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A review of hypertension and vascular cognitive impairment

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Abstract

Vascular cognitive impairment (VCI) is a cognitive dysfunction syndrome caused by various vascular-related risk factors, with hypertension regarded as one of the main pathogenic factors. Chronic hypertension can promote cognitive decline through abnormal microcirculation structure, white matter fiber injury, blood–brain barrier destruction, oxidative stress, and neuroinflammatory reaction, increasing the incidence of vascular dementia. To fully grasp the research status in this field, this study adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines for literature identification. A controlled vocabulary-based search strategy was employed to screen PubMed, Embase, Web of Science, and Cochrane Library for human studies published from January 2000 to March 2025, focusing on hypertension, VCI, dementia, antihypertensive treatment, and aerobic exercise intervention. Analysis of literature shows that angiotensin converting enzyme inhibitors and calcium channel blockers may play a neuroprotective role by increasing cerebral blood flow, reducing oxidative stress, and delaying amyloid deposition. However, these mechanisms and their clinical results are still controversial. Aerobic exercise, particularly moderate and high-intensity exercise, can continuously improve cerebral blood flow, promote neuroplasticity development, and enhance cognitive performance. However, significant limitations remain in the existing research. Thus, it is essential to conduct a systematic, integrated analysis and further strengthen standardized experimental design and personalization.

Keywords: Hypertension; Cognitive impairment; Antihypertensive therapy; Aerobic exercise

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1. Introduction

Vascular cognitive impairment (VCI) is a neurological dysfunction caused by the interaction of various vascular risk factors and cerebrovascular diseases. It is characterized by a progressive trajectory extending from mild cognitive impairment to post-stroke vascular dementia. The pathological mechanism of this disease includes both simple vascular injury and the compound mode of the superposition effect of neurodegenerative diseases, such as Alzheimer's disease. The key to effective prevention and treatment is prioritizing stroke prevention as the primary goal. It is imperative to comprehensively control vascular risk factors through systematic interventions and strengthen hypertension management. Hypertension is one of the common chronic diseases in China. With the acceleration of population aging, the prevalence of hypertension is rising, which has a more significant impact on the cognitive function of the elderly. Therefore, it is necessary to conduct early screening and take comprehensive prevention and control measures. Clinical research data have shown that regular exercise can reduce blood pressure levels, indicating the significance of auxiliary treatment. Although there is evidence that antihypertensive drugs positively improve cognitive function, their internal mechanism needs further discussion. This review aims to summarize the mechanisms of cognitive dysfunction associated with hypertension and to comprehensively evaluate the effects of aerobic exercise combined with multi-drug therapy on cognitive function. It offers theoretical insights and outlines a conceptual framework to support the clinical prevention and management of hypertension-related cognitive impairment.

2. Methodology

To enhance methodological transparency, we performed a narrative review in accordance with the key elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A systematic and comprehensive search was conducted across PubMed, Embase, Web of Science, and Cochrane Library to identify relevant articles published from January 2000 to March 2025. The search strategy employed a combination of Medical Subject Headings and free-text terms, such as "hypertension," "vascular cognitive impairment," "cognitive decline," "dementia," "cerebral small vessel disease," "lacunar infarct," "antihypertensive therapy," "angiotensin-converting enzyme inhibitors," "angiotensin receptor blockers," "beta-blockers," "calcium channel blockers," and "aerobic exercise." At the same time, the reference lists of pertinent articles and reviews were meticulously screened to uncover supplementary sources. The inclusion criteria encompassed (i) Peer-reviewed original research articles, systematic reviews, or meta-analyses that involve adult human populations, and (ii) Studies that address the association between hypertension and cognitive impairment, the mechanisms underlying VCI, or the impact of antihypertensive medications and/or aerobic exercise on cognitive outcomes. Case reports, conference abstracts, editorials, non-peer-reviewed publications, animal studies, and articles not available in English were excluded.

For the study selection and appraisal, one reviewer performed the initial screening of titles, abstracts, and full texts. In cases of uncertainty, eligibility was discussed and resolved in consultation with co-authors. Given the narrative nature of this review, a formal PRISMA protocol registration and quantitative meta-analysis were not undertaken. Nevertheless, we adhered to key PRISMA principles for transparency by prespecifying databases, timeframe, and search terms and defining explicit eligibility criteria. The included studies were qualitatively appraised with attention to study design, sample size, methodological rigor, risk of bias, and consistency of findings across populations.

