Review Article

Effect of Combined Antihypertensive and Lipid-Lowering Therapies on Cognitive Function: A New Treatment Strategy?

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Risk factors for cardiovascular disease such as hypertension and hyperlipidemia are associated with cognitive decline. However, there is still no clear evidence that the use of antihypertensive or lipid-lowering therapy can prevent or delay cognitive decline or development of dementia. To provide a reference for clinical treatment, we analyzed the potential mechanisms of cognitive dysfunction induced by hypertension and hyperlipidemia, the clinical research and controversy of antihypertensive and lipid-lowering therapies on cognitive function, and the clinical value of combined antihypertensive and lipid-lowering therapy. It is currently believed that hypertension and elevated blood cholesterol levels in middle-aged people may be related to cognitive impairment or dementia in the elderly. Some studies suggest that intensive antihypertensive or lipid-lowering therapies are better than standard antihypertensive or lipid-lowering therapy, yet further tests are needed to confirm their effects on cognitive function. Actively controlling potential risk factors from middle age may be important for Alzheimer’s disease (AD) prevention.

1. Introduction

Cardiovascular risk factors including hypertension and hyperlipidemia are associated with cognitive decline and dysfunction [1, 2]. However, it is still controversial whether controlling cardiovascular risk factors can prevent cognitive decline or dementia, despite some speculations that altering blood pressure, blood lipid levels, and other cardiovascular risk factors will reduce the incidence of dementia in these populations [3]. However, there is still a lack of long-term and large-scale clinical randomized controlled trials to explore the relationship between blood pressure, lipid levels, and cognitive impairment. In this review we will focus on whether antihypertensive, lipid-lowering, or combined therapy can prevent or delay the occurrence of cognitive impairment.

It is well-accepted that elevated middle-aged blood pressure is associated with cognitive decline [4, 5], but it is not clear whether antihypertensive therapy can prevent cognitive decline. On the other hand, hyperlipidemia is also associated with cognitive impairment, but the results are still controversial. Studies have shown that the apolipoprotein E (APOE) ε4 allele and elevated total cholesterol and systolic blood pressure (SBP) in middle age are independent risk factors for AD, and the combined risk of elevated total cholesterol and elevated blood pressure seems to be higher than that of the APOEε4 allele [6]. We hope to explore whether combined antihypertensive and lipid-lowering drugs can play a synergistic role and further prevent or slow down the decline of cognitive function or development of dementia based on the existing literature.

2. Effect of Hypertension and Antihypertensive Therapy on Cognitive Function

2.1. Potential Mechanism of Hypertension on Cognitive Dysfunction

Hypertension causes changes in the vascular walls which can lead to hypoperfusion, ischemia and hypoxia, and cognition decline [7]. Previous studies demonstrated that cerebral ischemia led to the accumulation of amyloid precursor protein (APP) and beta-amyloid peptides (Aβ), in addition to stimulating the expression of presenilin, a protein involved in Aβ synthesis [8]. Hypertension may also lead to dysfunction in the blood-brain barrier, worsen
vascular endothelial injury, change cerebral white matter lesion volume, and decrease total brain volume including hippocampal volume and angiosclerosis, which can damage cognitive function [9–11]. Elevated levels of Alzheimer-associated neuronal thread protein (AD7c-NTP) were found in the urine of elderly hypertensive patients with lower cognitive function, and insulin resistance may be involved in the process as well [12]. In rat hypertension model, Okura and Higaki demonstrated that nicotinic acetylcholine receptors were related to rats’ learning and memory ability, and hypertension caused the decline in number of neurons. This study provided the experimental evidence for the effects of hypertension on the cognitive impairments [13] (see Figure 1).

2.2. Controversy: Can Antihypertensive Therapy Affect Cognitive Impairment? In 2011, the American Heart Association (AHA)/American Stroke Association (ASA) made the following recommendations for blood pressure management and cognitive function protection in high-risk populations of dementia based on six large clinical randomized trials and five meta-analyses [14]: (1) in people with a history of stroke, antihypertensive therapy can effectively prevent poststroke dementia (Class I, Level of Evidence B); (2) in middle and younger ages, antihypertensive therapy can prevent dementia (Class IIA recommendation, Level of Evidence B); (3) in the population over age 80, the effectiveness of antihypertensive therapy for the prevention of dementia is not clear (Class IIB, Level of Evidence B); and (4) antihypertensive therapy is necessary in people with cognitive impairment caused by cardiovascular disease (Class I recommendation, Level of Evidence A). These statements only provide general recommendations of the relationship between antihypertensive therapy and protection of cognitive function. They do not give further advice on drug selection, timing of treatment, or blood pressure control and are, therefore, not practical for clinicians.

