



Vascular Cognitive Impairment (VCI)

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Accepted: 6 December 2021 / Published online: 22 December 2021
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Abstract

Vascular cognitive impairment (VCI) is predominately caused by vascular risk factors and cerebrovascular disease. VCI includes a broad spectrum of cognitive disorders, from mild cognitive impairment to vascular dementia caused by ischemic or hemorrhagic stroke, and vascular factors alone or in a combination with neurodegeneration including Alzheimer's disease (AD) and AD-related dementia. VCI accounts for at least 20–40% of all dementia diagnosis. Growing evidence indicates that cerebrovascular pathology is the most important contributor to dementia, with additive or synergistic interactions with neurodegenerative pathology. The most common underlying mechanism of VCI is chronic age-related dysregulation of CBF, although other factors such as inflammation and cardiovascular dysfunction play a role. Vascular risk factors are prevalent in VCI and if measured in midlife they predict cognitive impairment and dementia in later life. Particularly, hypertension, high cholesterol, diabetes, and smoking at midlife are each associated with a 20 to 40% increased risk of dementia. Control of these risk factors including multimodality strategies with an inclusion of lifestyle modification is the most promising strategy for treatment and prevention of VCI. In this review, we present recent developments in age-related VCI, its mechanisms, diagnostic criteria, neuroimaging correlates, vascular risk determinants, and current intervention strategies for prevention and treatment of VCI. We have also summarized the most recent and relevant literature in the field of VCI.

Keywords Vascular cognitive impairment · Vascular risk factors · Small vessel disease · Cognition · Neuroimaging · Biomarkers

Vascular cognitive impairment (VCI) is a recently recognized entity caused predominately by cerebrovascular disease [1, 2]. VCI includes an entire spectrum of cognitive disorders, from mild cognitive impairment (MCI) to vascular dementia caused by vascular ischemic or hemorrhagic etiology and vascular factors alone or in a combination with neurodegeneration and Alzheimer's disease (AD) [3]. In this review, we discuss recent developments in age-related VCI, including its mechanisms, diagnostic criteria, neuroimaging correlates, and vascular risk determinants. We also present current intervention strategies for prevention and treatment of VCI. Recently, several review articles have described VCI in the context of cerebral small vessel disease [4], asymptomatic carotid stenosis [5], stroke [6–8], heart disease [9, 10], and AD [11]. Here, we summarize these developments and the most recent literature in the field of VCI.

Epidemiology of VCI and the Aging Populations

Current projections suggest that 72 million people in the USA will be older than 65 years of age by 2030, which is a greater than tenfold increase in a century [12]. Age-related cognitive impairment is one of the major public health challenges of our time. The number of affected individuals in 2018 was estimated at 50 million worldwide and expected to triple by 2050 at a cost approaching \$4 trillion [13]. The prevalence of VCI may be lower in low-to-middle-income countries that are early in the process of demographic transition [14]. However, these countries now see the fastest increases in the prevalence of VCI.

Vascular risk factors are prevalent in the growing older population. For example, in the community-based Framingham Heart Study, the lifetime risk for development of hypertension is more than 90% [15]. Similarly, age-related neurological diseases have increased with prolonged life expectancy. One in three people over age 65 would experience stroke, dementia, or both of these conditions during their lifetimes [16]. VCI accounts for at least 20–40% of all

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dementia diagnosis. Growing evidence indicates that cerebrovascular pathology is the most important contributor to dementia, with additive or synergistic interactions with neurodegenerative pathology. In the clinical-pathological analysis from the Religious Orders Study and Memory and Aging Project, only 9% of autopsy sample had isolated AD, 40% had AD plus prominent vascular pathology (macroscopic infarcts, cerebral amyloid angiopathy, atherosclerosis or arteriolosclerosis), and 44% had AD plus vascular as well as another neurodegenerative pathology [17]. This is further supported by the contribution of vascular risk factors to dementia. Vascular risk factors measured in midlife predict cognitive impairment and dementia in later life [18]. Hypertension, high cholesterol, diabetes, and smoking at midlife are each associated with a 20 to 40% increased risk of dementia and, furthermore, in dose-dependent manner such that the risk for dementia increases from 1.3 for having one risk factor to 2.4 for having four risk factors [18].