3. Mechanisms of hypertension-induced cognitive impairment

3.1. Hypertension-induced structural alterations in cerebral vasculature

Preclinical studies have provided mechanistic evidence that sustained elevation of blood pressure induces adaptive structural changes in cerebral circulation.[1,2] These changes are characterized by a compensatory increase in cerebrovascular resistance, involving vascular remodeling of cerebral arteries and arterioles.[3] During this remodeling process, the ratio of vascular wall thickness to lumen diameter increases, leading to reduced wall stress and elevated segmental resistance.[4] Vascular smooth muscle cells may undergo reorganization. One pattern of reorganization involves cellular rearrangement that narrows the vascular lumen without altering the cross-sectional area of the vessel wall, a process known as eutrophic remodeling.[5] Another pattern involves hypertrophy or proliferation of vascular smooth muscle cells, which results in thickening of the vessel wall and further reduction in lumen diameter; this is referred to as hypertrophic remodeling.[6]

Hypertension can also lead to microvascular rarefaction, characterized by reduced vascular density, including decreased capillaries and small arterioles.[7] This phenomenon has been observed in both human patients and hypertensive animal models.[8] The underlying cause may be related to increased mechanical stress on the microvascular bed; however, the precise mechanisms remain incompletely understood.[9] Given that the white matter of the brain is relatively poorly vascularized, it is particularly susceptible to damage under hypertensive conditions. Typical microvascular pathologies associated with hypertension include hyaline deposition within vessel walls (lipohyalinosis) and fibrinoid necrosis of small vessels.[10] These changes are predominantly found in small arterioles within the white matter and may ultimately lead to the development of cerebral small vessel disease.[11] Cerebral small vessel disease represents a disruption of cerebrovascular structure and function that destabilizes cerebral homeostasis, impairs neuronal activity, and ultimately contributes to cognitive decline.[12]

The neuropathological features of Alzheimer's disease are characterized by the coexistence of vascular damage and the accumulation of β-amyloid (Aβ) protein.[13] Aβ aggregates into insoluble plaques primarily in the white matter and hippocampus. In addition to directly damaging neural tissue, Aβ promotes neurovascular injury by activating inflammatory responses, endothelial dysfunction, and oxidative stress. These processes accelerate atherosclerosis, induce neuronal apoptosis, and ultimately lead to cognitive decline. Multiple studies have shown that the duration of elevated blood pressure in hypertensive patients is correlated with the severity of arterial stiffness.[14] It is hypothesized that sustained hypertension contributes to vascular dysfunction and facilitates the deposition of Aβ within cerebral blood vessels. This impairs cerebrovascular autoregulation, exacerbates microcirculatory disturbances, and increases the risk of cognitive impairment and dementia.[3]

3.2. Hypertension-induced cerebrovascular functional alterations

3.2.1. Cerebral autoregulation

Cerebral autoregulation is the intrinsic capacity of cerebral vessels to maintain stable cerebral blood flow despite fluctuations in systemic blood pressure.[15,16] This mechanism involves myogenic, neurogenic, endothelial, and metabolic responses that adjust cerebral vascular resistance to preserve perfusion.[14,17] In chronic hypertension, the autoregulatory curve shifts rightward, requiring higher blood pressure to maintain consistent cerebral blood flow.[18,19]

Several studies have reported that this system is controlled by the 20-hydroxyeicosatetraenoic acid-transient receptor potential channel 6 pathway. 20-hydroxyeicosatetraenoic acid, derived from arachidonic acid, is made by enzymes called cytochrome P450.[20] It activates transient receptor potential channel 6 channels, elevating calcium levels inside smooth muscle cells in blood vessels, causing the vessels to contract more.[21] This response prevents too much blood from reaching the brain. However, if blood pressure remains high for a long time, the vessels can stay too tight.[22] This causes poor blood flow and damage, especially in deep brain areas like the white matter.[23]

White matter in the brain has a special blood supply, making it more likely to be harmed when blood flow drops. Due to this, it is often damaged in individuals with high blood pressure and small-vessel disease. This area is also where white matter hyperintensities are found.[24] Many brain scans and research studies have shown that white matter damage is linked to problems with thinking, especially in attention, planning, and processing speed.[25]

In addition to the myogenic mechanism, cerebral blood flow regulation is also modulated by neural and humoral factors. The local brain renin-angiotensin system (RAS) is critical in hypertension-related brain injury.[26] Activation of brain RAS—particularly persistent stimulation of the angiotensin II (Ang II) Type 1 receptor (AT1R)—leads to cerebrovascular endothelial dysfunction, basement membrane thickening, fibrosis, and vascular remodeling.[27] These alterations increase microcirculatory resistance and induce oxidative stress, chronic low-grade inflammation, and glial cell activation, ultimately disrupting the blood–brain barrier (BBB) and triggering neuronal dysfunction and death.[28,29]

