Current Hypertension Reports (2019) 21: 70
https://doi.org/10.1007/s11906-019-0973-4

SECONDARY HYPERTENSION: NERVOUS SYSTEM MECHANISMS (M WYSS, SECTION EDITOR)

Blood Pressure and Statin Effects on Cognition: a Review

Mia Yang[1] · Jeff Williamson[1]

Published online: 26 July 2019

Abstract

Purpose of Review This is a review of available data on the effects of blood pressure and statins on cognition.

Recent Findings Recent randomized clinical trials have shown that intensive control of systolic blood pressure in older adults prevented the development of mild cognitive impairment (MCI) and the combined effects of MCI and probable dementia. Previous randomized clinical trials have suggested that statin use may prevent a decline in cognition; however, no randomized clinical trials have clearly shown evidence of statin's either positive or negative effect on cognition.

Summary Continued follow-up of SPRINT-MIND participants is crucial to evaluate the long-term effects of intensive systolic blood pressure control on the prevention of cognitive decline. A well-conducted and adequately powered randomized control trial is needed to evaluate the effect of statins on cognition, especially for primary prevention of the cognitive decline in aging.

Keywords Blood pressure · Statin · Hypertension · Cognition · Cognitive impairment · Dementia

Introduction

Alzheimer's disease and related dementias (ADRD) are a leading cause of mortality and of placement into nursing homes and assisted living facilities, affecting > 46 million individuals globally and 5.8 million persons in the USA [1]. This number is expected to double by 2050. In 2018, the direct costs associated with the care of Alzheimer's disease in the USA were approximately $239 billion, with just under half of this cost being borne by Medicare [1].

Until recently, there were no strongly supported strategies that would reliably delay or prevent dementia, including Alzheimer's disease. Since vascular disease and its risk factors are implicated in a large proportion of dementias, including Alzheimer's dementia [2, 3], this suggests that strategies targeting the vascular system may provide effective mechanisms to treat cognitive loss in aging.

Blood Pressure and Cognition

Blood Pressure Control with Potential Harm on Cognition

An important scientific and medical issue has been that some observational studies reported an inverse correlation between achieved BP and the rate of progression to dementia [4, 5]. While at some level, low blood pressure is a concern for perfusion of all major organs, it has been hypothesized that, in older adults, there is an even greater increased potential for cerebral hypoperfusion [5]. Observational data indicated that daytime systolic blood pressure (SBP) ≤ 128 mmHg (with no lower limit) was associated with greater Mini-Mental Status Exam (MMSE) score decrease (mean − 2.8, SD 3.8) after a median 9 months of follow-up [4]. Prospective observational studies have also suggested that low DBP may adversely impact brain health [6, 7]. Low diastolic pressure (< 70 mmHg) was associated with an adjusted hazard ratio of 2.1 (95% CI = 1.05–4.32) for dementia among participants ≥ 75 years of age [7]. Because of these published associations, an editorial in the Annals of Neurology [8] strongly cautioned that the

This article is part of the Topical Collection on *Secondary Hypertension: Nervous System Mechanisms*

✉ Mia Yang
miyang@wakehealth.edu

[1] Department of Internal Medicine, Section on Gerontology & Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

recommendation that "physicians should seek to keep their patients' SBP below 120mmHg is potentially quite dangerous."

Blood Pressure Control with Potential Benefit on Cognition

Despite some observational evidence to the contrary [4–7], randomized clinical trials of SBP lowering have not demonstrated adverse effects on cognition and hypertension remains the primary risk factor for small vessel ischemic disease and cortical white matter abnormalities [9] associated with dementia. Additionally, the majority of observational and randomized studies have suggested better control of SBP may reduce the risk for ADRDs. Even prior to the publication of the Systolic Blood Pressure Intervention Trial dementia results (SPRINT-MIND) [10••], the evidence has been stronger for a cognitive benefit from blood pressure lowering in middle age than in the elderly [11, 12, 13•]. Several meta-analyses of the effect of BP lowering on the incidence of dementia generally suggested a beneficial effect of BP lowering, but the results were statistically inconclusive and suffered from methodological limitations. For example, previous trials such as PROGRESS (Perindopril Protection Against Recurrent Stroke Study), SCOPE (Study on Cognition and Prognosis in the Elderly trial), SHEP (Systolic Hypertension in the Elderly Program), Syst-Eur (Systolic Hypertension in Europe trial), and HYVET (Hypertension in the Very Elderly Trial) considered very different BP treatment goals (generally > 150 mmHg) and so are not informative concerning BP control to levels below 130–140 mmHg. They also did not include treatment durations greater than 3 years or follow-up beyond 4 to 5 years. None included a robust neuropsychological assessment sufficient to adjudicate mild cognitive impairment (MCI) [14]. Although there was no difference in cognitive function (based on non-adjudicated neuropsychological test scores) between the intensive and standard BP lowering groups in the Action to Control Cardiovascular Disease in Diabetes (ACCORD) trial, magnetic resonance imaging (MRI) results showed that lower BP targets were associated with greater rates of decline in total brain volume but decreases in abnormal white matter lesions [15] in those assigned to the intensive-treatment arm.