Disparities in cerebrovascular disease also translate in race-ethnic disparities in VCI and dementia. Non-Hispanic Black and Hispanics/Latino individuals have a greater burden of VCI and dementia compared to non-Hispanic white individuals [19–21]. In the Northern Manhattan Study (NOMAS), Hispanic and Black participants had greater likelihood of MCI (20%) and dementia (5%) than white participants after accounting for age and education differences [22]. Further research on the understanding of vascular risk factors, particularly in midlife as opposed to late life in the development of VCI in diverse cohorts, is needed, especially in those where participants live in the same community for comparison across groups without confounding introduced by heterogeneity in environmental and other local factors.

The most emphasis now is on identifying individuals with early cognitive impairment due to vascular risk factors and vascular pathology as these individuals are at greatest risk for developing VCI and dementia and would considerably benefit from preventive measures. However, more research is needed to understand epidemiology of a complete spectrum of VCI. Best way is to prospectively follow epidemiologic, aging, and clinical cohorts worldwide for vascular risk factors burden, structural and functional brain changes, and the intermediate vascular and cognitive phenotypes to determine their risk of transforming to VCI and clinical disease. This approach is feasible as many ongoing cohorts and aging studies are nationally or government funded (Table 1), and they are already focused on longitudinal cognitive outcomes and their prevention [23]. In this effort, major challenge remains in the harmonization of data collection, cognitive testing, and neuroimaging and other biomarkers. Based on the world pandemic of cognitive conditions, the World Stroke Organization has issued a proclamation that calls for joint prevention of stroke and dementia, data harmonization,

Table 1 Selected list of major longitudinal epidemiology and aging cohorts studying VCI in the USA and worldwide

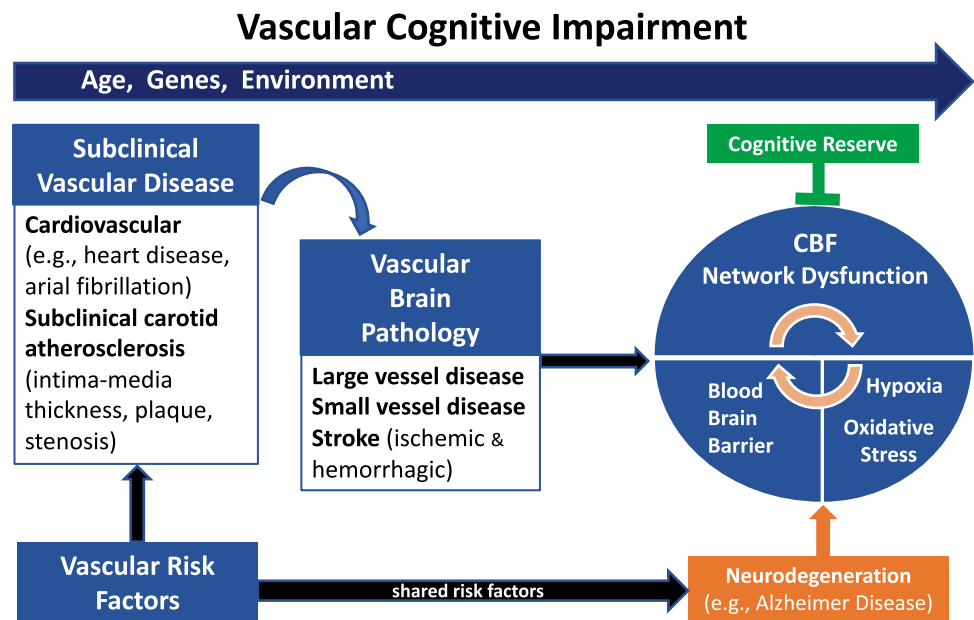
-
- Framingham Heart Study (FHS)
 - Atherosclerosis Risk in Communities (ARIC)
 - Multi-Ethnic Study of Atherosclerosis (MESA)
 - Northern Manhattan Study (NOMAS)
 - Hispanic Community Health Study-Study of Latinos (HCHS-SOL)
 - Reasons for Geographic and Racial Differences in Stroke (REGARDS)
 - Religious Orders Study
 - Rush Memory and Aging Project
 - Einstein Aging Study (EAS)
 - Health and Retirement Study (HRS)
 - Age, Genes/Susceptibility study Reykjavik (AGES-RS)
 - Three Cities study (3C)
 - Rotterdam Study (RS)
 - Austrian Study of Stroke Prevention (ASPS)
 - Study of Health in Pomerania (SHIP)
 - Singapore Longitudinal Aging Studies (SLAS)
 - English Longitudinal Study of Ageing (ELSA)
 - The Norwegian Life Course, Ageing and Generation Study (NorLAG)
 - The German Ageing Survey (DEAS)
 - Australian Longitudinal Study of Ageing (ALSA)
 - The Japanese Study of Aging and Retirement (JSTAR)
 - Taiwan Longitudinal Study on Aging (TLSA)
 - China Health and Retirement Longitudinal Study (CHARLS)
 - Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)
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and translation into action and is now endorsed by all major international organizations focused on brain and vascular health [24].

