Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

Review Article

Hypercholesterolaemia and vascular dementia

Jason P. Appleton[1], Polly Scutt[1], Nikola Sprigg[1] and Philip M. Bath[1]

[1]Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham NG5 1PB, U.K.

Correspondence: Philip Bath (Philip.bath@nottingham.ac.uk)

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.

Received: 17 December 2016
Revised: 8 March 2017
Accepted: 21 March 2017

Version of Record published: 30 June 2017

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

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 ($\leqslant$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 $\geqslant$1 copy of apolipoprotein E (APOE) ε2 were associated with early dementia but not delayed dementia. The APOE ε2 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 $\geqslant$1 copy of APOE ε4 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

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

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]. Paraoxonase 1 is an A-esterase with peroxidase-like activity present on the surface of HDL, which decreases peroxidation of LDL. Levels of paraoxonase 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 ($\leqslant$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 ε2 and ε4 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 ε4 allele increases the risk of AD by 3 and 15 times in heterozygotes and homozygotes respectively [93]. The ε4 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 homoeostasis [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

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

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

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

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

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

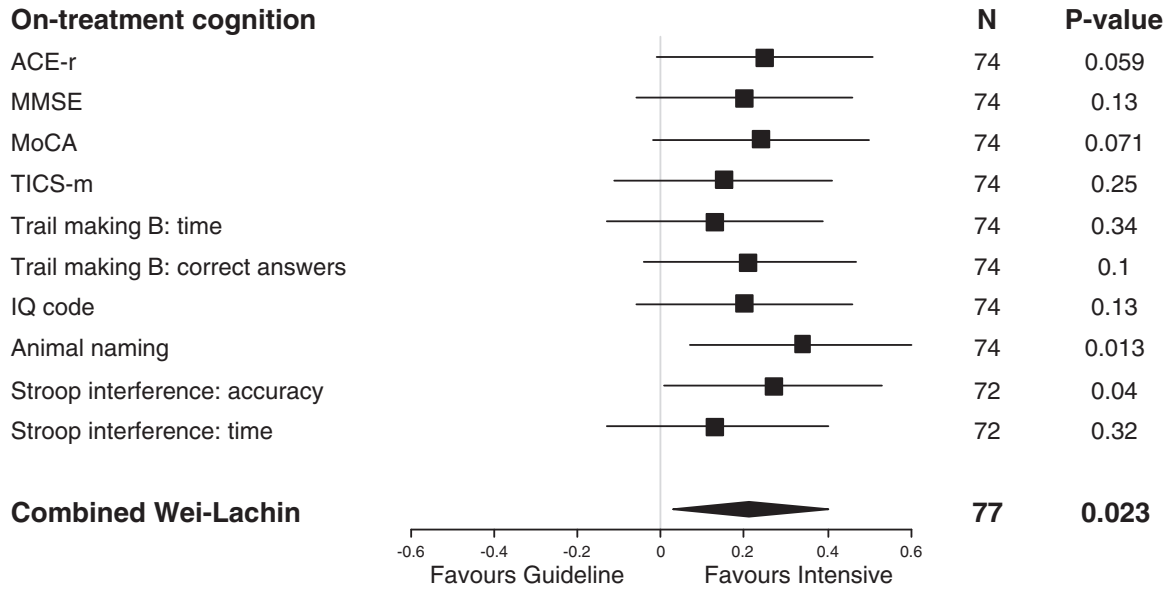

Figure 1. On-treatment global cognition: data from PODCAST

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).

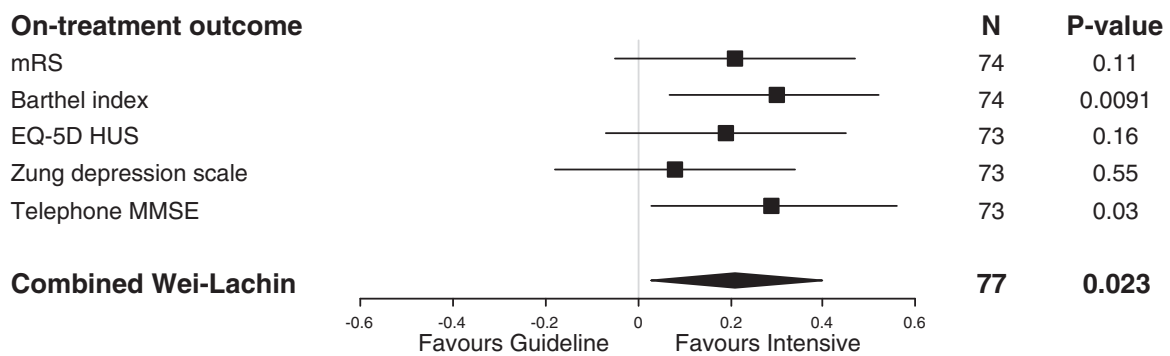

Figure 2. On-treatment global outcome: data from PODCAST

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

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

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/m^2; 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])

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

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.

Acknowledgements

P.M.B. is Stroke Association Professor of Stroke Medicine, and is a NIHR Senior Investigator.

Funding

PODCAST was funded jointly by Alzheimer's Society and The Stroke Association [grant number TSA 2008/09]; the British Heart Foundation (BHF RIGHT-2 trial) [grant number CS/14/4/30972 (to J.A.)]; and National Institute of Health Research Health Technology Assessment programme (NIHR HTA TARDIS trial) [grant number 10/104/24].

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.