Hypertension has recently been recognized as a risk factor of cognitive decline/dementia [15, 16]. It is currently believed that middle-aged hypertension is associated with cognitive impairment in the elderly and that elderly hypertension is associated with an increased risk of cognitive impairment [17–19]. The duration of hypertension and the trajectory of blood pressure (BP) over time seemed to significantly affect the risk of cognitive decline [20, 21]. However, another study showed that duration of arterial hypertension had no significant adverse effect on the Mini-Mental State Examination (MMSE), but age had a significant effect on cognitive impairment [22]. Early-onset hypertension in childhood and adolescence and a duration of hypertension over 25 years significantly increased the risk of dementia, with an increase in middle-aged BP combined with lower diastolic hypertension in the later years [20, 21, 23].

The 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension have little evidence of the beneficial effects of antihypertensive therapy on cognitive decline [24]. There is an urgent need to conduct trials to better determine if antihypertensive therapy can prevent cognitive decline or delay the potential effects of dementia when cognitive dysfunction already exists. However, an article published in PLoS Medicine in 2018 did not show any benefit from antihypertensive therapy in patients with mild-to-moderate AD [25]. Recent studies have demonstrated that short-term mild hypertension may be a protective factor for mild cognitive impairment in people over the age of 70 [26].

Therefore, it makes us think whether antihypertensive therapy can prevent or delay the occurrence of cognitive impairment. A previous longitudinal study found that subjects who developed dementia at age 79 to 85 had significantly higher blood pressures 15 years earlier [27]. Dementia may be the result of chronic and long-term high blood pressure, but not a transient process. Thereafter, the Honolulu-Asia aging study discovered that untreated hypertension was significantly associated with hippocampal atrophy, midlife cognitive decline, AD, and vascular dementia [28]. Interestingly, diastolic hypertension was more strongly associated with hippocampal atrophy than systolic hypertension [28]. In the HYVET study, a double-blind, placebo-controlled trial of antihypertensives in patients aged at least 80 years, it was demonstrated that a wider pulse pressure may indicate an increased risk for dementia, and it was also found that active treatment may change the relationship between diastolic hypertension and dementia [29]. Amazingly, a clinical trial showed that treating isolated systolic hypertension reduced Alzheimer’s dementia by 50% [30]. Therefore, active control of systolic hypertension from middle age is important for preventing AD [31].

Different types of antihypertensive drugs have different cognitive improvements. A network meta-analysis showed that antihypertensive treatment attenuates cognitive decline and prevents dementia, and indicated that these effects may differ from drug classes, among which angiotensin receptor blockers (ARBs) were the most effective [32]. Similarly, some researchers have shown that ARBs may have particular advantages [33]. Some researchers found that both calcium channel blockers (CCBs) and ARBs are independently associated with a decreased risk of dementia in older people [34]. In addition, antihypertensive adherence is an important factor impacting the odds of dementia, which is three times greater for those with moderate antihypertensive adherence compared to those with near perfect adherence [35].

2.3. Blood Pressure Control Prevents or Delays Cognitive Impairment: Intensive Treatment versus Conventional Treatment. Clinical research published in JAMA in 2019 holds the view that intensive systolic blood pressure control can prevent cognitive impairment [36]. The idea of reducing systolic blood pressure to 150 mmHg or lower has been controversial. One risk often mentioned is the possibility that hypotension and cerebral hypoperfusion have a negative impact on the brain. However, this trial did not observe this negative effect; specifically, these results indicated that after a
3.34-year median intervention period, blood pressure (BP) control did not impair cognitive perception during a total median follow-up of 5.11 years. In addition, there are some indications that may be beneficial to strengthen the control of BP. To the best of our knowledge, this is the first trial to demonstrate that an intervention can significantly reduce the incidence of mild cognitive impairment (MCI), which is a recognized risk factor for dementia. However, caution should be exercised in interpreting this result because MCI was not the primary cognitive outcome of the trial, and it is not clear what this effect might mean for the long-term morbidity of dementia. Although MCI increases the risk of dementia progression, this progression is uncertain, and it is possible for cognition to return to normal. A multicenter study in the United States showed a significant cognitive decline after 40 months of intensive BP control in patients with type 2 diabetes [37].

Information on all the clinical trials mentioned above, namely, research design, age at baseline, intervention, duration/follow-up, main results, and the number of participants, has been summarized in Table 1.

3. Effect of Hyperlipidemia and Statin Lipid-Lowering Therapy on Cognitive Function

3.1. Potential Mechanism of Hyperlipidemia on Cognitive Function. Previous studies using animal models showed that hypercholesterolemia is associated with increased Aβ peptide deposition, in addition to increased neurofibrillary tangles formation, neuroinflammation, dysfunction of cholinergic neurons, and cerebral microhemorrhages, which may contribute to cognitive decline [38, 39]. In addition, studies have shown that elevated circulating cholesterol levels are capable of compromising the integrity of the blood-brain barrier [40]. High-density lipoprotein (HDL) is an important carrier of cerebral cholesterol; low levels of HDL may cause increased sediment of Aβ proteins and induce inflammation [41]. In cases of hyperlipidemia, free-radical scavenger activity declines, which causes a large accumulation of lipid peroxide, accelerates the development and progression of atherosclerosis, and reduces cerebral blood flow, resulting in cerebral ischemia and hypoxia, brain tissue damage, and, ultimately, cognitive impairment [42] (see Figure 1).