As noted, the publication of the SPRINT cognitive impairment results have provided insights into a promising strategy for effective prevention of age-related cognitive impairment, including MCI, i.e., effectively treating hypertension. In SPRINT-MIND, 9361 individuals with a mean systolic blood pressure of 140 mmHg and increased cardiovascular risk, but without diabetes or advanced heart failure, were randomly assigned to either a systolic blood pressure target of less than 120 mmHg (intensive treatment) or one less than 140 mmHg (standard treatment) [16]. The primary cardiovascular disease outcomes included myocardial infarction, other acute coronary syndromes, stroke, heart failure, and cardiovascular death [16]. At 1 year, systolic blood pressure averaged 121.4 mmHg in the intensive-treatment group and 136.2 mmHg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.3 years due to a lower than expected rate of the primary outcomes in the intensive-treatment group (1.65% per year) compared with the standard-treatment group (2.19% per year; hazard ratio [HR] 0.75; 95% confidence interval [CI] of intensive to standard treatments, 0.64 to 0.89; $P < 0.001$) [16]. All-cause mortality was also reduced in the intensive-treatment group (HR 0.73; 95% CI 0.60 to 0.90; $p = 0.003$). Overall, there was no difference in adherence or all-cause serious adverse events between the 2 treatment groups, although higher rates of self-reported hypotension (2.4 intensive vs 1.4 standard), syncope (2.3 intensive vs 1.7 standard), acute kidney injury (4.1 intensive vs 2.5 standard), and electrolyte abnormalities (3.1 intensive vs 2.3 standard). Further follow-up has shown no increased incidence of end-stage renal disease in either group. Notably, the study did not report any injurious falls (2.2 intensive vs 2.3 standard) or clinical measured excess falls in orthostatic blood pressure [16].

SPRINT had specific pre-specified goals to test the effects of intensive SBP treatment on the incidence of adjudicated dementia or MCI and also tested the rate of decline in global, domain-specific cognitive function and CVD [17]. Characterizing the effects of intensive SBP lowering on multiple organ systems was a strength in the trial's design, but it was always recognized that earlier than expected positive or negative effects might be observed on the CVD outcomes, thus reducing the ability to follow-up on cognitive outcomes. Because SPRINT was stopped early due to strong CVD and mortality benefits, the final main study closeout visits that occurred before the planned follow-up sessions for the cognitive outcomes were completed. In the SPRINT cohort, the effect of intensive, 3.3-year BP lowering on dementia (including Alzheimer's disease) was not clear at that point, leading to additional follow-up and cognitive assessments beyond discontinuation of the intervention.

With a median of 5.5 years of follow-up, SPRINT-MIND demonstrated a positive effect of the 3.3-year intensive blood pressure treatment on lowering rates of mild cognitive impairment (MCI). Results were not conclusive for probable dementia [10••]. The estimated reduction in risk for probable dementia was in the same direction and of the same magnitude as for MCI (19%, $p = 0.008$), but the hazard ratio estimate for probable dementia was not statistically significant (17%, $p = 0.10$).

Consistent with this conclusion, the composite outcome of MCI or probable dementia (PD) demonstrated a 15% reduction (HR of 0.85, $p = 0.01$) [10••].

In SPRINT-MIND, the number of MCI events was 640, and the confidence interval for the estimated HR of 0.81 (19% reduction) excluded 1.0. Unfortunately, the lack of statistical significance for the probable dementia outcome has been interpreted as evidence of no effect, rather than as inconclusive due to low statistical power. However, persons with MCI are at much higher risk to become PD cases than those who have not. Some estimates are as high as 50% of persons with MCI to develop PD within 5 years. Because of the strong positive effect on MCI [10••] incidence, an extended follow-up of the SPRINT participants is proposed to assess the cohort for longer term impact on incident probable dementia.