Mechanism of VCI

Multiple cerebrovascular etiologies can cause VCI. They include cerebral small vessel disease (SVD), large-artery atherosclerosis, brain hemorrhages, cardioembolism, and other less common etiologies of stroke [25, 26]. Age, genetic, and environmental and lifestyle factors lead to the development of vascular risk factors, subclinical arterial and brain diseases, and ultimately cause cerebral blood flow (CBF) and network dysfunction, which are hallmarks of VCI (Fig. 1). Underlying neurodegeneration through shared genetic and environmental risk factors may accelerate VCI. This process is counteracted by the individual cognitive and functional reserve and resilience. The mechanisms by which vascular pathologies contribute to VCI are not well understood. The most common underlying mechanism of

Fig. 1 Mechanism of Vascular Cognitive Impairment



these etiologies is chronic age-related dysregulation of CBF, but hypoxia, increased permeability of blood–brain barrier (BBB), endothelial dysfunction, systemic inflammation, and inflammatory clock of aging (iAge), which are tracked with multimorbidity, immunosenescence, frailty, and cardiovascular aging, are additional mechanisms among others and have been recently reviewed [27, 28]. Also, vascular pathology commonly found in autopsy studies of clinical AD patients [29] seems to occur early in the AD continuum and biomarker trajectories [30, 31].

Regulation of CBF is complex. It must ensure adequate delivery of oxygen and nutrients and rapid adjustment to CBF fluctuations. While the brain only represents about 2% of the total body mass, it consumes about 20% of oxygen and about 25% of glucose in the human body [32]. While the brain has a high metabolic demand for oxygen and glucose relative to other organs, it only contains minute energy reserves and is thus highly dependent on constant CBF to supply energy substrates. CBF regulation has to maintain constant metabolic supply and normal blood flow, volume and intracranial pressure, and prevent injury from penetration of high pressure flow from large vessels to the distal microvasculature [33]. Evidence from animal models has shown that chronic reduction in CBF can cause brain atrophy, white matter injury, lacunar infarcts, hemorrhages, memory impairment, and potentially AD [34, 35]. Vascular risk factors, particularly hypertension, have profound impact on cerebral vessel wall structure and CBF regulation. Recent studies using BOLD and arterial spin labeling MRI have documented the alteration in cerebrovascular reactivity in patients with SVD [36, 37]. However, whether the CBF dysfunction is a cause of VCI or a consequence of reduced brain metabolic demands in aging and neurodegeneration is unclear and remains to be proven [38].