3.2. Disputes: Can Statin Lipid-Lowering Therapy Affect Cognitive Impairment/Dementia? The relationship between blood lipids and cognition is very complex and controversial. Elevated blood cholesterol in middle-aged patients increases the risk of AD and vascular dementia and emphasizes the need to resolve the risk factors of dementia before middle age or the onset of potential diseases or symptoms [43–45]. However, a longitudinal Japanese study with a 3-year follow-up showed that the presence of dyslipidemia and higher educational levels are protective factors of cognitive decline [46]. Meanwhile some observational studies have found that the use of statins promotes cognitive decline [47], and in 2012 a review published by the Food and Drug Administration (FDA) showed that there is some limited evidence that statin use can lead to cognitive impairment [48, 49]. However, contrary to these observational studies, meta-analysis of randomized trials did not reveal any adverse effects of statins on cognition [50].

The midlife measures of total cholesterol were significant predictors of cognitive impairment [51], especially the association between increased HDL cholesterol levels and better cognitive performance [52–54]. In contrast, high LDL levels were associated with lower risk of cognitive impairment in the oldest elderly (aged 80 and older), but not in the
| Title                                                                 | Research design                                                                 | Age at baseline | Intervention | Duration/ follow-up | Main results                                                                                                                                                                                                 | Number of participants |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------|--------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: the HUNT study | Large, population-based health study                                             | NF              | None         | 27 years            | An inverse association between dementia and systolic blood pressure (BP) in individuals over the age of 60 years. Low diastolic pressure predicts the risk of dementia among very old people.                                           | 24,638                |
| Low diastolic pressure and risk of dementia in very old people: a longitudinal study | Dementia-free cohort                                                             | ≥81             | None         | 3 years             | Hypertension was associated with decreased LOAD risk while type 2 diabetes and heart disease were not. A history of stroke conferred >2-fold increased risk for LOAD. It does not suggest any benefit of nilvadipine as a treatment in a population spanning mild-to-moderate AD. | 422                   |
| The role of cardiovascular risk factors and stroke in familial Alzheimer disease | Longitudinal study of families with multiple members affected with LOAD          | 77.0 ± 9        | None         | 2003 to 2015        | Untreated hypertension was significantly associated with hippocampal atrophy, midlife cognitive decline, AD, and vascular dementia. A wider pulse pressure may indicate an increased risk for dementia, and it was also found that active treatment may change the shape of the relationship between DBP and dementia. | 6553                  |
| Nilvadipine in mild-to-moderate Alzheimer disease: a randomized controlled trial | Large-scale phase III investigator-driven clinical trial                          | >50             | Placebo or nilvadipine | 18 months        | Untreated hypertension was significantly associated with hippocampal atrophy, midlife cognitive decline, AD, and vascular dementia. A wider pulse pressure may indicate an increased risk for dementia, and it was also found that active treatment may change the shape of the relationship between DBP and dementia. | 511                   |
| Brain aging in very old men with type 2 diabetes: the Honolulu-Asia aging study | Longitudinal population study                                                    | 81.6 ± 5.0      | None         | 1965 to 1996        | Untreated hypertension was significantly associated with hippocampal atrophy, midlife cognitive decline, AD, and vascular dementia. A wider pulse pressure may indicate an increased risk for dementia, and it was also found that active treatment may change the shape of the relationship between DBP and dementia. | 3,734                 |
| Brain aging in very old men with type 2 diabetes: the Honolulu-Asia aging study | Double-blind, placebo-controlled trial of antihypertensives in patients with an untreated SBP of 160–199 mmHg | ≥80             | Placebo or active treatment | 2.2 years     | Untreated hypertension was significantly associated with hippocampal atrophy, midlife cognitive decline, AD, and vascular dementia. A wider pulse pressure may indicate an increased risk for dementia, and it was also found that active treatment may change the shape of the relationship between DBP and dementia. | 3845                  |
| Prevention of dementia in randomized double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial | Double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial | Placebo or active treatment | 2 years    |                                                                  | Valsartan (160 mg) is more effective than enalapril (20 mg) in reducing BP and improves some of the components of cognitive function, particularly episodic memory. Both calcium channel blockers (CCBs) and ARBs are independently associated with a decreased risk of dementia in older people. | 2418                  |
| Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension | Prospective, randomized, open-label, blinded-endpoint study                     | 61 to 80        | Valsartan or enalapril | 16 weeks        | Valsartan (160 mg) is more effective than enalapril (20 mg) in reducing BP and improves some of the components of cognitive function, particularly episodic memory. Both calcium channel blockers (CCBs) and ARBs are independently associated with a decreased risk of dementia in older people. | 144                   |
| Lower dementia risk with different classes of antihypertensive medication in older patients | Randomized controlled trial                                                      | 74.4 ± 2.5      | Different antihypertensive medications | 6 to 8 years    |                                                                                                                                                                                                                                                                                                                                 | 1951                  |
younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males [56]. However, a recent study showed that high total serum cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males [56]. However, a recent study showed that high total serum cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]. Improved cognition was associated with lower triglyceride only in males younger elderly (aged 65 to 79 years) [53, 55]...
Table 2: Studies into the effect of lipid-lowering therapy on cognitive function.