Statin Therapy and Cognition

Clinicians often extrapolate findings from studies of young people or make practice decisions for older individuals based on their personal beliefs. The NIH and the FDA have raised requirements for older adults to be included in clinical trials, and an increasing number of trials focus exclusively on older adults [18]. While ample data exist for the use of statins in secondary prevention of cardiovascular disease (CVD) for older adults, limited information is available for primary prevention of cognitive impairment or physical disability [19]. In the National Health and Nutrition Examination Survey (NHANES), all adults 75 years and older without CVD had a 10-year risk score greater than 7.5%, the guideline threshold for considering statins for primary prevention [20]. Yet, relative hazards associated with elevated cholesterol diminish with age as reflected in risk estimators such as the Framingham risk score [21]. Following the release of the National Cholesterol Education Program guidelines in 2002 [22], the use of statins in patients 79 years and older for primary prevention rose steadily (8.8% in 2000, 34.1% in 2012), as it did for secondary prevention—in the absence of evidence for the former [23]. The 2018 cholesterol guidelines [24] again underscore the lack of evidence to support the use of statins in patients 75 years or older without CVD. If statins were shown to be effective for primary prevention in older adults 75 years or older, they would be cost-effective: could prevent 105,000 myocardial infarctions (MIs) and 68,000 coronary heart disease (CHD) deaths, at a cost of $25,200 per disability-adjusted life-year in up to an additional 8 million adults aged 75 to 94 years [25].

Possible Role of Statins in the Prevention of MCI and ADRD

The majority of ADRD patients display vascular pathology as a contributing factor to their dementia [26], making vascular cognitive impairment (VCI) the most common form of ADRD [27, 28]. As with ADRD, mild cognitive impairment (MCI) is prevalent in older populations and both are associated with incident disability, institutionalization, and death [29]. Clinical and subclinical CVD are associated with greater risk for vascular dementia and Alzheimer's disease [30]. Coronary artery calcium (CAC) scores, a reflection of atherosclerosis, are associated with higher incidence and shorter time to dementia in the Cardiovascular Health Study, further linking subclinical atherosclerosis to dementia [2, 31•, 32•] (Fig. 1). Midlife hypertension and dyslipidemia have been associated with abnormal white matter lesion development and dementia [33].

As with hypertension, observational studies have shown varying relationships between midlife cholesterol and cognitive impairment and dementia in later life [34, 35, 36]. The use of statins has been associated with a reduction in this risk [37–39]; however, in later life, associations vary substantially between statin use and dementia, as well as dementia-related brain abnormalities [40]. Some studies have found higher cholesterol associated with higher risk while others have reported either no relation or higher cholesterol being associated with a lower risk of developing dementia [40, 41, 42]. No relationship between low-density lipoprotein cholesterol (LDL-C) levels and the progression of abnormal brain white matter lesions has been identified [43, 44, 45]. Higher LDL-C levels have a well-known relationship to ischemic stroke and large cerebrovascular vessel injury, which contributes to cognitive impairment and dementia [46–48]. Statins are important in primary and secondary prevention of ischemic stroke, which is a significant contributor to dementia. Simvastatin was associated with a 20% reduction in stroke risk compared with placebo in the Heart Protection Study (HPS) [49]. Atorvastatin 80 mg vs 10 mg daily was associated with a 25% reduction in stroke risk in the Treating to New Targets (TNT) Study [50]. Two large meta-analyses also found that statin therapy significantly reduced stroke risk for each 1 mmol/L reduction in LDL-C [51, 52]. The Leukoaraiosis and Disability (LADIS) Study [43] ($n = 396$) found individuals with higher white matter lesion abnormalities on MRI had lower LDL-C, while the Rotterdam Scan Study [45] ($n = 668$) found individuals with carotid atherosclerosis and higher LDL-C had more incident lacunes. Incongruous findings between LDL-C levels and incident lacunes are similar to variance in the relation of hypertension to ADRD and are due to differing study designs, age of participants at enrollment (midlife vs later life), age at the time of cholesterol measurement, the rigor of dementia assessment, and length of follow-up. Existing evidence evaluating statin treatment in later life does not suggest an effect on cognitive