In animal models, inhibition of AT1R or angiotensin-converting enzyme (ACE) has effectively reversed vascular remodeling and reduced neuronal apoptosis in cognition-related brain regions such as the hippocampus and prefrontal cortex. In contrast, activating the Ang II Type 2 receptor initiates multiple neuroprotective processes, including anti-inflammatory, anti-apoptotic, and neuroregenerative effects.[30] Moreover, the Ang II Type 2 receptor enhances BBB integrity by regulating the expression of tight junction proteins in cerebral endothelial cells—a function that is particularly crucial under hypertensive conditions.[31]

Impaired cerebral autoregulation is considered a key mediator in the development of VCI caused by hypertension.[32] Once autoregulatory capacity is compromised, cerebral perfusion becomes more susceptible to fluctuations in systemic blood pressure, leading to chronic hypoperfusion or acute underperfusion, consequently contributing to irreversible neuronal injury and dysfunction.[33]

3.2.2. Impaired neurovascular coupling (NVC)

NVC constitutes an essential physiological mechanism that contributes significantly to preserving cerebral homeostasis. It relies on dynamic interactions among endothelial cells, neurons, astrocytes, and vascular smooth muscle cells. These components collectively regulate local cerebral blood flow. Specifically, during heightened neuronal activity, they facilitate a prompt and targeted increase in blood supply to neural regions with elevated metabolic and oxygen requirements, thereby ensuring appropriate support for neural function and energy metabolism.[33,34]

Hypertension is a major pathological factor that disrupts this finely tuned process. Empirical findings suggest that, despite the complexity of these interrelated mechanisms, a key pathological pathway involves the Ang II-nicotinamide adenine dinucleotide phosphate oxidase (NOX)-reactive oxygen species (ROS) signaling cascade.[35,36]

When blood pressure is high, Ang II activates the NOX2 enzyme through AT1Rs. This causes a buildup of ROS, which damages the inner lining of blood vessels and blocks the production of nitric oxide from endothelial cells. This stops the smooth transition of signals between neurons and the muscle cells in blood vessels, preventing blood vessels from properly adjusting blood flow in response to brain activity.[37,38]

Ang II also activates calcium-based signals in astrocytes. These signals cause the release of inflammation-related proteins like tumor necrosis factor alpha and interleukin 6, further impairing NVC. Persistent BBB leakage exacerbates this dysfunction by reducing clearance of neurotoxic metabolites.[39]

Animal studies of hypertension have shown markedly weakened neurovascular responses in brain regions like the hippocampus and prefrontal cortex, leading to reduced blood flow and impaired synaptic function.[28]

Moreover, activated macrophages—particularly perivascular macrophages—further amplify ROS generation through increased NOX2 and NOX4 expression. This promotes oxidative stress, disrupts the integrity of the BBB, and establishes a vicious cycle of "inflammation-oxidative stress-endothelial dysfunction."[40,41]

Importantly, similar mechanisms exist in the peripheral vascular system. In hypertension, mechanical pressure and shear stress stimulate endothelial cells in the peripheral microcirculation, inducing NOX activation and leading to peripheral endothelial dysfunction. This process may indirectly affect cerebral blood flow regulation through a "peripheral-to-central" communication pathway.[11] Clinical and experimental studies have found that peripheral endothelial impairment is closely associated with cognitive decline, highlighting the importance of addressing systemic microcirculation in regulating NVC.[42]

In recent years, treatments focusing on NVC have shown promise for VCI. One example is that blocking NOX2 activity in older mice restored normal NVC function in the hippocampus and improved spatial learning and memory.[43] Other studies found that using NOX blockers or drugs that block Ang II receptors helped brain blood flow and thinking ability in animals with high blood pressure.[44]

Studies have shown that modulating the interaction between astrocytes and endothelial cells in the neurovascular unit may have therapeutic benefits. Partial improvement in NVC has been observed following the upregulation of regulatory factors such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), which play essential roles in maintaining vascular integrity and neuronal function.[45]

3.2.3. BBB disruption

The BBB is a crucial structural component in maintaining central nervous system homeostasis. It comprises cerebral microvascular endothelial cells, a delicate basement membrane, pericytes, and astrocytic end-feet, forming a complex structure that intricately envelops the cerebral vasculature.[46,47] The BBB plays a crucial role in restricting the permeation of potentially harmful substances, immune cells, and toxins from the circulatory system into the brain parenchyma. In addition, it facilitates nutrient transport, modulates immune surveillance, and maintains ionic homeostasis within the cerebral microenvironment.[48]

Identified as an early pathological characteristic in hypertension-related cerebrovascular diseases, BBB dysfunction might act as a crucial mechanism contributing to the progression of VCI. Preclinical and neuroimaging studies suggest that increased BBB permeability may precede significant brain atrophy and neuronal degeneration. Early BBB leakage has been consistently detected in cognitive-related brain regions, including the striatum, hippocampus, and prefrontal cortex, across various experimental models of hypertension, such as spontaneously hypertensive rats and animals infused with Ang II.[49,50]