| Title | Research design | Age at baseline | Intervention | Duration/follow-up | Main results | Number of participants |
|-------|-----------------|-----------------|--------------|--------------------|--------------|------------------------|
| Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people | A cohort study of lipid-lowering agents (LLA) use and a case-control study of dementia in relation to LLA use | ≥65 | None | NF | In those younger than 80 years, the usage of lipid-lowering agents was associated with a lower risk of dementia and AD. The prevalence of probable AD in the cohort taking statins was 60–73% lower than the total patient population or compared with patients taking other medications typically used in the treatment of hypertension or cardiovascular disease. Individuals (≥50 years) who were prescribed statins had a substantially lower risk of developing dementia, independent of the presence or absence of untreated hyperlipidemia, or exposure to nonstatin LLAs. | 2305 |
| Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors | Cross-sectional study | ≥60 | None | 1996–1998 | | 57104 |
| Statins and the risk of dementia | Nested case-control study | ≥50 | None | NF | | 1364 |
| Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity: the Rotterdam study | Prospective, population-based Rotterdam study | ≥55 | None | 1990–1993 to 2005 | In the general population, the use of statins, but not of nonstatin cholesterol-lowering drugs, was associated with a lower risk of AD compared with the absence of cholesterol-lowering drug usage. Statin therapy was not associated with a decreased risk of dementia. Statin use and type were marginally associated with cognitive impairment. After adjusting for known variables that affect cognition, no association was observed. | 6992 |
| Statin use and the risk of incident dementia: the cardiovascular health study | Cohort study | ≥65 | None | NF | | 2798 |
| The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study | Cross-sectional study | ≥45 | None | 2003–2008 | | 24595 |
| The 32-year relationship between cholesterol and dementia from midlife to late life | Prospective population study | 38–60 | None | 32 years | Midlife cholesterol level was not associated with an increased risk of AD. | 1462 |
and significant lipid lowering in patients with cognitive decline not only may improve disease control but also could potentially slow the disease progression [71].

4.2. Combined Therapy versus Antihypertensive/Lipid-Lowering Therapy Alone. An article, which was published in Neurology in 2019 regarding elderly patients with moderate cardiovascular disease risk, showed that combined antihypertensive and lipid-lowering therapy has no effect on cognitive function decline [72]. It is important to note that Rosuvastatin did not show impairment of cognitive function in the HOPE-3 study, which is different from previous concerns that statins may cause memory loss. At the same time, it is suggested that patients with higher baseline BP and LDL levels have more benefit trends, and long-term blood pressure control may reduce the incidence of cognitive decline. However, the two inferences mentioned above need more clinical researches to confirm.

4.3. Which Patients Can Benefit from Combined Antihypertensive and Lipid-Lowering Therapy? Because of the controversy in the study, it is necessary to comprehensively consider some factors, such as age, baseline blood pressure, blood lipid and glucose levels, baseline cardiovascular risk, follow-up time, cognitive impairment at the time of enrollment, and the target value of blood pressure and lipid reduction. Gottesman et al. proposed an increasing number of midlife vascular risk factors that were significantly associated with elevated amyloid standardized uptake value ratios, which was not significant for late-life risk factors [7]. The main results from the PODCAST randomized controlled trial showed that, in patients with recent stroke and normal cognition, intensive BP and lipid lowering were feasible and safe but did not alter cognition over two years [67]. The small enrolled number, advanced age, and post-stroke status may account for these differences.

Therefore, we infer that people in their midlife may benefit from combined antihypertensive and lipid-lowering therapy. The FINGER study confirmed that, through comprehensive intervention including combined antihypertensive and lipid-lowering therapy, other vascular risk factors control, cognitive training, exercise, and diet, among others, can significantly reduce the risk of dementia after 2 years of follow-up [73]. This suggests that patients with mid-term intervention can benefit in their old age.

Besides early intervention, treatment compliance is also a key factor for the efficacy of combined antihypertensive and lipid-lowering therapy, especially for the elderly who have experienced MCI and memory and cognitive decline and also take medication regularly [74]. At the same time, elderly patients often suffer from a variety of diseases, and multiple drugs have become their routine. At present, the continuous emergence of single-pill compound preparations is lifting the burden of “double high” (hypertension and hyperlipidemia) patients, for example, a single-pill combination of amlodipine and atorvastatin, and a two-pronged combination of antihypertensive and lipid-lowering drugs [75, 76].