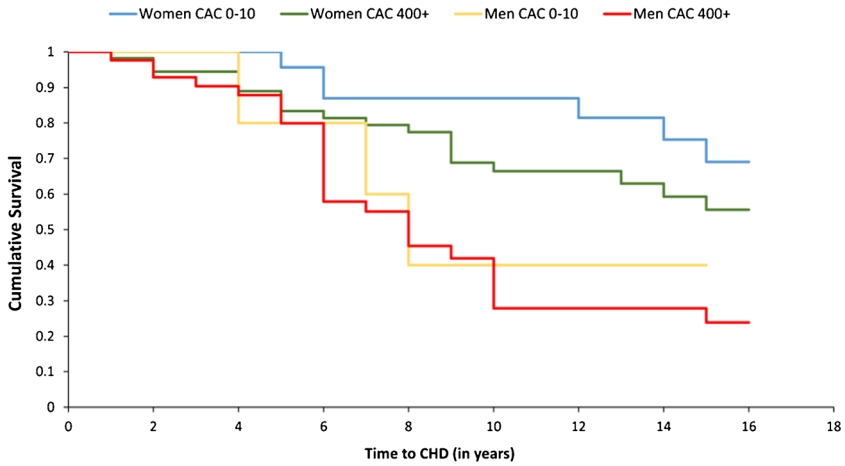

Fig. 1 Time to dementia by CAC score and sex

function [53]. The HPS showed that simvastatin had no effect using the modified Telephone Interview for Cognitive Status (TICS-m) [49]. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) showed pravastatin had no effect on change in the Mini–Mental State Examination (MMSE) [54]. Similarly, PROSPER ($n = 535$) and the Regression of Cerebral Artery Stenosis (ROCAS) ($n = 227$) sub-studies found statins did not alter white matter hyperintensity progression [55, 56]. However, the Prevention of Decline in Cognition After Stroke Trial (PODCAST) [57•] randomly assigned patients without dementia at 3 to 7 months after stroke to intensive (< 1.3 mmol/L LDL) vs guideline (< 3 mmol/L LDL) lipid-lowering therapy. Although there was no difference in the Addenbrooke's Cognitive Examination-Revised (ACE-R, the primary outcome) in these 83 participants at 24 months, intensive lipid-lowering therapy was associated with improvements in cognition (improved score in ACE-R at 6 months) [57•]. Although underpowered, PODCAST found in a post hoc analysis of multiple outcomes that intensive lipid-lowering therapy improved on-treatment global cognition [57•].

Cholesterol is relevant for brain health, since the brain is a lipid-rich organ. Elevated 24-hydroxycholesterol, an enzymatically oxidized by-product of brain cholesterol, signals alterations in brain cholesterol homeostasis associated with ADRD [58, 59]. The apolipoprotein E (APOE) protein involved in brain cholesterol transport, aggregation, and clearance of amyloid-β peptide is associated with Alzheimer's disease [60–62]. The amyloid cascade hypothesis suggests that an imbalance between production and clearance of amyloid-β contributes to ADRD [63]. Presence of the APOE $\varepsilon 4$ allele increases the risk of Alzheimer's disease many fold [64], and the $\varepsilon 4$ allele is associated with a risk of atherosclerosis and higher LDL-C [65]. However, the risk for Alzheimer's disease from treatable CVD risk factors—elevated total cholesterol level and blood pressure—appears greater than from the $\varepsilon 4$ allele alone [30].

Statins May Affect Global Brain Health Statins increase the integrity of the blood–brain barrier, improve endothelial cell function, and reduce platelet aggregation, smooth muscle cell proliferation, and inflammation [66, 67]. Some have raised concerns about the effect of lowering cholesterol on intramembranous lipid or intracellular cholesterol content in the brain [68, 69], but data from PCSK9 inhibitor trials and observational studies of individuals with loss of PCSK9 function demonstrated that very low serum LDL-C < 25 mg/dL, even lifelong, has no negative effect on neurocognitive function [70•, 71•].

Statin-Induced Cognitive Impairment Memory loss associated with statin use is a concern of participants reading FDA warnings on statins [72]. Randomized controlled trials, case reports, observational studies, and post marketing surveillance have also reported data regarding cognitive impairment by statins [73–78]. None of these symptoms have been shown to be serious, and most reversed within a few weeks of ceasing statin therapy. Three groups have systematically assessed the data and found no significant evidence that statins cause cognitive impairment. This includes a meta-analysis involving 14 randomized trials ($n = 27{,}643$), which found statins were not associated with cognitive impairment in cognitively normal participants or people with Alzheimer's disease [79–81]. A longitudinal study of older adults with normal cognition noted a slower rate of cognitive decline and better attention in statin users ($n = 1224$; mean age, 72.8 years) than in nonusers ($n = 2363$) [82]. A meta-analysis of only well-conducted studies suggested a potential beneficial role of long-term statin therapy with a 29% reduction in ADRD (hazard ratio (HR), 0.71; 95% CI, 0.61–0.82) [33].

Conclusions

In contrast, results from recent randomized clinical trials indicate that intensive blood pressure lowering improves cognitive decline. However, continued follow-up of SPRINT-MIND participants is crucial to evaluate the full spectrum of the effect of intensive SBP control on the prevention of dementia. The results for statin's effects on cognition are mixed in current literature and insufficient to recommend statin therapy for the prevention of cognitive decline or dementia. Methodologic challenges related to statin's effect on cognition [83] have not been a well-conducted randomized clinical trial, but this is exactly what is needed to answer the question of whether statins have beneficial or detrimental effects on cognition, i.e., a well-conducted and adequately powered randomized control trial to evaluate statin's effect on cognition.

Compliance with Ethical Standards

Conflict of Interest Dr. Williamson reports grants from the National Institutes of Health, during the conduct of the study; Dr. Yang declares no conflicts of interest relevant to this manuscript.