The BBB breakdown permits leakage of plasma proteins (e.g., fibrinogen, albumin, immunoglobulin G) into the brain parenchyma, provoking activation of microglia and astrocytes. The resulting neuroinflammatory cascade accelerates axonal injury and demyelination, thereby contributing to hypertension-related white matter degeneration and cognitive decline. Over time, this pathological process promotes progressive white matter degeneration, representing a critical mechanism in the evolution of cerebrovascular-related cognitive decline.[51,52]

Concurrent evidence shows that perivascular immune cells, such as perivascular macrophages and microglia, are activated in response to prolonged hypertension. These cells secrete proinflammatory mediators such as interleukin-1β and tumor necrosis factor alpha, which contribute to vascular damage and enable the infiltration of peripheral immune cells into the brain parenchyma. This inflammatory cascade progressively impairs BBB integrity and plays a role in the pathophysiology of hypertension-associated neurovascular dysfunction.[53]

Various aspects of cognitive performance have been significantly linked to the permeability of the BBB, as revealed by advanced neuroimaging research methodologies. For instance, according to Montagne *et al.*,[54] who employed a dynamic contrast-enhanced magnetic resonance imaging, individuals diagnosed with mild cognitive impairment demonstrated increased BBB leakage within the hippocampus, a finding that ostensibly correlates with memory impairment.[54] Considering the nuanced nature of these findings, subsequent investigations tend to support the notion that BBB dysfunction is associated with deficits in executive function and processing speed among older adults with hypertension.[55]

Persistent BBB leakage reduces clearance of neurotoxic metabolites, including Aβ and tau proteins. The accumulation of these factors plays a crucial role in contributing to the overlapping pathological mechanisms between VCI and Alzheimer's disease.[56] Within this broader analytical framework, damage to the BBB appears to be present in the early stages of AD, indicating that this damage tends to lead to nerve fiber deterioration, brain inflammation, and amyloid plaque accumulation.[57]

Recent studies have highlighted increasing interest in BBB-protective strategies aimed at ameliorating VCI. Given the complexity of the underlying mechanisms, data suggest that several therapeutic interventions—such as AT1R blockers (particularly valsartan and losartan), ACE inhibitors (ACEIs), and antioxidants including N-acetylcysteine—may serve as effective treatment options in this context.[58] Activators of the nuclear factor erythroid 2-related Factor 2 pathway have also been shown to lower BBB leakiness, reduce damage to white matter, and improve thinking ability. In animal studies, intermittent hyperbaric oxygen therapy has helped protect the blood vessel barrier, reduce inflammation and oxidative stress, and slow the progression of brain damage in VCI.

4. Effects of antihypertensive therapy on VCI

4.1. Ang II receptor blockers (ARBs)

The cognitive improvement mechanisms of ARBs may involve several aspects. First, the ability of ARBs to cross the BBB and enhance cerebral blood flow can potentially exert neuroprotective effects.[59] Second, ARBs block the AT1R and promote interaction between Ang II and the Ang II receptor; some studies have further suggested that ARB-mediated AT1R blockade may induce degradation of cerebral amyloid deposits, thus slowing the onset and progression of Alzheimer's disease.[60] However, clinical studies on the cognitive effects of ARBs have rarely targeted Alzheimer's disease prevention or treatment directly, and the results remain inconsistent. The SCOPE study did not conclude that candesartan treatment had a preventive effect on overall cognitive decline.[61] A study conducted in Taiwan found no reduction in Alzheimer's disease risk after five years of ARB therapy.[62] In contrast, the MOSES trial, which was the first to assess the secondary prevention of stroke by ARBs, reported that eprosartan had protective effects against cognitive decline.[63] A recent comprehensive meta-analysis, which rigorously examined 19 randomized controlled trials alongside 11 observational studies, has demonstrated that antihypertensive therapy may significantly decrease the risk of all-cause dementia. Notably, when the reduction in blood pressure was equivalent, ARBs demonstrated superior cognitive benefits compared to placebo, β-blockers, diuretics, and ACEIs, in descending order of efficacy. The cognitive protection effect of ARBs in clinical applications necessitates further exploration. As for the underlying mechanisms of ARBs' cognitive protection, although several have been proposed, additional studies are required to confirm these mechanisms and determine optimal strategies.[64]

4.2. Angiotensin-converting enzyme inhibitors

Within the brain parenchyma and cerebral vasculature, as well as in the pulmonary circulation, ACE serves a pivotal function in the RAS, particularly in the production of Ang II and the metabolic processing of Aβ.[65] Several studies have reported that ACEIs can reduce Aβ deposition by inhibiting the degradation of substance P. Substance P is known to activate neutral endopeptidase (also referred to as neprilysin), an enzyme capable of degrading Aβ and other neurotoxic peptides in the brain, thereby contributing to cognitive improvement.[66] In addition, ACEIs suppress RAS activity, reduce oxidative stress and inflammatory responses in glial cells, and promote acetylcholine release, which collectively help to protect neurons from damage and exert neuroprotective effects.[67]