5. Prospect

The combination of antihypertensive and lipid-lowering therapy attracts much more attention in clinical research.
although there are still some controversies regarding the effects of antihypertensive and lipid-lowering therapy on cognitive function. Hypertension and hyperlipidemia may lead to the accumulation of APP and Aβ, and blood-brain barrier dysfunction. It is currently believed that hypertension and elevated blood cholesterol levels in middle age may be related to cognitive impairment or dementia in old age. Actively controlling potential risk factors from middle age may be important for AD prevention. Intensive antihypertensive or lipid-lowering therapy may be better than standard antihypertensive or lipid-lowering therapy, but further tests are needed to confirm its effect on cognitive function.

Most researches have shown that there are multiple factors influencing the effects of antihypertensive and lipid-lowering therapy on the cognitive function of hypertension and hyperlipidemia patients, such as age, baseline BP, cholesterol and blood glucose levels, baseline cardiovascular risk, follow-up time, cognitive impairment at the time of enrollment, target value of blood pressure reduction and lipid lowering, and treatment compliance. The early combination of antihypertensive and lipid-lowering therapies can improve cognitive function as early as possible, especially in patients with better treatment compliance. Further researches are required for better clinical practice guidance. At the same time, elderly patients often suffer from multiple diseases, and multiple drugs have become their routine treatment. In the future, further researches are needed to prove the effects of combination of antihypertensive and lipid-lowering therapies on the improvement of cognitive function. In addition, the development of new single-pill drugs that can comanage multiple risk factors such as hypertension and dyslipidemia will bring more benefits to elderly patients.

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] D. Knopman, L. L. Boland, T. Mosley et al., “Cardiovascular risk factors and cognitive decline in middle-aged adults,” *Neurology*, vol. 56, no. 1, pp. 42–48, 2001.

[2] A. Dregan, R. Stewart, and M. C. Guillford, “Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study,” *Age and Ageing*, vol. 42, no. 3, pp. 338–345, 2012.

[3] R. Peters, J. Peters, A. Booth, and K. J. Anstey, “Trajectory of blood pressure, body mass index, cholesterol and incident dementia: systematic review,” *The British Journal of Psychiatry*, vol. 216, no. 1, pp. 1–13, 2019.

[4] A. Singhmanoux and M. Marmot, “High blood pressure was associated with cognitive function in middle-age in the Whitehall II study,” *Journal of Clinical Epidemiology*, vol. 58, no. 12, pp. 1308–1315, 2005.

[5] C. Sierra, “Hypertension and the risk of dementia,” *Frontiers in Cardiovascular Medicine*, vol. 7, no. 5, 2020.

[6] M. Kivipelto, E.-L. Helkala, M. P. Laakso 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,” *Annals of Internal Medicine*, vol. 137, no. 3, pp. 149–155, 2002.

[7] R. F. Gottesman, A. L. C. Schneider, Y. Zhou et al., “Association between midlife vascular risk factors and estimated brain amyloid deposition,” *Journal of the American Medical Association*, vol. 317, no. 14, pp. 1443–1450, 2017.

[8] A. Salminen, A. Kauppinen, and K. Kaarniranta, “Hypoxia/ischemia activate processing of amyloid precursor protein: impact of vascular dysfunction in the pathogenesis of Alzheimer’s disease,” *Journal of Neurochemistry*, vol. 140, no. 4, pp. 536–549, 2017.

[9] I. Marinescu, P. O. Stovicek, D. Marinescu, and L. Mogoanu, “Potential biological mechanisms with prophylactic action in rapid cognitive impairment in late-onset Alzheimer’s disease,” *Frontiers in Clinical Drug Research - Alzheimer Disorders*, vol. 8, pp. 191–261, 2019.

[10] I. M. Nasrallah, N. M. Pajewski, A. P. Auchus et al., “Association of intensive vs standard blood pressure control with cerebral white matter lesions,” *Journal of the American Medical Association*, vol. 322, no. 6, pp. 524–534, 2019.

[11] A. Triantafyllou, J. P. Ferreira, M. Kobayashi et al., “Longer duration of hypertension and MRI microvascular brain alterations are associated with lower hippocampal volumes in older individuals with hypertension,” *Journal of Alzheimer’s Disease*, vol. 74, no. 1, pp. 227–235, 2020.

[12] Y. Zhang, Y. Li, R. Wang, G. Sha, H. Jin, and L. Ma, “Elevated urinary AD7c-NTP levels in older adults with hypertension and cognitive impairment,” *Journal of Alzheimer’s Disease*, vol. 74, no. 1, pp. 237–244, 2020.

[13] T. Okura and J. Higaki, “Calcium antagonists: current and future applications based on new evidence. Calcium channel blockers and single-pill combination,” *Clinical Calcium*, vol. 20, no. 1, pp. 61–68, 2010.