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

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. *2019 Alzheimer's disease facts and figures includes a special report on Alzheimer's detection in the primary care setting: connecting patients and physicians*. https://alz.org/media/Documents/alzheimers-facts-and-figures-2019-r.pdf. Accessed April 2, 2019.
2. Bos D, Vernooij MW, Ee R, et al. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. https://doi.org/10.1016/j.jalz.2014.05.1758
3. Iadecola C, Yaffe K, Biller J, et al. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. Hypertens (Dallas, Tex 1979). 2016;68(6):e67–94. https://doi.org/10.1161/HYP.0000000000000053.
4. Mossello E, Pieraccioli M, Nesti N, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015;175(4):578. https://doi.org/10.1001/jamainternmed.2014.8164.
5. Sabayan B, Westendorp RGJ. Blood pressure control and cognitive impairment—why low is not always better. JAMA Intern Med. 2015;175(4):586. https://doi.org/10.1001/jamainternmed.2014.8202.
6. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. Neurology. 2003;15(61):1667–72.
7. Qiu C, Winblad B, Fratiglioni L. Low diastolic pressure and risk of dementia in very old people: a longitudinal study. Dement Geriatr Cogn Disord. 2009;28:213–9. https://doi.org/10.1159/000236913.
8. Saper CB. How low can you go? Ann Neurol. 2015;78(5):665–6. https://doi.org/10.1002/ana.24530.
9. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney cause and logic of therapy epidemiological studies and clinical trials. Hypertension. 2005;46:200–4. https://doi.org/10.1161/01.HYP.0000168052.00426.65.
10. •• Williamson JD, Pajewski NM, Auchus AP, et al. Effect of Intensive vs standard blood pressure control on probable dementia. *JAMA*. 2019;321(6):553. https://doi.org/10.1001/jama.2018.21442 **With a median of 5.5 years of follow-up, SPRINT-MIND demonstrated a positive effect of the mean 3.3 years of intensive blood pressure control for lowering rates of mild cognitive impairment (MCI). Results were not conclusive for probable dementia. The estimated reduction in risk for probable dementia was in the same direction and of the same magnitude as for MCI (19%, $p = 0.008$), but the hazard ratio estimate for probable dementia was not statistically significant (17%, $p = 0.10$). Consistent with this conclusion, the composite outcome of MCI or PD demonstrated a 15% reduction (HR of 0.85, $p = 0.01$).**
11. Rouch L, Cestac P, Hanon O, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. CNS Drugs. 2015;29(2):113–30. https://doi.org/10.1007/s40263-015-0230-6.
12. Yaffe K, Vittinghoff E, Pletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. Circulation. 2014;129(15):1560–7. https://doi.org/10.1161/CIRCULATIONAHA.113.004798.
13. • Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA Neurol. 2017;74(10):1246. https://doi.org/10.1001/JAMANEUROL.2017.1658 **Midlife vascular risk factors are associated with increased risk of dementia in black and white ARIC Study participants. Vascular risk factors include the following: midlife smoking (HR, 1.41; 95% CI, 1.23–1.61), diabetes (HR, 1.77; 95% CI, 1.53–2.04), prehypertension (HR, 1.31; 95% CI, 1.14–1.51), and hypertension (HR, 1.39; 95% CI, 1.22–1.59). The HR for dementia for diabetes was almost as high as that for APOE ε4 genotype.**
14. Elias MF, Torres RV, Davey A. Clinical trials of blood pressure lowering and antihypertensive medication: is cognitive measurement state-of-the-art? *Am J Hypertens*. 2018;31(6):631–42. https://doi.org/10.1093/ajh/hpy033.
15. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med. 2014;174(3):324–33. https://doi.org/10.1001/jamainternmed.2013.13656.
16. SPRINT Research Group TSR, Wright JT, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16. https://doi.org/10.1056/NEJMoa1511939.
17. Ambrosius WT, Sink KM, Foy C, et al. The design and rationale of a multi-center clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials. 2014;11(5):532–46. https://doi.org/10.1177/1740774514537404.
18. Bernard MA, Clayton JA, Lauer MS. Inclusion across the lifespan. JAMA. 2018;320(15):1535. https://doi.org/10.1001/jama.2018.12368.

