.57). Further data are needed over longer follow-up duration to establish the efficacy of PCSK-9 inhibitors at reducing incident strokes.

Although there is no evidence regarding PCSK-9 inhibitors and prevention or treatment of dementia, there have been reports of increased neurocognitive adverse events (confusion, memory problems) with these agents compared with placebo [176]. Clearly, further research and monitoring are required before these agents can be used in the setting of primary or secondary prevention of stroke or dementia.

In summary, a large meta-analysis of 78 trials ($n=266,973$) of lipid-lowering therapy found no significant effect of non-statin lipid-lowering on stroke risk (diet: OR 0.92, 95% CI 0.69–1.23; fibrates: OR 0.98, 95% CI 0.86–1.12; other drugs: OR 0.81, 95% CI 0.61–1.08, Table 3) [177].

Ideal cardiovascular health

As discussed previously, stroke and its recurrence are predictors of dementia [8]. In addition, other vascular diseases – namely coronary artery disease, peripheral arterial disease, AF, renal disease and cardiac failure – have all been associated with cognitive impairment and VaD [26]. Stroke and these other vascular diseases probably represent markers of cumulative exposure to multiple vascular risk factors. In addition to hypercholesterolaemia, modifiable vascular risk factors comprise diabetes, hypertension, obesity, physical inactivity and smoking, which are all independently associated with cognitive impairment and dementia in later life [178–182]. In order to promote cardiovascular health (CVH) and reduce deaths from CVD and stroke by 20% by 2020, the American Heart Association developed the CVH index, a 7-point score ranging from 0 to 7, with one point awarded for each of: current non-smoker; body mass index (BMI) >18.5 and <25 kg/m²; adequate physical activity; a healthy diet; untreated total cholesterol <5.2 mmol/l; untreated blood pressure <120/80 mmHg; and fasting blood glucose <5.6 mmol/l [183]. Higher scores indicating ideal CVH have predicted less coronary artery disease and stroke (IS and ICH) in at least three separate cohorts in the U.S. [184–186] and one in China [187,188]. One prospective cohort study aimed to assess whether ideal CVH

Box 1 Unanswered questions for future research regarding hypercholesterolaemia in VaD

FOURIER, Further Cardiovascular Outcomes Research with PCSK-9 Inhibition in Subjects with Elevated Risk.

Prevention	Comment
What is the relationship between dementia onset and cholesterol level?	As cholesterol level increases is the relationship with disease onset linear?
Does lowering of 'normal' cholesterol levels influence the timing of dementia onset?	If so, when should this be done – middle age, late age? Is there an age cut-off above which cholesterol should not be lowered?
Does (the degree of) lowering of cholesterol levels influence the severity or progression of dementia in a pre-symptomatic population?	Does the concept of over excessive cholesterol lowering exist i.e. can 'too low' be detrimental?
Does timing of lipid-lowering therapy influence dementia onset or severity?	Does treatment started in midlife have a benefit over starting later in life?
Does targeting ideal CVH in midlife influence onset/severity of dementia [189]?	Further data are needed. A large RCT could answer this question but would be potentially prohibitively expensive.
Treatment of existing dementia	
Are statins of benefit in the treatment of VaD?	In order to accurately test efficacy, should people with mild cognitive impairment (at worst) be recruited to future trials?
Does targeting ideal CVH in an at-risk population in later life influence severity/progression of dementia?	FINGER showed that a multi-domain intervention can prevent deterioration in cognitive functioning over 2 years in those in later life [191]. Whether this effect is maintained, is unclear.
Lipid-lowering therapy	
Cholesterol level target versus class of lipid-lowering therapy	Is target lipid-lowering more or less effective than the choice of lipid-lowering agent?
Lipophilic versus hydrophilic statins	Lipophilic statins can cross the BBB, whilst hydrophilic statins cannot. Some authors advocate that lipophilic statins should be assessed above other statins in preventing/treating dementia due to this property [131].
Are PCSK-9 inhibitors safe and efficacious at reducing stroke in primary and/or secondary stroke prevention?	Concern surrounds the safety of PCSK-9 inhibitors in this population given their reported neurocognitive adverse effects. Although a recent press release stated that evolocumab was non-inferior to placebo regarding effects on cognition in a study involving FOURIER participants [197]. Further monitoring and trials are required to answer these questions.

was associated with lower risk of stroke, cognitive impairment and dementia in the Framingham Heart Study Offspring cohort [189]. The authors assessed whether ideal CVH scores at two time-points – recent (1998–2001) and remote (1991–1995) – were associated with 10-year risk of stroke ($n=2,631$), cognitive impairment and dementia ($n=1,364$). Higher remote ideal CVH was associated with a lower 10-year risk of incident stroke (HR 0.79, 95% CI 0.66–0.94), AD (HR 0.79, 95% CI 0.64–0.98), VaD (HR 0.61, 95% CI 0.39–0.95) and all-cause dementia (HR 0.80, 95% CI 0.67–0.97), whilst recent ideal CVH scores were associated with a lower 10-year risk of stroke (HR 0.80, 95% CI 0.67–0.95) and VaD (HR 0.49, 95% CI 0.30–0.81), but not AD and all-cause dementia. These differences probably highlight that stroke is a relatively acute sequela of poor CVH, whilst dementia is an insidious process developing over decades. Higher recent and remote ideal CVH scores were associated with less decline in visual memory, reasoning and verbal comprehension. Two other studies corroborate the data above that ideal CVH was associated with better neuropsychological outcomes in multiple cognitive areas [188,190]. In addition, higher recent ideal CVH was associated with less frontal brain atrophy but not global atrophy on MRI, whilst higher remote ideal CVH was associated with global but not frontal atrophy ($n=1,287$); no association was seen between ideal CVH at either time point and WMH volume [189].