References

1 National Institute for Health and Care Excellence (2006) Dementia: supporting people with dementia and their carers in health and social care., NICE clinical guideline 42, http://www.guidance.nice.org.uk/guidance/CG42
2 Burns, A. and Iliffe, S. (2009) Dementia. BMJ **338**, b75 CrossRef PubMed
3 Prince, M., Wimo, A., Guerchet, M., Ali, G.C., Wu, Y.T., Prina, M. et al. (2015), World alzheimer report 2015: The global impact of dementia – an analysis of prevalence, incidence, cost and trends, http://www.worldalzreport2015.org/downloads/world-alzheimer-report-2015-summary-sheet.pdf
4 McGuinness, B., Craig, D., Bullock, R. and Passmore, P. (2016) Statins for the prevention of dementia. Cochrane Database Syst. Rev. **4**, CD003160
5 Rizzi, L., Rosset, I. and Roriz-Cruz, M. (2014) Global epidemiology of dementia: Alzheimer's and vascular types. BioMed Res. Int. **2014**, 908915 CrossRef PubMed
6 Ji, Y., Shi, Z., Zhang, Y., Liu, S., Liu, S., Yue, W. et al. (2015) Prevalence of dementia and main subtypes in rural northern china. Dement. Geriatr. Cogn. Disord. **39**, 294–302 CrossRef PubMed
7 Mackay, J. and Mensah, G. (2004) The atlas of heart disease and stroke., WHO Library. Myriad Editions Ltd., Geneva, http://www.Who.Int/cardiovascular_diseases/resources/atlas/en/
8 Leys, D., Henon, H., Mackowiak-Cordoliani, M.-A. and Pasquier, F. (2005) Poststroke dementia. Lancet Neurol. **4**, 752–759 CrossRef PubMed
9 Ott, A., Slooter, A.J., van Harskamp, F., Witteman, J.C., Van Broeckhoven, C., van Duijn, C.M. et al. (1998) Smoking and risk of dementia and alzheimer's disease in a population-based cohort study: The rotterdam study. Lancet **351**, 1840–1843 CrossRef PubMed
10 Posner, H.B., Tang, M.X., Luchsinger, J., Lantigua, R., Stern, Y. and Mayeux, R. (2002) The relationship of hypertension in the elderly to ad, vascular dementia, and cognitive function. Neurology **58**, 1175–1181 CrossRef PubMed
11 Stewart, R. and Liolitsa, D. (1999) Type 2 diabetes mellitus, cognitive impairment and dementia. Diabet. Med. **16**, 93–112 CrossRef PubMed
12 Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K. and Brayne, C. (2014) Potential for primary prevention of alzheimer's disease: an analysis of population-based data. Lancet Neurol **13**, 788–794 CrossRef PubMed
13 Ostergaard, L., Sondergaard, T., Moreton, F., Hansen, M.B., Wardlaw, J.M., Dalkara, T. et al. (2015) Cerebral small vessel disease: capillary pathways to stroke and cognitive decline. J. Cereb. Blood Flow Metab. **38**, 302–325
14 Wardlaw, J., Smith, C. and Dichgans, M. (2013) Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. **12**, 483–497 CrossRef PubMed
15 Bailey, E.L., Smith, C., Sudlow, C.L. and Wardlaw, J.M. (2012) Pathology of lacunar ischemic stroke in humans–a systematic review. Brain Pathol. **22**, 583–591 CrossRef PubMed
16 Wiseman, S., Marlborough, F., Doubal, F., Webb, D.J. and Wardlaw, J. (2014) Blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-lacunar stroke and non-stroke: systematic review and meta-analysis. Cerebrovasc. Dis. **37**, 64–75 CrossRef PubMed
17 Stevenson, S.F., Doubal, F.N., Shuler, K. and Wardlaw, J.M. (2010) A systematic review of dynamic cerebral and peripheral endothelial function in lacunar stroke versus controls. Stroke **41**, e434–e442 CrossRef PubMed
18 Rost, N.S., Rahman, R.M., Biffi, A., Smith, E.E., Kanakis, A., Fitzpatrick, K. et al. (2010) White matter hyperintensity volume is increased in small vessel stroke subtypes. Neurology **75**, 1670–1677 CrossRef PubMed
19 Wardlaw, J.M., Lewis, S.C., Keir, S.L., Dennis, M.S. and Shenkin, S. (2006) Cerebral microbleeds are associated with lacunar stroke defined clinically and radiologically, independently of white matter lesions. Stroke **37**, 2633–2636 CrossRef PubMed
20 Debette, S. and Markus, H.S. (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ **341**, c3666 CrossRef PubMed
21 Vermeer, S.E., Longstreth, Jr, W.T. and Koudstaal, P.J. (2007) Silent brain infarcts: a systematic review. Lancet Neurol. **6**, 611–619 CrossRef PubMed
22 Bath, P.M. and Wardlaw, J.M. (2015) Pharmacological treatment and prevention of cerebral small vessel disease: a review of potential interventions. Int. J. Stroke **10**, 469–478 CrossRef PubMed
23 Manly, J.J., Bell-McGinty, S., Tang, M.X., Schupf, N., Stren, Y. and Mayeux, R. (2005) Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. Arch. Neurol. **62**, 1739–1746 CrossRef PubMed
24 Cordoliani-Mackowiak, M.A., Henon, H., Pruvo, J.P., Pasquier, F. and Leys, D. (2003) Post-stroke dementia: influence of hippocampal atrophy. Arch. Neurol. **60**, 585–590 CrossRef PubMed
25 Pohjasvaara, T., Mantyla, R., Aronen, H.J., Leskela, M., Salonen, O., Kaste, M. et al. (1999) Clinical and radiological determinants of prestroke cognitive decline in a stroke cohort. J. Neurol. Neurosurg. Psychiar. **67**, 742–748 CrossRef
26 Gorelick, P.B., Scuteri, A., Black, S.E., DeCarli, C., Greenberg, S.M., Iadecola, C. et al. (2011) Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke **42**, 2672–2713 CrossRef PubMed
27 Badjatia, N. and Rosand, J. (2005) Intracerebral hemorrhage. Neurologist **11**, 311–324 CrossRef PubMed
28 Poon, M.T., Fonville, A.F. and Al-Shahi Salman, R. (2014) Long-term prognosis after intracerebral haemorrhage: Systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry **85**, 660–667 CrossRef PubMed
29 Pantoni, L. (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. **9**, 689–701 CrossRef PubMed
30 Biffi, A., Halpin, A., Towfighi, A., Gilson, A., Busi, K., Rost, N. et al. (2010) Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. Neurology **75**, 693–698 CrossRef PubMed
31 Koennecke, H.C (2006) Cerebral microbleeds on mri: prevalence, associations, and potential clinical implications. Neurology **66**, 165–171 CrossRef PubMed