19. Singh S, Zieman S, Go AS, et al. Statins for primary prevention in older adults-moving toward evidence-based decision-making. J Am Geriatr Soc. 2018;66(11):2188–96. https://doi.org/10.1111/jgs.15449.
20. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk. Circulation. 2014;129(25 suppl 2):49–73. https://doi.org/10.1161/01.cir.0000437741.48606.98.
21. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–8. https://doi.org/10.1161/CIRCULATIONAHA.105.548206.
22. Bonow RO. Primary prevention of cardiovascular disease: a call to action. *Circulation*. 2002;106(25):3140–1. https://doi.org/10.1161/01.CIR.0000048067.86569.E1.
23. Johansen ME, Green LA. Statin use in very elderly individuals , 1999–2012 Rates of kidney transplantation from living and deceased donors for Blacks and Whites in the United States , 1998 to 2011. JAMA Intern Med. 2015;175(10):20–1. https://doi.org/10.1001/jamainternmed.2015.4302.Author.
24. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425–35. https://doi.org/10.1056/NEJMoa050461.
25. Odden MC, Pletcher MJ, Coxson PG, et al. The population impact and cost-effectiveness of statins for primary prevention in adults 75 and older in the United States. Ann Intern Med. 2015;162(8):533–41. https://doi.org/10.7326/M14-1430.
26. Smith EE. Clinical presentations and epidemiology of vascular dementia. Clin Sci. 2017;131(11):1059–68. https://doi.org/10.1042/CS20160607.
27. Snyder HM, Corriveau RA, Craft S, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease HHS public access. Alzheimers Dement. 2015;11(6):710–7. https://doi.org/10.1016/j.jalz.2014.10.008.
28. Petersen RC, Lopez O, Armstrong MJ, et al. Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on. Neurol ®. 2018;90:126–35. https://doi.org/10.1212/WNL.0000000000004826.
29. Aliberti MJR, Cenzer IS, Smith AK, et al. Risk assessment of adverse outcomes for older adults: the need to include both physical and cognitive elements. J Am Geriatr Soc. 2019;67(3):477–83. https://doi.org/10.1111/jgs.15683.
30. Kivipelto M, Helkala E-L, Laakso MP, et al. Apolipoprotein E ϵ4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002;137(3):149. https://doi.org/10.7326/0003-4819-137-3-200208060-00006.
31.• Kuller LH, Lopez OL, Becker JT, et al. Risk of dementia and death in the long-term follow-up of the Pittsburgh Cardiovascular Health STudy-Cognition Study. Alzheimer's Dement. 2016;12(2):170–83. https://doi.org/10.1016/j.jalz.2015.08.165 **More participants with normal cognition had coronary artery calcium scores < 10 compared to those with dementia or died.**
32.• Kuller LH, Lopez OL, Mackey RH, et al. Subclinical cardiovascular disease and death, dementia, and coronary heart disease in individuals age 80+. J Am Coll Cardiol. 2016;67(9):1013–22. https://doi.org/10.1016/j.jacc.2015.12.034 **Subclinical measure of cardiovascular disease, CAC, or coronary artery calcium is associated with the incidence of dementia in individuals age 80+. White women with low CAC scores had significantly decreased incidence of dementia.**
33. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. Mayo Clin Proc. 2013;88(11):1213–21. https://doi.org/10.1016/j.mayocp.2013.07.013.
34. Tan ZS, Seshadri S, Beiser A, Wilson Peter WF, Kiel DP, Tocco M, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. JAMA Intern Med. 2003;163:1053–7.
35. Mainous A. G; Eschenbach, Stephanie L; Wells, Brian J; Everett, Charles J; Gill JM. Cholesterol, transferrin saturation, and the development of dementia and Alzheimer's disease: results from an 18-year population-based cohort. Fam Med. 2005;37(1):36–42 https://fammedarchives.blob.core.windows.net/imagesandpdfs/fmhub/fm2005/January/Arch36.pdf.
36. Hayden KM, Zandi PP, Lyketsos CG, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County Study. Alzheimer Dis Assoc Disord. 2006;20(2):93–100. https://doi.org/10.1097/01.wad.0000213814.43047.86.
37. Solomon A, Sippola R, Soininen H, et al. Treatment and prevention lipid-lowering treatment is related to decreased risk of dementia: a population-based study (FINRISK). Neurodegener Dis. 2010;7:180–2. https://doi.org/10.1159/000295659.
38. Solomon A, Kåreholt I, Ngandu T, et al. Serum total cholesterol, statins and cognition in non-demented elderly. Neurobiol Aging. 2009;30:1006–9. https://doi.org/10.1016/j.neurobiolaging.2007.09.012.
39. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord. 2009;28:75–80. https://doi.org/10.1159/000231980.
40. Reitz C, Tang M-X, Schupf N, et al. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. Arch Neurol. 2010;67(12):1491–7. https://doi.org/10.1001/archneurol.2010.297.
41. Mielke MM, Zandi PP, Sjogren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005;64(10):1689–95. https://doi.org/10.1212/01.WNL.0000161870.78572.A5.
42. Reitz C, Tang M-X, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004;61(5):705–14. https://doi.org/10.1001/archneur.61.5.705.
43. Gouw AA, Van Der Flier WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the leukoaraiosis and disability study. Stroke. 2008;39(5):1414–20. https://doi.org/10.1161/STROKEAHA.107.498535.
44. Longstreth WT, Arnold AM, Beauchamp NJ, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the cardiovascular health study. Stroke. 2005;36(1):56–61. https://doi.org/10.1161/01.STR.0000149625.99732.69.
45. Van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences Rotterdam Scan Study. *Stroke*. 2008:2712–9. https://doi.org/10.1161/STROKEAHA.107.513176.
46. Sturgeon JD, Folsom AR, Longstreth WT, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007;38(10):2718–25. https://doi.org/10.1161/STROKEAHA.107.487090.
47. Bonaventure A, Kurth T, Pico F, et al. Triglycerides and risk of hemorrhagic stroke vs. ischemic vascular events: the Three-City Study. Atherosclerosis. 2010;210:243–8. https://doi.org/10.1016/j.atherosclerosis.2009.10.043.
48. Wieberdink RG, Poels MMF, Vernooij MW, et al. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam study. Arterioscler Thromb Vasc Biol. 2011;31(12):2982–9. https://doi.org/10.1161/ATVBAHA.111.234948.

49. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebocontrolled trial. *Lancet*. 2002;360(9326):7–22. https://doi.org/10.1016/S0140-6736(02)09327-3
50. LaRosa JC, Grundy SM, Waters DD, et al. *Intensive lipid lowering with atorvastatin in patients with stable coronary disease*. Vol 352.; 2005. www.nejm. Accessed May 14, 2019.
51. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009;8(5):453–63. https://doi.org/10.1016/S1474-4422(09)70058-4.
52. Cholesterol Treatment Trialists' Collaboration CTT. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet (London, England). 2019;393(10170):407–15. https://doi.org/10.1016/S0140-6736(18)31942-1.
53. Gorelick P, Black E, DeCarli C, et al. Vascular contributions to cognitive impairment and dementia: Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Surgery and Anesthesia. Stroke. 2011;42(9):2672–713. https://doi.org/10.1161/STR.0b013e3182299496.
54. Trompet S, Peter AE, Ae V, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol. 2010;257:85–90. https://doi.org/10.1007/s00415-009-5271-7.
55. Fu JH, Mok V, Lam W, et al. Effects of statins on progression of subclinical brain infarct. Cerebrovasc Dis. 2010;30(1):51–6. https://doi.org/10.1159/000313614.
56. Ten Dam VH, Van Den Heuvel DMJ, Van Buchem MA, et al. Effect of pravastatin on cerebral infarcts and white matter lesions. Neurology. 2005;64(10):1807–9. https://doi.org/10.1212/01.WNL.0000161844.00797.73.
57.• Bath PM, Scutt P, Blackburn DJ, et al. 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. 2017. https://doi.org/10.1371/journal.pone.0164608 **In patients with recent stroke and normal cognition, intensive blood pressure and lipid lowering were feasible and safe but did not alter cognition as measured by Addenbrooke's Cognitive Examination-Revised (ACE-R) over two years. Intensive lipid lowering therapy was associated with some secondary outcomes such as trail making A, modified Rankin Scale, and Euro-Qol Visual Analogue Scale, suggesting a need for further clinical trial.**
58. Lütjohann D, Papassotiropoulos A, Björkhem I, et al. *Plasma 24S-hydroxycholesterol (cerebrosterol) is increased in Alzheimer and vascular demented patients. Supplementary key words brain cholesterol Apolipoprotein E Cell Membrane Isotope Dilution-Mass Spectrometry Hippocampus Senile Plaques Depression Blood-Brain Barrier*. Vol 41.; 2000. www.jlr.org. Accessed May 23, 2019.
59. Dietschy JMTS. Cholesterol metabolism in the brain. Curr Opin Lipidol. 2001;12(2):105–12. https://doi.org/10.1007/BF02531730.
60. Strittmatter WJ, Weisgraber KH, Huang DY, et al. *Binding of human apolipoprotein e to synthetic amyloid ,B peptide: isoform-specific effects and implications for late-onset Alzheimer disease*. Vol 90.; 1993. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC47295/pdf/pnas01474-0198.pdf. Accessed May 23, 2019.
61. K. C, GK. W, S. L. APOE epsilon 4 influences the pathological phenotype of Alzheimer's disease by favouring cerebrovascular over parenchymal accumulation of A beta protein. Neuropathol Appl Neurobiol. 2003;29(3 PG-231-8):231–238. NS -.
62. Thal Rudolf D, Capetillo-Zarate E, Shultz C, et al. Apolipoprotein E co-localizes with newly formed amyloid b-protein (Ab) deposits lacking immunoreactivity against N-terminal epitopes of Ab in a genotype-dependent manner. Acta Neuropathol. 2005;110:459–71. https://doi.org/10.1007/s00401-005-1053-1.
63. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer 's disease. Science (80-). 2002;297(5580):353–357.
64. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer's disease HHS Public Access. 2017;74(10):1178–1189. doi:https://doi.org/10.1001/jamaneurol.2017.2188
65. Phillips MC. Apolipoprotein e isoforms and lipoprotein metabolism. IUBMB Life. 2014;66(9):616–23. https://doi.org/10.1002/iub.1314.