The tightly controlled interaction between brain cells and the cerebral blood vessels is a central function in the mechanism of VCI, and it is conceptualized through the neurovascular unit [39, 40]. The neurovascular unit (NVU) is a complex functional and anatomical structure composed of specialized endothelial cells of the BBB surrounded by a basal lamina and the interacting neurons, astrocytes, microglia, pericytes, and an extracellular matrix. The key function of the NVU is coupling of neural activity and CBF. Growing evidence indicates that NVU dysfunction critically contributes to brain pathologies, including VCI and neurodegenerative diseases [41, 42].

There is significant heterogeneity in the interactions between neurons and cerebral vessels as well as the vasculature of the collateral circulation pathways across the brain. The circle of Willis is an anastomotic system of arteries that forms a network of collateral CBF circulation to supply nutrients to the internal brain parenchyma as well as the surface within the subarachnoid space via pial arteries and arterioles. Pial arteries dive into the substance of the brain surrounded by an extension of the subarachnoid space forming the perivascular spaces (PVS) or Virchow-Robin spaces [43]. Although the precise function of PVS is not completely understood, a perivascular pathway has long been proposed as a drainage system through retrograde travel with drainage into cervical lymph nodes [44]. This system is now known as the glymphatic system, a brain-wide network through which cerebrospinal fluid is exchanged with the interstitial fluid as a waste clearance mechanism within the brain parenchyma. The critical role of PVS is in the exchange of energy substrates, maintaining the brain immune system, and clearing of interstitial β -amyloid [45, 46]. PVS have little to no resistance to flow [47] and have been proposed in the mechanisms

of neurodegenerative disorders through a common pathway of vascular hemodynamic dysregulation and failure of the glymphatic system [48].

Multiple large and small infarcts were proposed as causes of dementia in early 1970s [49] and have been associated with high risk of dementia or worsening of cognitive function if large in size, across multiple territories or in greater number [25, 50], and particularly for those infarcts in supratentorial regions and in anterior circulation [51, 52]. There is a large interindividual variation in cognitive response to multiple infarcts and potential underlying neurodegenerative pathology; therefore, no clear infarct volume threshold has been proposed. Single infarcts may cause cognitive decline if located in strategic regions (called strategic infarcts) such as the thalamus, angular gyrus, and basal ganglia [53, 54]. Specific white matter tracks that are integrated into cortical-subcortical cognitive networks are likely playing a key role in cognitive impairments associated with these lesions [55].

Subclinical cerebral white matter lesions and microinfarcts are most common causes of VCI [56–58]. Prevalence of white matter lesions is as high as 50% in those aged 45 to 95% in those aged 80 [59, 60]. Subclinical, silent cerebral infarcts (SBIs) are prevalent up to 40%, depending on age and the burden of vascular risk factors [61, 62]. In the Rotterdam Study and the Framingham Offspring Study, SBIs doubled the risk of dementia [63, 64]. In the NOMAS, greater burden of white matter lesions and SBIs was associated with worse global cognitive performance and psychomotor speed [65]. Furthermore, those 70 years or older with greater burden of white matter performed worse in episodic and semantic memory, which is likely driven by the cumulative effects of vascular risk factors and subclinical age-related neurodegenerative pathology on cerebrovascular integrity. In Religious Orders Study, cerebral microinfarcts were associated with disturbances in episodic memory, semantic memory, and perceptual speed [66]. In support of these observations, a meta-analysis of data from different cohorts worldwide has shown prevalence of cerebral microinfarcts to be twice as high in people who died with diagnosis of dementia [67].

PVS are highly associated with other markers of SVD, including white matter hyperintensities and cerebral microinfarcts, and by many are considered a hallmark of SVD [68]. In NOMAS, PVS were associated with increased age, hypertension, presence of atherosclerotic carotid plaque, and of risk of vascular events [69, 70], most likely through the mechanism of arterial stiffness and pulse-wave reflection and propagation to the aging brain. Other proposed mechanisms for enlargement of PVS include brain atrophy, inflammation, and dysfunction of perivascular flow [45, 71]. The evidence for the associations between PVS and cognitive impairment and dementia has been conflicting; however, recent