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

32 Zhu, Y.C., Chabriat, H., Godin, O., Dufouil, C., Rosand, J., Greenberg, S.M. et al. (2012) Distribution of white matter hyperintensity in cerebral hemorrhage and health aging. J. Neurol. **259**, 530–536 CrossRef PubMed
33 Biffi, A., Bailey, D., Anderson, C.D., Ayres, A.M., Gurol, E.M., Greenberg, S.M. et al. (2016) Risk factors associated with early vs delayed dementia after intracerebral hemorrhage. JAMA Neurol. **73**, 969–976 CrossRef PubMed
34 Biffi, A., Anderson, C.D., Jagiella, J.M., Schmidt, H., Kissela, B., Hansen, B.M. et al. (2011) Apoe genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurol. **10**, 702–709 CrossRef PubMed
35 Brouwers, H.B., Biffi, A., Ayres, A.M., Schwab, K., Cortellini, L., Romero, J.M. et al. (2012) Apolipoprotein e genotype predicts hematoma expansion in lobar intracerebral hemorrhage. Stroke **43**, 1490–1495 CrossRef PubMed
36 Gottesman, R. (2016) Dementia after intracerebral hemorrhage. JAMA Neurol. **73**, 916–917 CrossRef PubMed
37 Reitz, C., Tang, M.X., Luchsinger, J. and Mayeux, R. (2004) Relation of plasma lipids to alzheimer disease and vascular dementia. Arch. Neurol. **61**, 705–714 CrossRef PubMed
38 Sharrett, A.R., Patsch, W., Sorlie, P.D., Heiss, G., Bond, M.G. and Davis, C.E (1994) Associations of lipoprotein cholesterols, apoilpoproteins a-i and b, and triglycerides with carotid atherosclerosis and coronary heart disease. The atheroslerosis risk in communities (aric) study. Arterioscler. Thromb. **14**, 1098–1104 CrossRef PubMed
39 Breteler, M.M., Claus, J.J., Grobbee, D.E. and Hofman, A. (1994) Cardiovascular disease and distribution of cognitive function in elderly people: The rotterdam study. BMJ **308**, 1604–1608 CrossRef PubMed
40 Mulder, M. and Terwel, D. (1998) Possible link between lipid metabolism and cerebral amyloid angiopathy in alzheimer's disease: a role for high-density lipoproteins?. Haemostasis **28**, 174–194 PubMed
41 Matsuda, Y., Hirata, K., Inoue, N., Suematsu, M., Kawashima, S., Akita, H. et al. (1993) High-density lipoprotein reverses inhibitory effect of oxidized low-density lipoprotein on endothelium-dependent arterial relaxation. Circ. Res. **72**, 1103–1109 CrossRef PubMed
42 Cockerill, G.W., Rye, K.A., Gamble, J.R., Vadas, M.A. and Barter, P.J. (1995) High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler. Thromb. Vasc. Biol. **15**, 1987–1994 CrossRef PubMed
43 Witztum, J.L. (1994) The oxidation hypothesis of atherosclerosis. Lancet **344**, 793–795 CrossRef PubMed
44 Braughler, J.M. and Hall, E.D. (1992) Involvement of lipid peroxidation in cns injury. J. Neurotrauma **9**, S1–S7 CrossRef PubMed
45 Dantoine, T.F., Debord, J., Merle, L., Lacroix-Ramiandrisoa, H., Bourzeix, L. and Charmes, J.-P. (2002) Paraoxonase 1 activity: a new vascular marker of dementia?. Ann. N.Y. Acad. Sci. **977**, 96–101 CrossRef PubMed
46 Polidori, M.C., Mattioli, P., Aldred, S., Cecchetti, R., Stahl, W., Griffiths, H. et al. (2004) Plasma antioxidant status, immunoglobulin g oxidation and lipid peroxidation in demented patients: relevance to alzheimer disease and vascular dementia. Dement. Geriatr. Cogn. Disord. **18**, 265–270 CrossRef PubMed
47 Ryglewicz, D., Rodo, M., Kunicki, P.K., Bednarska-Makaruk, M., Graban, A., Lojkowska, W. et al. (2002) Plasma antioxidant activity and vascular dementia. J. Neurol. Sci. **203–204**, 195–197 CrossRef
48 Chan, L. (1992) Apolipoprotein b, the major protein component of triglyceride-rich and low density lipoproteins. J. Biol. Chem. **267**, 25621–25624
49 Elovson, J., Chatterton, J.E., Bell, G.T., Schumaker, V.N., Reuben, M.A., Puppione, D.L. et al. (1988) Plasma very low density lipoproteins contain a single molecule of apolipoprotein b. J. Lipid Res. **29**, 1461–1473
50 Anderson, T.J., Gregoire, J., Hegele, R.A., Couture, P., Mancini, G.B., McPherson, R. et al. (2013) 2012 update of the canadian cardiovascular society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can. J. Cardiol. **29**, 151–167 CrossRef
51 Goff, Jr, D.C., Lloyd-Jones, D.M., Bennett, G., Coady, S., D'Agostino, R.B., Gibbons, R. et al. (2014) 2013 acc/aha guideline on the assessment of cardiovascular risk: a report of the american college of cardiology/american heart association task force on practice guidelines. Circulation **129**, S49–S73 CrossRef PubMed
52 Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verschuren, M. et al. (2012) European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur. Heart J. **33**, 1635–1701 CrossRef PubMed
53 Gatz, M., Reynolds, C.A., Finkel, D., Pedersen, N.L. and Walters, E. (2010) Dementia in swedish twins: predicting incident cases. Behav. Genet. **40**, 768–775 CrossRef PubMed
54 Tynkkynen, J., Hernesniemi, J.A., Laatikainen, T., Havulinna, A.S., Sundvall, J., Leiviska, J. et al. (2016) Apolipoproteins and hdl cholesterol do not associate with the risk of future dementia and alzheimer's disease: The national finnish population study (finrisk). Age (Dordr) **38**, 465–473 CrossRef PubMed
55 Gouw, A.A., van der Flier, W.M., Fazekas, F., van Straaten, E.C., Pantoni, L., Poggesi, A. et al. (2008) Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: The leukoaraiosis and disability study. Stroke **39**, 1414–1420 CrossRef PubMed
56 Longstreth, Jr, W.T., Dulberg, C., Manolio, T.A., Lewis, M.R., Beauchamp, Jr, N.J., O'Leary, D. et al. (2002) Incidence, manifestations, and predictors of brain infarcts by serial cranial magnetic resonance imaging in the elderly: The cardiovascular health study. Stroke **33**, 2376–2382 CrossRef PubMed
57 van Dijk, E.J., Prins, N.D., Vrooman, H.A., Hofman, A., Koudstaal, P.J. and Breteler, M.M. (2008) Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam scan study. Stroke **39**, 2712–2719 CrossRef PubMed
58 Longstreth, Jr, W.T., Arnold, A.M., Beauchamp, Jr, N.J., Manolio, T.A., Lefkowitz, D., Jungreis, C. et al. (2005) Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The cardiovascular health study. Stroke **36**, 56–61 CrossRef PubMed
59 Jimenez-Conde, J., Biffi, A., Rahman, R., Kanakis, A., Butler, C., Sonni, S. et al. (2010) Hyperlipidaemia and reduced white matter hyperintensity volume in patients with ischemic stroke. Stroke **41**, 437–442 CrossRef PubMed
60 Vuorinen, M., Solomon, A., Rovio, S., Nieminen, L., Kareholt, I., Tuomilehto, J. et al. (2011) Changes in vascular risk factors from midlife to late life and white matter lesions: A 20-year follow-up study. Dement. Geriatr. Cogn. Disord. **31**, 119–125 CrossRef PubMed
61 Carmelli, D., Swan, G.E., Reed, T., Wolf, P.A., Miller, B.L. and DeCarli, C. (1999) Midlife cardiovascular risk factors and brain morphology in identical older male twins. Neurology **52**, 1119–1124 CrossRef PubMed
62 Bezerra, D.C., Sharrett, A.R., Matsushita, T., Gottesman, R.F., Shibata, D., Mosley, Jr, T.H. et al. (2012) Risk factors for lacune subtypes in the atherosclerosis risk in communities (aric) study. Neurology **78**, 102–108 CrossRef PubMed
63 Schilling, S., Tzourio, C., Dufouil, C., Zhu, Y., Berr, C., Alperovitch, A. et al. (2014) Plasma lipids and cerebral small vessel disease. Neurology **83**, 1844–1852 CrossRef PubMed
64 Park, K., Yasuda, N., Toyonaga, S., Yamada, S.M., Nakabayashi, H., Nakasato, M. et al. (2007) Significant association between leukoaraiosis and metabolic syndrome in healthy subjects. Neurology **69**, 974–978 CrossRef PubMed