Numerous studies have extensively explored the relationship between ACEIs and cognitive function. The HOPE study, encompassing 9,297 hypertensive patients with a follow-up period of 4–5 years, revealed that the incidence of cognitive impairment, motor weakness, and speech or swallowing difficulties was 41% lower in patients administered ramipril than in those who received a placebo.[68] The PROGRESS study found that individuals with brain blood vessel disease who took perindopril and indapamide for four years had a 19% lower chance of overall memory and thinking problems. Their risk of memory problems after a stroke dropped by 45%.[69]

Different ACEIs can cross the BBB in varying amounts, which may affect how well they protect the brain. Fat-soluble drugs like perindopril and ramipril can enter the brain more easily and may work better on the central nervous system. Water-soluble drugs like captopril do not enter the brain as well and may have weaker effects.[70]

Animal research has shown that ACEIs might reduce brain cell death and help brain repair by changing the phosphoinositide 3-kinase/protein kinase B signaling pathway and blocking nuclear factor kappa B activity in the brain.[71] In mouse models of Alzheimer's disease, administering ACEIs over a long period facilitated memory and thinking, reduced brain cell damage, and improved brain cell connection and communication.[72]

Evidence has also suggested that combining ACEIs with calcium channel blockers or ARBs may have synergistic anti-dementia effects, although the underlying mechanisms remain unclear.[73]

In summary, ACEIs lower peripheral blood pressure to alleviate cerebrovascular burden and exert cognitive protective effects through multiple central mechanisms. These include reducing Aβ accumulation, suppressing inflammation and oxidative stress, and enhancing neuroplasticity. Further clinical studies are needed to determine the efficacy and safety of different ACEIs across various VCI stages and explore their potential in combination therapy.

4.3. Beta-blockers

The potential effects of beta-blockers on cognitive function remain unclear. Some studies have reported that beta-blockers may delay cognitive decline. For instance, a study involving 2,197 Asian hypertensive men with a mean age of 77 years demonstrated that monotherapy utilizing beta-blockers was significantly correlated with a diminished risk of cognitive decline. In diabetic individuals and men over 75-years-old with a pulse pressure of ≥70 mmHg, the efficacy of beta-blockers in alleviating cognitive impairment was more significant.[74] However, other researchers argue that beta-blockers have no beneficial effect on cognitive impairment and may even exacerbate cognitive deficits.[75,76] While Richards *et al.*[77] suggested that beta-blockers could potentially reduce the risk of VCI. Their analysis of 2,212 community-dwelling African Americans aged ≥65 years indicated that centrally acting sympatholytic agents might be associated with an increased risk of Alzheimer's disease-related cognitive decline in the context of antihypertensive medication usage. Consequently, some scholars have suggested that the cognitive impact of beta-blockers is contingent on their capacity to penetrate the BBB.[78] Typically, in healthy individuals, beta-blockers do not lead to cognitive dysfunction, whereas beta-blockers with central action may adversely affect delayed memory function in cognitively impaired patients by attenuating central noradrenergic pathways.[79,80] In light of the inconsistent findings reported, further investigation is imperative to elucidate the cognitive effects of beta-blockers, with particular emphasis on large-scale randomized controlled trials that can ascertain their efficacy and safety across diverse population groups. These findings further underscore the necessity for clinicians to consider personalized pharmacotherapy strategies within clinical practice settings.

4.4. Calcium channel blockers

Maintaining intracellular calcium homeostasis is crucial in sustaining neuronal activity, modulating synaptic plasticity, and regulating cerebral blood flow. In chronic cerebrovascular conditions such as hypertension and stroke, aging is associated with impaired calcium regulation. The activation of calcium-dependent enzymes, such as calpain, phospholipases, and nitric oxide synthase, triggered by elevated intracellular calcium levels, subsequently leads to mitochondrial dysfunction, excessive production of ROS, and the induction of apoptosis. Implicated in the development of cognitive decline, this cascade plays a crucial role in contributing to progressive neuronal injury through complex pathological mechanisms.[81,82] Hypertension worsens brain injury by reducing long-term blood supply, increasing oxidative stress, and amplifying neuronal excitotoxic damage. These trigger abnormal calcium channel function and promote neurodegeneration, leading to cerebrovascular-related cognitive decline.[82,83]