[14] P. B. Gorelick, A. Scuteri, S. E. Black et al., “Vascular contributions to cognitive impairment and dementia,” *Stroke*, vol. 42, no. 9, pp. 2672–2713, 2011.

[15] K. A. Walker, M. C. Power, and R. F. Gottesman, “Defining the relationship between hypertension, cognitive decline, and dementia: a review,” *Current Hypertension Reports*, vol. 19, no. 3, p. 24, 2017.

[16] C. Iadecola, K. Yaffe, J. Biller et al., “Impact of hypertension on cognitive function: a scientific statement from the American heart association,” *Hypertension*, vol. 68, no. 6, pp. e67–e94, 2016.

[17] J. M. Gabin, K. Tambs, I. Saltvedt, E. Sund, and J. Holmen, “Association between blood pressure and alzheimer disease measured up to 27 years prior to diagnosis: the hUNT study,” *Alzheimer’s Research & Therapy*, vol. 9, no. 1, p. 37, 2017.

[18] C. Qiu, B. Winblad, and L. Fratiglioni, “Low diastolic pressure and risk of dementia in very old people: a longitudinal study,” *Dementia and Geriatric Cognitive Disorders*, vol. 28, no. 3, pp. 213–219, 2009.

[19] G. Tosto, T. D. Bird, D. A. Bennett et al., “The role of cardiovascular risk factors and stroke in familial alzheimer disease,” *JAMA Neurology*, vol. 73, no. 10, pp. 1231–1237, 2016.

[20] G. E. Swan, D. Carmelli, and A. Larue, “Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults,” *Stroke*, vol. 29, no. 11, pp. 2334–2340, 1998.

[21] M. C. Power, E. J. T. Tchetgen, D. Sparrow et al., “Blood pressure and cognition: factors that may account for their
inconsistent association,” *Epidemiology (Cambridge, Mass.),* vol. 24, no. 6, 2013.

[22] J. Kapusta, T. M. Kidawa, M. Rynkowska-Kidawa et al., “Evaluation of frequency of occurrence of cognitive impairment in the course of arterial hypertension in an elderly population,” *Psychogeriatrics, 2020.*

[23] L. Glodzik, H. Rusinek, E. Pirraglia et al., “Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly,” *Neurobiology of Aging,* vol. 35, no. 1, pp. 64–71, 2014.

[24] B. Williams, G. Mancia, W. Spiering et al., “2018 ESC/ESH guidelines for the management of arterial hypertension,” *European Heart Journal,* vol. 39, no. 33, pp. 3021–3104, 2018.

[25] B. Lawlor, R. Segurado, S. Kennelly et al., “Nilvadipine in mild to moderate alzheimer disease: a randomised controlled trial,” *PLoS Medicine,* vol. 15, no. 9, Article ID e1002660, 2018.

[26] F. Wang, D. Li, L. Wang, J. Zhu, M. Zhao, and P. Lei, “Mild hypertension protects the elderly from cognitive impairment: a 7-year retrospective cohort study,” *Psychogeriatrics, 2020.*

[27] I. Skoog, L. Nilsson, G. Persson et al., “15-Year longitudinal study of blood pressure and dementia,” *The Lancet,* vol. 347, no. 9009, pp. 1141–1145, 1996.

[28] E. S. C. Korf, L. R. White, P. Scheltens, and L. J. Launer, “Brain aging in very old men with type 2 diabetes: the honolulu-asia aging study,” *Diabetes Care,* vol. 29, no. 10, pp. 2268–2274, 2006.

[29] R. Peters, N. Beckett, R. Fagard et al., “Increased pulse pressure linked to dementia: further results from the hypertension in the very elderly trial–HYVET,” *Journal of Hypertension,* vol. 31, no. 9, pp. 1868–1875, 2013.

[30] F. Forette, M.-L. Seux, J. A. Staessen et al., “Prevention of hypertension and Alzheimer’s disease: a systematic review and meta-analysis,” *Journal of Alzheimer’s Disease,* vol. 71, no. 1, pp. 1–10, 2019.

[31] N. L. Marsipillat, I. Macquin-Mavier, A.-I. Tropeano et al., “Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis,” *Journal of Hypertension,* vol. 31, no. 6, pp. 1073–1082, 2013.

[32] R. Fogari, A. Mugellini, A. Zoppi et al., “Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension,” *European Journal of Clinical Pharmacology,* vol. 59, no. 12, pp. 863–868, 2004.

[33] T. van Middelaar, L. A. van Vught, L. A. van Vught, E. P. M. van Charante et al., “Lower dementia risk with different classes of antihypertensive medication in older patients,” *Journal of Hypertension,* vol. 35, no. 10, pp. 2095–2101, 2017.

[34] Z. A. Marcum, R. L. Walker, B. L. Jones et al., “Patterns of antihypertensive and statin adherence prior to dementia: findings from the adult changes in thought study,” *BMC Geriatrics,* vol. 19, no. 1, p. 41, 2019.