65 Ridker, P.M., Buring, J.E., Cook, N.R. and Rifai, N. (2003) C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially health american women. Circulation **107**, 391–397 CrossRef PubMed
66 Satizabal, C.L., Zhu, Y.C., Mazoyer, B., Dufouil, C. and Tzourio, C. (2012) Circulating il-6 and crp are associated with mri findings in the elderly: The 3c-dijon study. Neurology **78**, 720–727 CrossRef PubMed
67 van Dijk, E.J., Prins, N.D., Vermeer, S.E., Vrooman, H.A., Hofman, A., Koudstaal, J. et al. (2005) C-reactive protein and cerebral small-vessel disease: The rotterdam scan study. Circulation **112**, 900–905 CrossRef PubMed
68 Schilling, S., DeStefano, A.L., Sachdev, P.S., Choi, S.H., Mather, K.A., DeCarli, C.D. et al. (2013) Apoe genotype and mri markers of cerebrovascular disease: a systematic review and meta-analysis. Neurology **81**, 292–300 CrossRef PubMed
69 Bae, J.H., Bassenge, E., Kim, Y.N., Kim, K.S., Lee, H.J., Moon, K.C. et al. (2001) Postprandial hypertriglyceridemia impairs endothelial function by enhanced oxidant stress. Atherosclerosis **155**, 517–523 CrossRef PubMed
70 Fernando, M.S., Simpson, J.E., Matthews, F., Brayne, C., Lewis, C.E., Barber, R. et al. (2006) White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. Stroke **37**, 1391–1398 CrossRef PubMed
71 Manktelow, B.N. and Potter, J.F (2009) Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst. Rev. **8**, CD002091
72 Amarenco, P., Labreuche, J., Lavallee, P. and Touboul, P.-J. (2004) Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke **35**, 2902–2909 CrossRef PubMed
73 Solomon, A., Kareholt, I., Ngandu, T., Wolozin, B., Macdonald, S.W., Winblad, B. et al. (2009) Serum total cholesterol, statins and cognition in non-demented elderly. Neurobiol. Aging **30**, 1006–1009 CrossRef PubMed
74 Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J. and Whitmer, R.A (2009) Midlife serum cholesterol and increased risk of alzheimer's and vascular dementia three decades later. Dement. Geriatr. Cogn. Disord. **28**, 75–80 CrossRef PubMed
75 Mielke, M.M., Zandi, P.P., Sjogren, M., Gustafson, D., Ostling, S., Steen, B. et al. (2005) High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology **64**, 1689–1695 CrossRef PubMed
76 Trompet, S., van Vliet, P., de Craen, A.J., Jolles, J., Buckley, B.M., Murphy, M.B. et al. (2010) Pravastatin and cognitive function in the elderly. Results of the prosper study. J. Neurol. **257**, 85–90 CrossRef PubMed
77 Kivipelto, M., Helkala, E.L., Laakso, M.P., Hanninen, T., Hallikainen, M., Alhainen, K. et al. (2002) Apolipoprotein e epilson4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life alzheimer disease. Ann. Intern. Med. **137**, 149–155 CrossRef PubMed
78 Skoog, I. (1998) Status of risk factors for vascular dementia. Neuroepidemiology **17**, 2–9 CrossRef PubMed
79 Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kareholt, I., Winblad, B. et al. (2005) Obesity and vascular risk factors at midlife and the risk of dementia and alzheimer disease. Arch. Neurol. **62**, 1556–1660 CrossRef PubMed
80 Jarvik, G.P., Wijsman, E.M., Kukull, W.A., Schellenberg, G.D., Yu, C. and Larson, E.B. (1995) Interactions of apolipoprotein e genotype, total cholesterol level, age, and sex in prediction of alzheimer's disease: a case-control study. Neurology **45**, 1092–1096 CrossRef PubMed
81 Notkola, I.L., Sulkava, R., Pekkanen, J., Erkjuntti, T., Ehnholm, C., Kivinen, P. et al. (1998) Serum total cholesterol, apolipoprotein e episilon 4 allele, and alzheimer's disease. Neuroepidemiology **17**, 14–20 CrossRef PubMed
82 Mainous, III, A.G., Eschenbach, S.L., Wells, B.J., Everett, C.J. and Gill, J.M (2005) Cholesterol, transferrin saturation, and the development of dementia and alzheimer's disease: results from an 18-year population-based cohort. Fam. Med. **37**, 36–42 PubMed
83 Mielke, M.M., Zandi, P.P., Shao, H., Waem, M., Ostling, S., Guo, X. et al. (2010) The 32-year relationship between cholesterol and dementia from midlife to late life. Neurology **75**, 1888–1895 CrossRef PubMed
84 Romas, S.N., Tang, M.X., Berglund, L. and Mayeux, R. (1999) Apoe genotype, plasma lipids, lipoproteins, and ad in community elderly. Neurology **53**, 517–521 CrossRef PubMed
85 Tan, Z.S., Seshadri, S., Beiser, A., Wilson, P.W., Kiel, D.P., Tocco, M. et al. (2003) Plasma total cholesterol level as a risk factor for alzheimer disease: The framingham study. Arch. Intern. Med. **163**, 1053–1057 CrossRef PubMed
86 Hayden, K.M., Zandi, P.P., Lyketsos, C.G., Khachaturian, A.S., Bastian, L.A., Charoonruk, G. et al. (2006) Vascular risk factors for incident alzheimer disease and vascular dementia: The cache county study. Alzheimer Dis. Assoc. Disord. **20**, 93–100 CrossRef PubMed
87 Moroney, J.T., Tang, M.-X., Berglund, L., Small, S., Merchant, C., Bell, K. et al. (1999) Low-density lipoprotein cholesterol and the risk of dementia with stroke. J. Am. Med. Assoc. **282**, 254–260 CrossRef
88 Kalmijn, S., Foley, D., White, L., Burchfield, C.M., Curb, J.D., Petrovitch, H. et al. (2000) Metabolic cardiovascular syndrome and risk of dementia in japanese-american elderly men. The honolulu-asia aging study. Arterioscler. Thromb. Vasc. Biol. **20**, 2255–2260 CrossRef PubMed
89 Strittmatter, W.J., Weisgraber, K.H., Huang, D.Y., Dong, L.M., Salvesen, G.S., Pericak-Vance, M. et al. (1993) Binding of human apolipoprotein e to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset alzheimer disease. Proc. Nat. Acad. Sci. U.S.A. **90**, 8098–8102 CrossRef
90 Naslund, J., Thyberg, J., Tjemberg, L.O., Wernstedt, C., Karlstrom, A.R., Bogdanovic, N. et al. (1995) Characterization of stable complexes involving apoilpoprotein e and the amyloid beta peptide in alzheimer's disease brain. Neuron **15**, 219–228 CrossRef PubMed
91 Wisniewski, T., Lalowski, M., Golabek, A., Vogel, T. and Frangione, B. (1995) Is alzheimer's disease an apolipoprotein e amyloidosis?. Lancet **345**, 956–958 CrossRef PubMed
92 Hardy, J. and Selkoe, D.J. (2002) The amyloid hypothesis of alzheimer's disease: progress and problems on the road to therapeutics. Science **297**, 353–356 CrossRef PubMed
93 Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R. et al. (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein e genotype and alzheimer disease. A meta-analysis. Apoe and alzheimer disease meta analysis consortium. J. Am. Med. Assoc. **278**, 1349–1356 CrossRef
94 Mahley, R.W. and Rall, Jr, S. (2000) Apolipoprotein e: far more than a lipid transport protein. Annu. Rev. Genomics Hum. Genet. **1**, 507–537 CrossRef PubMed
95 Beecham, G.W., Hamilton, K., Naj, A.C., Martin, E.R., Huentelman, M., Myers, A.J. et al. (2014) Genome-wide association meta-analysis of neuropathologic features of alzheimer's disease and related dementias. PLoS Genet **10**, e1004606 CrossRef PubMed
96 Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M.L. et al. (2009) Genome-wide association study identifies variants at clu and picalm associated with alzheimer's disease. Nat. Genet. **41**, 1088–1093 CrossRef PubMed
97 Meng, Y., Lee, J.H., Cheng, R., St George-Hyslop, P., Mayeux, R. and Farrer, L.A. (2007) Association between sorl1 and alzheimer's disease in a genome-wide study. Neuroreport **18**, 1761–1764 CrossRef PubMed
98 Dietschy, J.M. and Turley, S.D. (2001) Cholesterol metabolism in the brain. Curr. Opin. Lipidol. **12**, 105–112 CrossRef PubMed