Studies have demonstrated that dihydropyridine-type calcium channel blockers, such as nimodipine, amlodipine, and felodipine, can penetrate the BBB and exert direct pharmacological effects on cerebral vasculature and vascular smooth muscle cells. Despite the complexity of the underlying mechanisms, these agents improve regional cerebral blood flow and enhance the neuronal microenvironment, providing potential therapeutic benefits for cerebrovascular dysfunction through multifaceted physiological modulation.[84,85] Nimodipine has demonstrated cognitive benefits in both clinical and preclinical models of cerebral ischemia, stroke, and Alzheimer's disease. These findings support its therapeutic potential in various cerebrovascular and neurodegenerative disorders.[84,86]

A comprehensive meta-analysis encompassing 14 clinical trials, which included patients diagnosed with Alzheimer's disease, vascular dementia, and mixed dementia, revealed that a 12-week therapeutic regimen with nimodipine led to a statistically significant enhancement in global cognitive function. Moreover, in comparison to those who did not receive such treatment, patients administered calcium channel blockers exhibited a reduced risk of cognitive dysfunction and Alzheimer's disease.[87]

The role of calcium channel blockers in regulating cerebral blood flow is also noteworthy. Studies in hypertensive animal models have shown that calcium channel blockers increase cerebral cortex and hippocampus blood flow, mitigate NVC dysfunction, and indirectly improve cognitive function by alleviating endothelial injury and inflammatory responses.[86] In addition, calcium channel blockers may confer neuroprotection by inhibiting Ang II-induced activation of NOX, thereby reducing oxidative stress levels.[88,89]

Notably, calcium homeostasis involves multiple cellular components and signaling pathways, including glutamate receptors, transient receptor potential channels, calcium/calmodulin-dependent kinase II, and calcium-regulated gene transcription mechanisms. Therefore, targeting calcium channels alone may be insufficient to completely regulate this complex network. Future research should explore combination therapies that pair calcium channel blockers with agents targeting mitochondrial function, synaptic repair, and inflammation to achieve multi-targeted, synergistic interventions for cognitive impairment.

4.5. Diuretics

Although most clinical trials have primarily assessed diuretics in combination therapies rather than as standalone treatments, these antihypertensive agents have garnered significant attention in the medical community. In the PROGRESS trial, perindopril combined with indapamide significantly reduced dementia risk and slowed cognitive decline among patients with prior stroke or transient ischemic attack over ~3.9 years.[90] In a randomized trial involving 160 elderly hypertensive individuals aged between 61 and 75, the combination of telmisartan and hydrochlorothiazide demonstrated superior reductions in ambulatory blood pressure compared to lisinopril and hydrochlorothiazide and significant enhancement in episodic memory, including word-list memory and recall tasks, as well as visuospatial executive function as measured by Trails B. These improvements were observed consistently at the 12-week and 24-week follow-ups; notably, the combination of lisinopril and hydrochlorothiazide failed to elicit similar cognitive benefits.[91]

Further observational cohort data indicate that the utilization of diuretics can reduce the incidence of Alzheimer's disease and preserve both cognitive and cardiovascular functions, particularly over extended follow-up durations.[29]

To delineate the effects of diuretics on cognition more clearly, future studies should treat diuretics as primary therapy, clarify the biological mechanisms involved (e.g., vascular integrity, amyloid accumulation, oxidative stress, and BBB effects), and establish optimal dosing, duration, and combination strategies.

Table 1 summarizes the antihypertensive drug classes and their mechanisms in cognitive protection.

5. Effects of aerobic exercise on VCI

5.1. Structural remodeling of the brain

Recent large-scale randomized controlled trials and meta-analyses have demonstrated that engaging in moderate-intensity aerobic exercise, performed at 60–75% of maximal oxygen consumption (VO_2max) over a period of 12–24 weeks, not only significantly enhances gray matter volume in the hippocampus and prefrontal cortex but also mitigates age-related cortical atrophy.[92] A meta-analysis published in 2025 reported that long-term moderate-to-high-intensity aerobic training modestly delays the decline in fluid cognitive function and is associated with cortical thickening.[93] Another review further noted that, among patients with Alzheimer's disease, aerobic programs within the 50–75% VO_2max range could suppress hippocampal volume loss.[94] The proposed mechanism involves activating the p-tropomyosin receptor kinase B/p-protein kinase B/C signaling pathway and reducing Aβ and tau phosphorylation.[95] In addition, animal and human studies evidence reveals that aerobic exercise significantly enhances neurogenesis, synaptic plasticity, and white matter integrity, exerting particularly robust effects on the dentate gyrus of the hippocampus, the cerebellum, and the striatum.[96]

5.2. Neurotrophic factors and molecular mechanisms

Aerobic exercise significantly elevates key neurotrophic factors—BDNF, insulin-like growth factor 1 (IGF-1), and VEGF—critical for neuronal survival, synaptic plasticity, and angiogenesis, underpinning its cognitive and neurovascular benefits.[97] A 2025 study, which included both patients diagnosed with Parkinson's disease and healthy control subjects, revealed that prolonged aerobic exercise not only elevated peripheral concentrations of BDNF, IGF-1, and VEGF but also enhanced the expression of other factors associated with the muscle–brain axis, such as glial cell line-derived neurotrophic factor, glycosylphosphatidylinositol-specific phospholipase D1, and sirtuin 3.[98] Further meta-analytical evidence has substantiated the significant elevation in peripheral concentrations of BDNF, IGF-1, and VEGF following moderate-to-high-intensity aerobic training interventions.[99,100] These factors can cross the BBB, supporting neuronal survival and angiogenesis. While acute aerobic exercise may induce transient increases in these neurotrophic factors, sustained intervention is required to maintain cognitive benefits.