66. Yang D, Knight RA, Han Y, et al. Statins protect the blood brain barrier acutely after experimental intracerebral hemorrhage. J Behav Brain Sci. 2013;3(1):100–6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3583226/pdf/nihms434278.pdf. Accessed May 23, 2019.
67. Miida T, Hirayama S, Nakamura Y. Cholesterol-independent effects of statins and new therapeutic targets: ischemic stroke and dementia. J Atheroscler Thromb. 2011;11(5):253–64. https://doi.org/10.5551/jat.11.253.
68. Fan J, Donkin J, Wellington C. Greasing the wheels of Aβ clearance in Alzheimer's disease: the role of lipids and apolipoprotein e. BioFactors. 2009;35(3):239–48. https://doi.org/10.1002/biof.37.
69. Reiss AB, Siller KA, Rahman MM, Chan ESL, Ghiso J, De Leon MJ. Cholesterol in neurologic disorders of the elderly: stroke and Alzheimer's disease. Neurobiol Aging. 2004;25:977–89. https://doi.org/10.1016/j.neurobiolaging.2003.11.009.
70.• Mefford MT, Rosenson RS, Cushman M, et al. PCSK9 variants, LDL-cholesterol, and neurocognitive impairment: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. 2Circulation. 2018;137(12):1260–9. https://doi.org/10.1161/CIRCULATIONAHA.117.029785 **PCSK9 loss-of-function (LOF) variants result in lifelong low LDL-C. The REGARDS investigators investigated the association between PCSK9 LOF variants and neurocognitive impairment among African-American participants with the variants compared with those without the variants. Low PCSK9 levels and low LDL-C were not associated with neurocognitive effects in African Americans.**
71.• Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017;377(7):633–43. https://doi.org/10.1056/NEJMoa1701131 **Evolocumab is a PCSK9 inhibitor that has shown to reduce rate of cardiovascular events among patients with established cardiovascular disease. In a subgroup of patients from randomized, placebo-controlled trial of evolocumab added to statin therapy, cognitive function was prospectively assessed in 1204 patients followed for a median of 19 months. There were no significant between-group differences in evolocumab and placebo groups.**
72. FDA. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-important-safety-label-changes-cholesterol-lowering-statin-drugs. Published 2016.
73. Bettermann K, Arnold AM, Williamson J, et al. Statins, risk of dementia, and cognitive function: secondary analysis of the Ginkgo Evaluation of Memory Study. J Stroke Cerebrovasc Dis. 2012;21(6):436–44. https://doi.org/10.1016/j.jstrokecerebrovasdis.2010.11.002.
74. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy. 2009;29(7):800–11. https://doi.org/10.1592/phco.29.7.800.
75. Orsi A, Pharm D, Sherman O, Pharm D, Woldeselassie Z, Pharm D. Simvastatin-associated memory loss. Pharmacotherapy. 2001;21(6):767–9.

76. Wagstaff LR, Mitton MW, Arvik BML, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003;23(7):871–80. https://doi.org/10.1592/phco.23.7.871.32720.
77. E. Z, G. M, J.M. R. Association between statin use and Alzheimer's disease. Neuroepidemiology. 2004;23(1–2):94–8. https://doi.org/10.1159/000073981.
78. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? Arch Gen Psychiatry. 2005;62:217–24.
79. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD. Review statins and cognitive function. Ann Intern. 2013;159:688–97.
80. Kelley BJ, Glasser S. Cognitive effects of statin medications. CNS Drugs. 2014;28(5):411–9. https://doi.org/10.1007/s40263-014-0147-5.
81. Ott BR, Daiello LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. J Gen Intern Med. 2014;30(3):348–58. https://doi.org/10.1007/s11606-014-3115-3.
82. Steenland K, Zhao L, Goldstein FC, Levey AI. Statins and cognitive decline in older adults with normal cognition or mild cognitive impairment. https://doi.org/10.1111/jgs.12414
83. Giannopoulos S, Katsanos AH, Kosmidou M, Tsivgoulis G. Statins and vascular dementia: a review. J Alzheimer's Dis. 2014;42:315–20. https://doi.org/10.3233/JAD-132366.