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

99 Lane, R.M. and Farlow, M.R. (2005) Lipid homeostasis and apolipoprotein e in the development and progression of alzheimer's disease. J. Lipid Res. **46**, 949–968 CrossRef PubMed

100 Lutjohann, D., Papassotiropoulos, A., Bjorkhem, I., Locatelli, S., Bagli, M., Oehring, R.D. et al. (2000) Plasma 24s-hydroxycholesterol (cerebrosterol) is increased in alzheimer and vascular demented patients. J. Lipid Res. **41**, 195–198 PubMed

101 Reiss, A.B., Siller, K.A., Rahman, M.M., Chan, E.S., Ghiso, J. and de Leon, M.J. (2004) Cholesterol in neurologic disorders of the elderly: stroke and alzheimer's disease. Neurobiol. Aging **25**, 977–989 CrossRef PubMed

102 Wu, C.W., Liao, P.C., Lin, C., Kuo, C.J., Chen, S.T., Chen, H.I. et al. (2003) Brain region-dependent increases in beta-amyloid and apolipoprotein e levels in hypercholesterolemic rabbits. J. Neural. Transm. (Vienna) **110**, 641–649 CrossRef PubMed

103 Jendroska, K., Poewe, W., Daniel, S.E., Pluess, J., Iwerssen-Schmidt, H., Paulsen, J. et al. (1995) Ischemic stress induces deposition of amyloid beta immunoreactivity in human brain. Acta Neuropathol **90**, 461–466 CrossRef PubMed

104 Riekse, R.G., Leverenz, J.B., McCormick, W., Bowen, J.D., Teri, L., Nochlin, D. et al. (2004) Effect of vascular lesions on cognition in alzheimer's disease: A community-based study. J. Am. Geriatr. Soc. **52**, 1442–1448 CrossRef PubMed

105 Leppala, J.M., Virtamo, J., Fogelholm, R., Albanes, D. and Heinonen, O.P (1999) Different risk factors for different stroke types: association of blood pressure, cholesterol, and antioxidants. Stroke **30**, 2535–2540 CrossRef PubMed

106 Zhang, X., Patel, A., Horibe, H., Wu, Z., Barzi, F., Rodgers, A. et al. (2003) Cholesterol, coronary heart disease, and stroke in the asia pacific region. Int. J. Epidemiol. **32**, 563–572 CrossRef PubMed

107 Kurth, T., Everett, B.M., Buring, J.E., Kase, C.S., Ridker, P.M. and Gaziano, J.M. (2007) Lipid levels and the risk of ischemic stroke in women. Neurology **68**, 556–562 CrossRef PubMed

108 Bots, M.L., Elwood, P.C., Nikitin, Y., Salonen, J.T., Freire de Concalves, A., Inzitari, D. et al. (2002) Total and hdl cholesterol and risk of stroke. Eurostroke: a collaborative study among research centres in europe. J. Epidemiol. Commun. Health **56** (Suppl 1), i19–i24 CrossRef

109 Shaher, E., Chambless, L.E., Rosamond, W.D., Boland, L.L., Ballantyne, C.M., McGovern, P.G. et al. (2003) Plasma lipid profile and incident ischemic stroke: The atherosclerosis risk in communities (aric) study. Stroke **34**, 623–631 CrossRef PubMed

110 Horenstein, R.B., Smith, D.E. and Mosca, L. (2002) Cholesterol predicts stroke mortality in the women's pooling project. Stroke **33**, 1863–1868 CrossRef PubMed

111 Lindenstrom, E., Boysen, G. and Nyboe, J. (1994) Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: The copenhagen city heart study. BMJ **309**, 11–15 CrossRef PubMed

112 Sacco, R.L., Benson, R.T., Kargman, D.E., Boden-Albala, B., Tuck, C., Lin, I.F. et al. (2001) High-density lipoprotein cholesterol and ischemic stroke in the elderly: The northern manhattan stroke study. J. Am. Med. Assoc. **285**, 2729–2735 CrossRef

113 Psaty, B.M., Anderson, M., Kronmal, R.A., Tracy, R.P., Orchard, T., Fried, L.P. et al. (2004) The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: The cardiovascular health study. J. Am. Geriatr. Soc. **52**, 1639–1647 CrossRef PubMed