[35] J. D. Williamson, N. M. Pajewski, A. P. Auchen et al., “Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial,” *Journal of the American Medical Association,* vol. 321, no. 6, pp. 553–561, 2019.

[36] J. D. Williamson, L. J. Launer, R. N. Bryan 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 Internal Medicine,* vol. 174, no. 3, pp. 324–333, 2014.

[37] F. Rihtarielli, E. Canepa, B. Marengo et al., “Cholesterol and Alzheimer’s disease: a still poorly understood correlation,” *IUBMB Life,* vol. 64, no. 12, pp. 931–935, 2012.

[38] C. Ulrich, M. Pirchl, and C. Humpel, “Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits,” *Molecular and Cellular Neuroscience,* vol. 45, no. 4, pp. 408–417, 2010.

[39] Z. Xue-Shan, P. Juan, W. Qi et al., “Imbalanced cholesterol metabolism in Alzheimer’s disease,” *Clinica Chimica Acta,* vol. 456, pp. 107–114, 2016.

[40] E. B. Button, J. Robert, T. M. Caffrey, J. Fan, W. Zhao, and C. L. Wellington, “HDL from an Alzheimer’s disease perspective,” *Current Opinion in Lipidology,* vol. 30, no. 3, pp. 224–234, 2019.

[41] M. E. Gómez-Gómez and S. C. Zapico, “Frailty, cognitive decline, neurodegenerative diseases and nutrition interventions,” *International Journal of Molecular Sciences,* vol. 20, no. 11, p. 2842, 2019.

[42] A. Solomon, I. Kareholt, T. Ngandu et al., “Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study,” *Neurology,* vol. 68, no. 10, pp. 751–756, 2007.

[43] A. Solomon, M. Kivipelto, B. Wolozin, J. Zhou, and R. A. Whitmer, “Midlife serum cholesterol and increased risk of Alzheimer’s and vascular dementia three decades later,” *Dementia and Geriatric Cognitive Disorders,* vol. 28, no. 1, pp. 75–80, 2009.

[44] K. J. Anstey, K. Ashby-Mitchell, and R. Peters, “Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis,” *Journal of Alzheimer’s Disease,* vol. 56, no. 1, pp. 215–228, 2017.

[45] W. Sritumusuk, M. Kabayama, Y. Gondo et al., “The importance of stroke as a risk factor of cognitive decline in community dwelling older and oldest peoples: the sonic study,” *BMC Geriatrics,* vol. 20, no. 1, p. 24, 2020.

[46] A. Solomon, R. Sippola, H. Soininen et al., “Lipid-lowering treatment is related to decreased risk of dementia: a population-based study (FINRISK),” *Neurodegenerative Diseases,* vol. 7, no. 1–3, pp. 180–182, 2010.

[47] Z. A. Marcum, J. P. Vande Griek, and S. A. Linnebur, “FDA drug safety communications: a narrative review and clinical considerations for older adults,” *The American Journal of Geriatric Pharmacotherapy,* vol. 10, no. 4, pp. 264–271, 2012.

[48] K. Richardson, M. Schoen, B. French et al., “Statins and cognitive function: a systematic review,” *Annals of Internal Medicine,* vol. 159, no. 10, pp. 688–697, 2013.

[49] Y. Song, H. Nie, Y. Xu, L. Zhang, and Y. Wu, “Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies,” *Geriatrics & Gerontology International,* vol. 13, no. 4, pp. 817–824, 2013.

[50] A. Solomon, I. Kåreholt, T. Ngandu et al., “Serum total cholesterol, statins and cognition in non-demented elderly,” *Neurobiology of Aging,* vol. 30, no. 6, pp. 1006–1009, 2009.

[51] G. E. Crichton, M. F. Elias, A. Davey, K. J. Sullivan, and R. A. Whitmer, “Higherhdl cholesterol is associated with better cognitive performance among Chinese elderly,” *Neurodegenerative Diseases,* vol. 137, p.104756, 2020.

[52] Y.-B. Lv, Z. X. Yin, C.-L. Chei 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,” *Journal of Internal Medicine,* vol. 20, no. 10, pp. 961–970, 2014.

[53] Z.-B. Lv, Z. X. Yin, C.-L. Chei et al., “Serum cholesterol levels within the high normal range are associated with better cognitive performance among Chinese elderly,” *The Journal of Nutrition, Health & Aging,* vol. 20, no. 3, pp. 280–287, 2016.

[54] G. E. Crichton, M. F. Elias, A. Davey, K. J. Sullivan, and M. A. Robbins, “Higher hdl cholesterol is associated with better cognitive function: the Maine-syracuse study,” *Journal of the International Neuropsychological Society,* vol. 20, no. 10, pp. 961–970, 2014.
[55] Z.-X. Yin, X.-M. Shi, V. Kraus et al., "High normal plasma triglycerides are associated with preserved cognitive function in Chinese oldest-old," Age and Ageing, vol. 41, no. 5, pp. 600–606, 2012.