meta-analysis supports the role of PVS in cognitive impairment [72]. In a recent study, PVS were associated with greater decline in global cognition over 4 years independent of other markers of SVD and with a 2.9-fold increased risk of dementia across 8 years of follow-up [73]. The presence of PVS visible on MRI is not specific for SVD, but they are also frequently found in patients with AD, Parkinson's disease, and multiple sclerosis [71]. Nevertheless, the mechanism behind VCI in the presence of various imaging markers of SVD (PVS, white matter lesions, SBI) remains difficult to elucidate because of shared and multiple disease processes, diffuse location, the presence of yet unrecognized pathology, and individual cognitive reserve and resilience [25].

Brain hemorrhages, intracerebral hemorrhages (ICH), and cerebral microbleeds are also associated with cognitive impairment and dementia [74, 75]. Hypertensive small vessel disease is the most common cause of deep ICH and cerebral amyloid angiopathy of lobar ICH [76]. Cerebral microbleeds (CMBs) are well-defined small and round black structures seen on MRI gradient echo T2*-weighted imaging. The prevalence of CMBs is reported to be 3–27% in elderly individuals [77–80]. In NOMAS, the prevalence of CMBs was 5%; and 37% participants had only deep CMBs, 48% had only lobar CMBs, and 15% had CMBs in both locations [81]. The underlying mechanisms of CMBs are heterogeneous and associated with recent or old hemorrhages, vasculopathies, and various degrees of chronic ischemic injury [82]. CMBs affect cognition and risk of dementia independent of vascular risk factors and other markers of SVD [78, 79]. The mechanisms by which CMBs affect cognition are unclear, but evidence suggests that it is mediated by reduced structural brain network efficiency and disrupted connectivity [83, 84].

Cerebral amyloid angiopathies (CAA) include heterogeneous sporadic and genetic conditions characterized by amyloid deposition in the walls of cerebral arteries and arterioles. Sporadic CAA is the most common in the elderly and is characterized by vascular deposition of amyloid-beta ($A\beta$) [85]. The prevalence of CAA is about 2–20%, depending on age, and is present in over 80% of patients with AD on autopsy [85–87]. CAA is associated with greater number of neurofibrillary tangles, neuritic plaques, and ApoE4 presence [88]. CAA manifests with or without intracranial hemorrhage and has been associated with cognitive decline, perceptual speed, episodic memory, and semantic memory [89]. One of the key features of CAA is cortical superficial siderosis (cSS), which represents deposits of blood-breakdown products within the subarachnoid space, the leptomeninges, and the superficial cortical layers [84]. cSS is associated with transient focal neurological episodes and a high risk of future intracerebral hemorrhage. It requires appropriate blood-sensitive MR sequences that are implemented in routine scanning of patients with suspected cerebrovascular events and VCI [90].

In the Framingham and Rotterdam studies of community-dwelling older adults, 6.6% of individuals had deep microbleeds, 12.8% had strictly lobar microbleeds without cortical superficial siderosis, and 0.43% had cSS [91]. Participants with cSS were older, had the APOE $\epsilon 4$ allele more frequently, and had greater prevalence of intracerebral hemorrhage. During a mean follow-up of 5.6 years, 42% participants with cSS developed a stroke, 19% transient neurological deficits, and 4% incident dementia. Besides cSS and cerebral micro- and macro-bleeds, the mechanisms of cognitive decline in CAA also include ischemic injury to the white matter and disruption of structural and functional network integrity [92]. The CCA pathophysiology, treatment, and role of the fibrinolytic system have been recently extensively reviewed elsewhere [93].