114 Bowman, T.S., Sesso, H.D., Ma, J., Kurth, T., Kase, C.S., Stampfer, M.J. et al. (2003) Cholesterol and the risk of ischemic stroke. Stroke **34**, 2930–2934 CrossRef PubMed

115 Freiberg, J.J., Tybjaerg-Hansen, A., Jensen, J.S. and Nordeestgaard, B.G. (2008) Nonfasting triglycerides and risk of ischemic stroke in the general population. J. Am. Med. Assoc. **300**, 2142–2152 CrossRef

116 Bansal, S., Buring, J.E., Rifai, N., Mora, S., Sacks, F.M. and Ridker, P.M. (2007) Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. J. Am. Med. Assoc. **298**, 309–316 CrossRef

117 Iso, H., Jacobs, Jr, D.R., Wentworth, D., Neaton, J.D. and Cohen, J.D (1989) Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N. Engl. J. Med. **320**, 904–910 CrossRef PubMed

118 Suh, I., Jee, S.H., Kim, H.C., Nam, C.M., Kim, I.S., Appel, L.J. et al. (2001) Low serum cholesterol and haemorrhagic stroke in men: Korea medical insurance corporation study. Lancet **357**, 922–925 CrossRef PubMed

119 Sturgeon, J.D., Folsom, A.R., Longstreth, Jr, W.T., Shahar, E., Rosamond, W.D. and Cushman, M. (2007) Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke **38**, 2718–2725 CrossRef PubMed

120 Bonaventure, A., Kurth, T., Pico, F., Barberger-Gateau, P., Ritchie, K., Stapf, C. et al. (2010) Triglycerides and risk of hemorrhagic stroke vs. ischemic vascular events: The three-city study. Atherosclerosis **210**, 243–248 CrossRef PubMed

121 Wieberdink, R.G., Poels, M.M., Vernooji, M.W., Koudstaal, P.J., Hofman, A., van der Lugt, A. et al. (2011) Serum lipids and the risk of intracerebral hemorrhage: The rotterdam study. Arterioscler. Thromb. Vasc. Biol. **31**, 2982–2989 CrossRef PubMed

122 Wang, X., Dong, Y., Qi, X., Huang, C. and Hou, L. (2013) Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke **44**, 1833–1839 CrossRef PubMed

123 Shor, R., Wainstein, J., Oz, D., Boaz, M., Matas, Z., Fux, A. et al. (2007) Low serum ldl cholesterol levels and the risk of fever, sepsis, and malignancy. Ann. Clin. Lab. Sci. **37**, 343–348 PubMed

124 Chrostek, L., Supronowicz, L., Panasiuk, A., Cylwik, B., Gruszewska, E. and Flisiak, R. (2014) The effect of the severity of liver cirrhosis on the level of lipids and lipoproteins. Clin. Exp. Med. **14**, 417–421 CrossRef PubMed

125 Labreuche, J., Deplanque, D., Touboul, P.J., Bruckert, E. and Amarenco, P. (2010) Association between change in plasma triglyceride levels and risk of stroke and carotid atherosclerosis: systematic review and meta-regression analysis. Atherosclerosis **212**, 9–15 CrossRef PubMed

126 Bilheimer, D.W., Grundy, S.M., Brown, M.S. and Goldstein, J.L (1983) Mevinolin stimulates receptor-mediated clearance of low density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Trans. Assoc. Am. Physicians **96**, 1–9 PubMed

127 Scandinavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The scandinavian simvastatin survival study (4s). Lancet **344**, 1383–1389 PubMed

128 Wassmann, S., Laufs, U., Baumer, A.T., Muller, K., Ahlbory, K., Linz, W. et al. (2001) Hmg-coa reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. Hypertension **37**, 1450–1457 CrossRef PubMed

129 Ruocco, A., Postiglione, A., Santillo, M., Seru, R., Avvedimento, E.V., Cuda, G. et al. (2002) New possible role of statins in age-related diseases. J. Am. Geriatr. Soc. **50**, 2099–2100 CrossRef PubMed

130 Comparato, C., Altana, C., Bellosta, S., Baetta, R., Paoletti, R. and Corsini, A. (2001) Clinically relevant pleiotropic effects of statins: drug properties or effects of profound cholesterol reduction?. Nutr. Metab. Cardiovas. Dis. **11**, 328–343

131 McGuinness, B., Craig, D., Bullock, R., Malouf, R. and Passmore, P. (2014) Statins for the treatment of dementia (review). Cochrane Database Syst. Rev. **4**, CD007514

132 Heart Protection Study Collaborative Group (2002) Mrc/bhf heart protection study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet **360**, 7–22 CrossRef PubMed