Table 1. Antihypertensive drug classes and cognitiveprotection mechanisms

Drug class	Mechanism of action	Evidence
ARBs	Crosses the blood–brain barrier, increases cerebral blood flow, blocks AT1 receptors, stimulates AT2 receptors, and may promote amyloid-β degradation	The MOSES trial showed cognitive benefit with eprosartan;[63] a systematic review indicated superior cognitive protection of ARBs over other antihypertensives[64]
ACEIs	Suppress central renin-angiotensin system activity, reduce oxidative stress and inflammation; enhance acetylcholine release; inhibit substance *P* degradation to reduce amyloid-β accumulation	The HOPE trial reported reduced risk of cognitive impairment with ramipril;[68] the PROGRESS trial showed cognitive benefits of perindopril+indapamide[69]
BBs	Lower sympathetic activity and peripheral blood pressure; centrally acting BBs may delay memory impairment by modulating noradrenergic pathways	Monotherapy associated with reduced cognitive decline in elderly Asian males;[74] central BBs may impair memory in cognitively impaired individuals[79,80]
CCBs	Maintain intracellular calcium homeostasis, alleviate mitochondrial dysfunction, improve regional cerebral blood flow, and reduce oxidative stress by inhibiting nicotinamide adenine dinucleotide phosphate oxidase activation	Nimodipine significantly improved cognition in Alzheimer's disease/vascular dementia patients;[87] animal studies demonstrated improved cerebral blood flow and neuroprotection[86]
Diuretics	Lower blood pressure and cerebrovascular burden; may indirectly enhance cognition by improving water-salt balance	Indapamide+perindopril reduced post-stroke dementia risk;[90] telmisartan/hydrochlorothiazide improved memory and visuospatial function[91]

Abbreviations: AT: Angiotensin; ARBs: Angiotensin II receptor blockers; ACEIs: Angiotensin-converting enzyme inhibitors; BBs: Beta blockers; CCBs: Calcium channel blockers.

Moreover, recent molecular studies suggest that aerobic exercise enhances transcription of *BDNF* and *VEGF* genes through DNA demethylation, while simultaneously downregulating protein phosphatase 1 and DNA methyltransferases, which are known to inhibit memory-related gene expression.[101]

5.3. Improvements in cerebral hemodynamics

An increasing volume of empirical evidence underscores the significant contribution of aerobic exercise to the augmentation of cerebral blood flow. A meta-analysis focusing on older adults in 2023 demonstrated that aerobic training significantly enhanced cerebral blood flow velocity, as assessed through transcranial Doppler ultrasound, with a mean difference of approximately 3.6 cm/s.[96] Similarly, a study conducted in 2024 revealed that regular aerobic exercise not only enhanced cerebral perfusion but also potentially played a role in delaying cognitive decline. Furthermore, an earlier randomized controlled trial from 2019 demonstrated that eight weeks of moderate-intensity aerobic exercise resulted in a 27% increase in cerebral blood flow within the prefrontal cortex and cingulate gyrus, correlating with significant improvements in executive function.[102] Despite some reviews pointing out that the direct link between increased cerebral blood flow and cognitive enhancement is still partially ambiguous, it is generally accepted that enhanced regional perfusion, coupled with elevated neurotrophic factor levels and neuronal activity, exerts a synergistic effect on both neuroprotection and cognitive modulation.[103]

5.4. Regulation of neuroinflammation and oxidative stress

Recent reviews have shown that aerobic exercise can suppress inflammatory pathways, such as activating the NLR family pyrin domain-containing 3 inflammasome, and reducing oxidative stress.[104] These effects are accompanied by increased neuroplasticity mediated by factors such as BDNF, particularly in post-stroke cognitive recovery.[105] This suggests that the benefits of aerobic exercise extend beyond structural remodeling, encompassing anti-inflammatory and antioxidative mechanisms that collectively slow down neurodegenerative processes.[106]