The authors advocate promoting ideal CVH, targeting the middle-aged in particular, to protect against all forms of vascular brain injury [189].

A large Finnish RCT [191] included 2,654 people aged 60–77 years with a CAIDE [192] score of 6 or higher (comprising age, sex, education, systolic blood pressure, BMI, total cholesterol and physical activity [range 0–15])

and cognition at the mean or slightly lower than expected for age. Participants were randomized to either a 2-year multi-domain intervention (diet, exercise, cognitive training and monitoring of vascular risk) or control (general health advice). The primary outcome was mean change in cognition (neuropsychological test battery Z-scores) at 2 years. The estimated between group difference in the change in cognitive performance per year was 0.022 (95% CI 0.002–0.042, $p = 0.03$) in favour of the intervention. Therefore, a multi-domain intervention can improve or at least maintain cognition in an at-risk cohort in later life. The authors did not establish the contribution of the individual components of the multi-domain intervention to the effect seen overall [191].

On-going and future research possibilities

The European Society of Hypertension–Chinese Hypertension League–Stroke in Hypertension Optimal Treatment (ESH–CHL–SHOT) trial is a factorial design RCT with two different LDL cholesterol targets and three different blood pressure targets aiming to recruit 925 participants with hypertension and stroke or TIA within the preceding 1 to 6 months prior to randomization. Investigators are able to prescribe a statin of their choosing and cognition is assessed using the Montreal Cognitive Assessment (MoCA) as a secondary outcome over 4 years of follow-up [193].

Unanswered questions future research should seek to address are detailed in Box 1.

Conclusion

The associations between cholesterol and SVD, stroke, cognitive impairment and subsequent dementia are complex and as yet not fully understood. Given the ageing population, there is an urgent need to find treatments to prevent and treat dementia. In the absence of evidence to guide clinical practice, it seems appropriate to treat those patients with vascular risk factors that meet criteria for lipid-lowering therapy, in terms of primary and secondary prevention of cardiovascular and cerebrovascular events, in line with current guidelines [26,194]. As we have alluded to, management of the individual patient in a holistic manner according to their own vascular risk profile is recommended. Overall, there is no evidence to support lipid-lowering therapy in patients for the management of VaD or AD. Giving statins in later life to prevent or treat dementia is not recommended, whilst in midlife data are lacking. Although this paucity of randomized controlled evidence makes for challenging clinical decision making, it provides multiple opportunities for on-going and future research.

Author contribution

J.P.A. wrote the first draft. P.S. performed PODCAST analyses referred to here. All authors (J.P.A., P.S., N.S. and P.M.B.) reviewed and commented on the text.

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Competing interests

P.M.B. was chief investigator of the academic/non-commercial PODCAST trial that investigated the effect of intensive versus guideline lipid lowering in patients after stroke.

Abbreviations

ACE-R, Addenbrooke's Cognitive Examination-Revised; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; AF, atrial fibrillation; ApoB, apolipoprotein B; APOE, apolipoprotein E; ARIC, Atherosclerosis Risk in Communities; BBB, blood–brain barrier; BMI, body mass index; CAIDE, Finnish Cardiovascular Risk Factors, Aging and Dementia; CI, confidence interval; CMB, cerebral microbleeds; CT, computed tomography; CVD, cardiovascular disease; CVH, cardiovascular health; DM, diabetes mellitus; ESH–CHL–SHOT, European Society of Hypertension–Chinese Hypertension League–Stroke in Hypertension Optimal Treatment; HDL, high-density lipoprotein; HMGCoA, 3-hydroxy 3-methylglutaryl coenzyme A; HPS, Heart Protection Study; HR, hazard ratio; ICD-9, International Classification of Diseases-9; ICH, intracerebral haemorrhage; IS, ischaemic stroke; LDL, low-density lipoprotein; MI, myocardial infarction; MMSE, mini-mental state examination; MoCA, Montreal

Cognitive Assessment; MRI, magnetic resonance imaging; OSLER, Open-label Study of Long-term Evaluation against LDL Cholesterol; PCSK-9, proprotein convertase subtilisin-kexin type 9; PODCAST, Prevention Of Decline in Cognition After Stroke Trial; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; RCT, randomized controlled trial; ROCAS, Regression of Cerebral Artery Stenosis; RR, relative risk; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial; SVD, small vessel disease; TIA, transient ischaemic attack; TICS-m, Modified Telephone Interview for Cognitive Status; TNT, Treating to New Targets; VaD, vascular dementia; VISTA, Virtual International Stroke Trials Archive; WMH, white matter hyperintensities.

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