133 LaRosa, J.C., Grundy, S.M., Waters, D.D., Shear, C., Barter, P., Fruchart, J.C. et al. (2005) Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N. Engl. J. Med. **352**, 1425–1435 CrossRef PubMed
134 Amarenco, P. and Labreuche, J. (2009) Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. **8**, 453–463 CrossRef PubMed
135 Baigent, C., Blackwell, L., Emberson, J., Holland, L.E., Reith, C. et al. (2010) Efficacy and safety of more intensive lowering of ldl cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet **376**, 1670–1681 CrossRef PubMed
136 Amarenco, P., Bogousslavsky, J., Callahan, III, A., Goldstein, L.B., Hennerici, M., Rudolph, A.E. et al. (2006) High-dose atorvastatin after stroke or transient ischemic attack. N. Engl. J. Med. **355**, 549–559 CrossRef PubMed
137 Scheitz, J., MacIsaac, R.L., Abdul-Rahim, A., Siegerink, B., Bath, P., Endres, M. et al. (2016) Statins and risk of poststroke hemorrhagic complications. Neurology **86**, 1590–1596 CrossRef PubMed
138 McKinney, J.S. and Kostis, W.J (2012) Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke **43**, 2149–2156 CrossRef PubMed
139 Wong, W.B., Lin, V.W., Boudreau, D. and Devine, E.B. (2013) Statins in the prevention of dementia and alzheimer's disease: a meta-analysis of observational studies and an assessment of confounding. Pharmacoepidemiol. Drug Saf. **22**, 345–358 CrossRef PubMed
140 Song, Y., Nie, H., Xu, Y., Zhang, L. and Wu, Y. (2013) Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies. Geriatr. Gerontol. Int. **13**, 817–824 CrossRef PubMed
141 Swiger, K., Manalac, R., Blumenthal, R., Blaha, M. and Martin, S. (2013) Statins and cognition: a systematic review and meta-analysis of short and long term cognitive effects. Mayo Clin. Proc. **88**, 1213–1221 CrossRef PubMed
142 Giannopoulos, S., Katsanos, A.H., Kosmidou, M. and Tsivgoulis, G. (2014) Statins and vascular dementia: a review. J. Alzheimers Dis. **42**, S315–S320 PubMed
143 ten Dam, V.H., van den Heuvel, D.M., van Buchem, M.A., Westendorp, R.G., Bollen, E.L., Ford, I. et al. (2005) Effect of pravastatin on cerebral infarcts and white matter lesions. Neurology **64**, 1807–1809 CrossRef PubMed
144 Mok, V.C., Lam, W.W., Fan, Y.H., Wong, A., Ng, P.W., Tsoi, T.H. et al. (2009) Effects of statins on the progression of cerebral white matter lesion: Post hoc analysis of the rocas (regression of cerebral artery stenosis) study. J. Neurol. **256**, 750–757 CrossRef PubMed
145 Bath, P.M., Scutt, P., Blackburn, D., Ankolekar, S., Krishnan, K., Ballard, C. et al. (2016) Intensive versus guideline blood pressure and lipid lowering in patients with previous stroke: main results from the pilot 'prevention of decline in cognition after stroke trial' (podcast) randomised controlled trial. PLoS One **12**, e0164608 CrossRef
146 Scutt, P., Blackburn, D., Krishnan, K., Ballard, C., Burns, A., Ford, G.A. et al. (2015) Baseline characteristics, analysis plan and report on feasibility for the prevention of decline in cognition after stroke trial (podcast). Trials **16**, 509 CrossRef PubMed
147 Lachin, J. (2014) Applications of the wei-lachin multivariate one-sided test for multiple outcomes on possibly different scales. PLoS One **9**, e108784 CrossRef PubMed
148 Masse, I., Bordet, R., Deplanque, D., Al Khedr, A., Richard, F., Libersa, C. et al. (2005) Lipid lowering agents are associated with a slower cognitive decline in alzheimer's disease. J. Neurol. Neurosurg. Psychiatry **76**, 1624–1629 CrossRef PubMed
149 Bettermann, K., Arnold, A.M., Williamson, J., Rapp, S., Sink, K., Toole, J.F. et al. (2012) Statins, risk of dementia, and cognitive function: secondary analysis of the gingko evaluation of memory study. J. Stroke Cerebrovasc. Dis. **21**, 436–444 CrossRef PubMed
150 Winblad, B., Jelic, V., Kershaw, P. and Amatniek, J. (2007) Effects of statins on cognitive function in patients with alzheimer's disease in galantamine clinical trials. Drugs Aging **24**, 57–61 CrossRef PubMed
151 Sparks, D.L., Sabbagh, M.N., Connor, D.J., Lopez, J., Launer, L.J., Brown, P. et al. (2005) Atorvastatin for the treatment of mild to moderate alzheimer disease. Arch. Neurol. **62**, 753–757 CrossRef PubMed
152 Feldman, H.H., Doody, R.S., Kivipelto, M., Sparks, D.L., Waters, D.D., Jones, R.W. et al. (2010) Randomized controlled trial of atorvastatin in mild to moderate alzheimer disease: Leade. Neurology **74**, 956–964 CrossRef PubMed
153 Sano, M., Bell, K.L., Galasko, D., Galvin, J.E., Thomas, R.G., van Dyck, C.H. et al. (2011) A randomized, double-blind, placebo-controlled trial of simvastatin to treat alzheimer disease. Neurology **77**, 556–563 CrossRef PubMed
154 Simons, M., Schwarzler, F., Lutjohann, D., von Bergmann, K., Beyreuther, K., Dichgans, J. et al. (2002) Treatment with simvastatin in normocholesterolemic patients with alzheimer's disease: a 26-week randomized, placebo-controlled, double-blind trial. Ann. Neurol. **52**, 346–350 CrossRef PubMed
155 Ankolekar, S., Geeganage, C., Anderton, P., Hogg, C. and Bath, P.M. (2010) Clinical trials for preventing post stroke cognitive impairment. J. Neurol. Sci. **299**, 168–174 CrossRef PubMed
156 Suribhatla, S., Dennis, M.S. and Potter, J.F. (2005) A study of statin use in the prevention of cognitive impairment of vascular origin in the uk. J. Neurol. Sci. **229–230**, 147–150 CrossRef
157 Evans, M.A. and Golomb, B.A. (2009) Statin-associated adverse cognitive effects: Survey results from 171 patients. Pharmacotherapy **29**, 800–811 CrossRef
158 Orsi, A., Sherman, O. and Woldeselassie, Z. (2001) Simvastatin-associated memory loss. Pharmacotherapy **21**, 767–769 CrossRef
159 Wagstaff, L.R., Mitton, M.W., Arvik, B.M. and Doraiswamy, P.M. (2003) Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy **23**, 871–880 CrossRef
160 Zamrini, E., McGwin, G. and Roseman, J.M. (2004) Association between statin use and alzheimer's disease. Neuroepidemiology **23**, 94–98 CrossRef
161 Zandi, P.P., Sparks, D.L., Khachaturian, A.S., Tschanz, J., Norton, M., Steinberg, M. et al. (2005) Do statins reduce risk of incident dementia and alzheimer disease? The cache county study. Arch. Gen. Psychiatry **62**, 217–224 CrossRef
162 Richardson, K., Schoen, M., French, B., Umscheid, C.A., Mitchell, M.D., Arnold, S.E. et al. (2013) Statins and cognitive function: a systematic review. Ann. Intern. Med. **159**, 688–697 CrossRef
163 Kelley, B.J. and Glasser, S. (2014) Cognitive effects of statin medications. CNS Drugs **28**, 411–419 CrossRef
164 Ott, B.R., Daiello, L.A., Dahabreh, I.J., Springate, B.A., Bixby, K., Murali, M. et al. (2015) Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. J. Gen. Intern. Med. **30**, 348–358 CrossRef
165 Yaghi, S. and Elkind, M.S. (2015) Lipids and cerebrovascular disease: research and practice. Stroke **46**, 3322–3328 CrossRef
166 Lavigne, P.M. and Karas, R.H. (2013) The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. J. Am. Coll. Cardiol. **61**, 440–446 CrossRef
167 Bloomfield Rubins, H., Davenport, J., Babikian, V., Brass, L.M., Collins, D., Wexler, L. et al. (2001) Reduction in stroke with gemfibrozil in men with coronary heart disease and low hdl cholesterol: The veterans affairs hdl intervention trial (va-hit). Circulation **103**, 2828–2833 CrossRef