In summary, an increasing volume of empirical evidence underscores the significant role of aerobic exercise in enhancing cognitive function and decelerating the progression of VCI, with underlying mechanisms encompassing the upregulation of neurotrophic factor expression, augmentation of brain structural plasticity, optimization of cerebral blood flow, and modulation of neuroinflammatory and oxidative stress responses.[107] Among hypertensive patients, regular aerobic exercise has been demonstrated to produce clinically significant reductions in blood pressure, with systolic values typically decreasing by approximately 7 mmHg and diastolic values by 6 mmHg, magnitudes associated with substantial decreases in cardiovascular risk. It is estimated that a reduction of every 5 mmHg in systolic pressure can lead to respective declines of 7%, 14%, and 9% in all-cause mortality, stroke mortality, and coronary heart disease mortality.[108]

Experimental studies have demonstrated that 12 weeks of moderate-intensity aerobic training in older male patients with hypertension significantly improved perceptual speed and working memory.[109] Similarly, a three-month aerobic exercise intervention improved hemodynamic abnormalities and enhanced short-term information processing in elderly hypertensive individuals.[110] Overall, aerobic exercise exerted a positive regulatory effect on cognitive function in the aging population, particularly those with cognitive decline.

To maximize the effectiveness of such interventions, current research emphasizes the following practical recommendations. First, appropriate control of exercise intensity and dosage is critical. Moderate-to-high intensity aerobic activity (50–75% VO_2max), performed three to five times per week for 20–60 minutes per session over a minimum of 12 weeks, is widely recommended as a baseline prescription. Evidence suggests that, within tolerable limits, increasing the total exercise volume may yield more pronounced structural and cognitive benefits.[111]

Second, the cognitive benefits of aerobic exercise result from multiple synergistic pathways rather than a single mechanism. Aerobic exercise exerts neuroprotective effects through upregulation of BDNF and IGF-1, volumetric gains in the hippocampus and prefrontal cortex, enhancement of cerebral hemodynamics, and suppression of neuroinflammatory and oxidative stress pathways.

Third, precision-based interventions should account for individual variability. Factors such as patient age, baseline cognitive status, hypertension control, and exercise tolerance should be considered when developing a tailored aerobic exercise regimen. This personalized approach is essential to optimize compliance and intervention outcomes.

6. Discussion

Hypertension is a major modifiable risk factor for VCI. Progressive cognitive decline results from vascular remodeling, white matter injury, BBB dysfunction, oxidative stress, and neuroinflammation, all of which are driven by hypertension.

Although antihypertensive agents, particularly calcium channel blockers, ACEIs, and ATR2 blockers, potentially provide neuroprotective effects extending beyond blood pressure regulation, the existing evidence remains inconclusive due to limited sample sizes, heterogeneous trial designs, and the predominant use of surrogate endpoints.

Lacunar infarction is a central small-vessel phenotype. Nearly half of first-ever cases present with subcortical vascular-type mild cognitive impairment, an early predictor of vascular dementia, underscoring the need for cognitive screening and follow-up in hypertensive patients.[112]

Aerobic exercise improves cerebral blood flow, enhances neurotrophic signaling, supports plasticity, and reduces inflammation. Clinical studies report benefits for executive function and processing speed, though protocols and adherence vary.

Our findings are broadly consistent with Arboix's study,[113] which identified hypertension as a significant determinant of lacunar infarction and vascular dementia. Building on this foundation, the present review incorporates more recent mechanistic evidence—such as vascular remodeling, impaired autoregulation, neurovascular uncoupling, and amyloid pathology—and evaluates antihypertensive drug classes and aerobic exercise. Moving beyond epidemiological associations, our review provides updated insights with direct therapeutic relevance for clinical practice and future research.

This review has limitations at both the evidence and methodological levels. The available studies are heterogeneous in design and quality, often limited by residual confounding, small samples, and surrogate endpoints, with inconsistent findings across populations. As a narrative review, we did not register a formal protocol, restricted inclusion to English-language publications, and performed no quantitative meta-analysis. These factors may introduce bias, and future well-powered randomized controlled trials with standardized cognitive outcomes are needed to strengthen the evidence base.

7. Conclusion

Hypertension is a major driver of VCI. It acts through structural remodeling, functional disruption of the cerebral vasculature, impaired autoregulation, and persistent neuroinflammation. Evidence supports strict blood pressure control and aerobic exercise as practical measures to slow cognitive decline. However, no antihypertensive class has demonstrated clear superiority, and reported differences should be interpreted cautiously. Lacunar infarction and small-vessel disease are early indicators of cognitive risk. Their recognition calls for routine cognitive screening and long-term follow-up in hypertensive patients. Looking ahead, research should prioritize large randomized trials with cognition as the primary endpoint, direct drug-class comparisons, and pragmatic designs that combine pharmacologic and lifestyle interventions. Such efforts are essential to transform mechanistic insights into effective strategies for preventing and managing hypertension-related cognitive decline.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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