[56] D. L. Waters, L. Vlietstra, C. Qualls, J. E. Morley, and B. Vellas, "Sex-specific muscle and metabolic biomarkers associated with gait speed and cognitive transitions in older adults: a 9-year follow-up," GeroScience, 2020.

[57] K. Rockwood, S. Kirkland, D. B. Hogan et al., "Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people," Archives of Neurology, vol. 59, no. 2, pp. 223–227, 2002.

[58] B. Wolozin, W. Killman, P. Rousseau et al., "Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors," Archives of Neurology, vol. 57, no. 10, pp. 1439–1443, 2000.

[59] H. Jick, G. Zornberg, S. Jick, S. Seshadri, and D. Drachman, "Statins and the risk of dementia," The Lancet, vol. 356, no. 9242, pp. 1627–1631, 2000.

[60] M. D. M. Haag, A. Hofman, B. H. C. Stricker, and M. M. B. Breteler, "Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity: The Rotterdam Study," Journal of Neurology, Neurosurgery & Psychiatry, vol. 80, no. 1, pp. 13–17, 2009.

[61] K. Samaras, S. R. Makkar, J. D. Crawford et al., "Effects of statins on memory, cognition, and brain volume in the elderly," Journal of the American College of Cardiology, vol. 74, no. 21, pp. 2554–2568, 2019.

[62] N. Geifman, R. D. Brinton, R. E. Kennedy et al., "Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer’s disease," Alzheimer’s Research & Therapy, vol. 9, no. 1, p. 10, 2017.

[63] T. D. Rea, J. C. Breitner, B. M. Psaty et al., "Statin use and the risk of incident dementia: the cardiovascular health study," Archives of Neurology, vol. 62, no. 7, pp. 1047–1051, 2005.

[64] S. P. Glasser, V. Wadley, S. Judd et al., "The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (regards) study," Clinical Cardiology, vol. 33, no. 5, pp. 280–288, 2010.

[65] M. M. Mielke, P. P. Zandi, H. Shao et al., "The 32-year relationship between cholesterol and dementia from midlife to late life," Neurology, vol. 75, no. 21, pp. 1888–1895, 2010.

[66] J. P. Appleton, P. Scutt, N. Sprigg, and P. M. Bath, "Hypercholesterolaemia and vascular dementia," Clinical Science, vol. 131, no. 14, pp. 1561–1578, 2017.

[67] P. M. Bath, P. Scutt, D. J. Blackburn 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, vol. 12, no. 1, Article ID e0164608, 2017.

[68] K. T. Lappegard, M. Pop-Purculeanu, W. van Heerde et al., "Improved neurocognitive functions correlate with reduced inflammatory burden in atrial fibrillation patients treated with intensive cholesterol lowering therapy," Journal of Neuroinflammation, vol. 10, p. 78, 2013.

[69] T. Kurata, V. Lukic, M. Kozuki et al., "Long-term effect of telmisartan on Alzheimer’s amyloid genesis in SHR-SR after tMCAO," Translational Stroke Research, vol. 6, no. 2, pp. 107–115, 2015.

[70] A. Dey, R. Bhattacharya, A. Mukherjee, and D. K. Pandey, "Natural products against Alzheimer’s disease: pharmaco-therapeutics and biotechnological interventions," Biotechnology Advances, vol. 35, no. 2, pp. 178–216, 2017.

[71] V. Dhikav and K. Anand, "Potential predictors of hippocampal atrophy in Alzheimer’s disease," Drugs & Aging, vol. 28, no. 1, pp. 1–11, 2011.

[72] J. Bosch, M. O’Donnell, B. Swaminathan et al., "Effects of blood pressure and lipid lowering on cognition: results from the hope-3 study," Neurology, vol. 92, no. 13, pp. e1435–e1446, 2019.

[73] A. Rosenberg, T. Ngandu, M. Rusanen et al., "Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: the finger trial," Alzheimers and Dement, vol. 14, no. 3, pp. 263–270, 2018.

[74] A. Coca, E. Agabiti-Rosei, R. Cifkova, A. J. Manolis, J. Redón, and G. Mancia, "The polypill in cardiovascular prevention: evidence, limitations and perspective—position paper of the European society of Hypertension," Journal of Hypertension, vol. 35, no. 8, pp. 1546–1553, 2017.

[75] V. Selak, C. Bullen, S. Stepien et al., "Do polypill lead to neglect of lifestyle risk factors? Findings from an individual participant data meta-analysis among 3140 patients at high risk of cardiovascular disease," European Journal of Preventive Cardiology, vol. 23, no. 13, pp. 1393–1400, 2016.

[76] V. I. Podzolkov, A. E. Bragina, and K. K. Osadchiy, "A fixed-dose lisinopril +amlodipine +rosuvastatin combination: prospects for its use in patients with hypertension and concomitant dyslipidemia," Terapevticheskii Arkhiv, vol. 89, no. 12, pp. 133–140, 2017.