Clinical Science (2017) **131** 1561–1578
DOI: 10.1042/CS20160382

168 Jun, M., Foote, C., Lv, J., Neal, B., Patel, A., Nicholls, S.J. et al. (2010) Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet **375**, 1875–1884 CrossRef
169 Rockwood, K., Kirkland, S., Hogan, D.B., MacKnight, C., Merry, H., Verreault, R. et al. (2002) Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch. Neurol. **59**, 223–227 CrossRef
170 Jick, H., Zornberg, G.L., Jick, S.S., Seshadri, S. and Drachman, D.A. (2000) Statins and the risk of dementia. Lancet **356**, 1627–1631 CrossRef
171 Cannon, C.P., Blazing, M.A., Giugliano, R.P., McCagg, A., White, J.A., Theroux, P. et al. (2015) Ezetimibe added to statin therapy after acute coronary syndrome. N. Engl. J. Med. **372**, 2387–2397 CrossRef
172 McKenney, J.M., Koren, M.J., Kereiakes, D.J., Hanotin, C., Ferrand, A.C. and Stein, E.A (2012) Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, sar236553/regn727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J. Am. Coll. Cardiol. **59**, 2344–2353 CrossRef
173 Navarese, E.P., Kolodziejczak, M., Schulze, V., Gurbel, P.A., Tantry, U., Lin, Y. et al. (2015) Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia. Ann. Intern. Med. **163**, 40–51 CrossRef
174 Sabatine, M.S., Giugliano, R.P., Wiviott, S.D., Raal, F.J., Blom, D.J., Robinson, J. et al. (2015) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N. Engl. J. Med. **372**, 1500–1509 CrossRef
175 Robinson, J.G., Farnier, M., Krempf, M., Bergeron, J., Luc, G., Averna, M. et al. (2015) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N. Engl. J. Med. **372**, 1489–1499 CrossRef
176 Milionis, H., Barkas, F., Ntaios, G., Papavasileiou, V., Vemmos, K., Michel, P. et al. (2016) Proprotein convertase subtilisin kexin 9 (pcsk9) inhibitors to treat hypercholesterolemia: effect on stroke risk. Eur. J. Intern. Med. **34**, 54–57 CrossRef
177 De Caterina, R., Scarano, M., Lucisano, G., Palma, F., Tatasciore, A. and Marchioli, R. (2010) Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials. J. Am. Coll. Cardiol. **55**, 198–211 CrossRef
178 Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A. and D'Agostino, R.B. (2003) Lower cognitive function in the presence of obesity and hypertension: The framingham heart study. Int. J. Obesity **27**, 260–268 CrossRef
179 Francis, H. and Stevenson, R. (2013) The longer-term impacts of western diet on human cognition and the brain. Appetite **63**, 119–128 CrossRef
180 Rovio, S., Kareholt, I., Helkala, E.L., Viitanen, M., Winblad, B., Tuomelihto, J. et al. (2005) Leisure-time physical activity at midlife and the risk of dementia and alzheimer's disease. Lancet Neurol **4**, 705–711 CrossRef
181 Whitmer, R.A., Sidney, S., Selby, J., Johnston, S.C. and Yaffe, K. (2005) Midlife cardiovascular risk factors and risk of dementia in late life. Neurology **64**, 277–281 CrossRef
182 Yaffe, K., Blackwell, T., Kanaya, A.M., Davidowitz, N., Barrett-Connor, E. and Krueger, K. (2004) Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology **63**, 658–663 CrossRef
183 Lloyd-Jones, D.M., Hong, Y., Labarthe, D., Mozaffarian, D., Appel, L.J., Van Horn, L. et al. (2010) Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association's strategic impact goal through 2020 and beyond. Circulation **121**, 586–613 CrossRef
184 Dong, C., Rundek, T., Wright, C.B., Anwar, Z., Elkind, M.S. and Sacco, R.L. (2012) Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across white, blacks and hispanics. Circulation **125**, 2975–2984 CrossRef
185 Folsom, A.R., Yatsuya, H., Nettleton, J.A., Lutsey, P.L., Cushman, M., Rosamond, W.D. et al. (2011) Community prevalence of ideal cardiovascular health, by the american heart association definition, and relationship with cardiovascular disease incidence. J. Am. Coll. Cardiol. **57**, 1690–1696 CrossRef
186 Xanthakis, V., Enserro, D.M., Murabito, J.M., Polak, J.F., Wollert, K.C., Januzzi, J.L. et al. (2014) Ideal cardiovascular health: associations with biomarkers and subclinical disease and impact on incidence of cardiovascular disease in the framingham offspring study. Circulation **130**, 1676–1683 CrossRef
187 Wu, S., Huang, Z., Yang, X., Zhou, Y., Wang, A., Chen, L. et al. (2012) Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern chinese industrial city. Cir. Cardiovasc. Qual. Outcomes **5**, 487–493 CrossRef
188 Zhang, Q., Zhou, Y., Gao, X., Wang, C., Zhang, S., Wang, A. et al. (2013) Ideal cardiovascular health metrics and the risks of ischemic and intracerebral hemorrhagic stroke. Stroke **44**, 2451–2456 CrossRef
189 Pase, M.P., Beiser, A., Enserro, D., Xanthakis, V., Aparicio, H., Satizabal, C.L. et al. (2016) Association of ideal cardiovascular health with vascular brain injury and incident dementia. Stroke **47**, 1201–1206 CrossRef
190 Crichton, G.E., Elias, M.F., Davey, A. and Alkerwi, A. (2014) Cardiovascular health and cognitive function: The maine-syracuse longitudinal study. PLoS One **9**, e89317 CrossRef
191 Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R. et al. (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (finger): a randomised controlled trial. Lancet **385**, 2255–2263 CrossRef
192 Kivipelto, M., Ngandu, T., Laatikainen, T., Winblad, B., Soininen, H. and Tuomilehto, J. (2006) Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. **5**, 735–741 CrossRef
193 Zanchetti, A., Liu, L., Mancia, G., Parati, G., Grassi, G., Stramba-Badiale, M. et al. (2014) Blood pressure and ldl-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patients: design of the european society of hypertension-chinese hypertension league stroke in hypertension optimal treatment randomized trial. J. Hypertens **32**, 1888–1897 CrossRef
194 National Institute for Health and Care Excellence (2014), Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE Clinical Guideline 181. 2014, https://www.nice.org.uk/guidance/cg181/resources/cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-35109807660997
195 Seshadri, S. and Wolf, P.A. (2007) Lifetime risk of stroke and dementia: current concepts, and estimates from the framingham study. Lancet Neurol **6**, 1106–1114 CrossRef
196 Ivan, C., Seshadri, S., Beiser, A., Au, R., Kase, C., Kelly-Hayes, M. et al. (2004) Dementia after stroke: The framingham study. Stroke **35**, 1264–1268 CrossRef
197 Amgen. (2017), Amgen announces repatha® (evolocumab) significantly reduced the risk of cardiovascular events in fourier outcomes study. 2017, https://www.amgen.com/media/news-releases/2017/02/amgen-announces-repatha-evolocumab-significantly-reduced-the-risk-of-cardiovascular-events-in-fourier-outcomes-study/