Cardiac disease such as heart failure, ischemic heart disease, and atrial fibrillation has been associated with VCI. The most common cause of cognitive decline in heart failure is cardiac systolic dysfunction that leads to reduced cerebral perfusion [10]. Neurohormonal activation, oxidative stress, inflammation, glial activation, dendritic spine loss, and brain programmed cell death have also been proposed contributors of cognitive impairment in heart failure. A novel hypothesis has recently emerged as the misfolded protein disease is found both in the brain and the heart [94]. Elevated levels of A β in the heart and skeletal muscles of AD individuals indicate a possible contributor to elevated concentrations of A β plasma levels and potentially indirectly contributing to A β deposits in cerebral blood vessels and brain parenchyma [95]. Atrial fibrillation (AF) is another important cause of cognitive impairment through its thromboembolic risk, association with cerebral SVD, vascular inflammation, and genetic factors [96, 97]. New evidence shows that the use of oral anticoagulants (OACs) in AF is associated with a lower risk of cognitive impairment and dementia compared to non-OAC and antiplatelet use [98, 99].

Subclinical atherosclerosis, including carotid intima-media thickness (cIMT), atherosclerotic plaque, and carotid stenosis, has been associated with VCI. cIMT reflects thickening of the intimal and medial layers of the vessel wall, and carotid plaque represents significant atherosclerotic disease in the vessel lumen that leads to stenosis and CBF reduction [100]. Global hypoperfusion from these causes has been strongly associated with neuropathological imaging showing watershed infarcts, white matter lesions, and hippocampal sclerosis [101–103]. Although cIMT, plaque, and stenosis are validated markers of subclinical vascular disease [104–108], less is known about their ability to predict cognitive impairment and with conflicting evidence. In NOMAS, cIMT was associated with impairments in episodic and semantic memories, and processing speed, but only among APOE $\epsilon 4$ carriers, who represented 24% of the cohort [109], suggesting that increased cIMT may

exacerbate cognitive dysfunction in those at higher risk for AD. Carotid plaque was not associated with cognitive dysfunction. In the Tromso study, however, carotid plaque but not cIMT was associated with cognition dysfunction, particularly in verbal memory [110]. The effect of aging, vascular risk factors, and their control likely affected not only the discrepancy between the studies, but also the mechanisms by which these subclinical vascular phenotypes affect cognition may differ [111]. Greater cIMT may result in increased arterial stiffness, pulsatile wave propagation to the brain, and endothelial injury, while carotid plaque may progress to significant stenosis or be a major source of cerebral emboli. Both of these mechanisms may lead to dysregulation of CBF and cerebral hypoperfusion. Carotid stenosis is a flow reduction lesion and a strong predictor of cerebrovascular events as well as cognitive impairment, although the studies with cognitive outcomes are inconsistent [5]. The mechanism by which carotid stenosis causes cognitive impairment is not fully understood. Few studies have addressed the role of SVD in the presence of carotid stenosis. Better evidence supports the role of CBF dysregulation caused by impaired cerebrovascular reserve in patients with severe carotid stenosis and who more likely have cognitive impairment and suffer further cognitive decline with time [112]. Therefore, cognitive decline can be potentially reversed by carotid revascularization and this concept is currently being tested in the CREST-H (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis — Hemodynamics) study, an ancillary study of the CREST-2 randomized clinical trial [113, 114].

Specific genetic and sporadic forms of arteriopathy are associated with VCI. The most frequent monogenic cause is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) caused by NOTCH3 mutations and less common cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CAASIL) condition caused by HTRA1 mutations [115–117]. Although ApoE4 is a strong risk factor for AD, it seems less important for VCI [118]. Further discussion on these conditions is outside the scope of this review and is summarized elsewhere [119–121].

In some instances, there is a reversibility of cognition in VCI. Transient cognitive impairment can return to normal in about 20% patients shortly after stroke [122], depression [123], and heart failure [124]. Transient cognitive impairment in VCI does not include post-stroke delirium that is observed in up to 25% of hospitalized stroke patients [125], or post-stroke depression, found in up to 50% of stroke patients [126]. Post-stroke cognitive impairment is reversible to normal in both of these conditions.

Despite the established relationships between clinical stroke and subclinical infarcts and dementia, these relations are understudied in a systematic way in a large and diverse

populations. To fill the gap in our understanding of pathophysiology of VCI, the NIH has recently established the DISCOVERY study (Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery), a large consortium to study cognitive trajectories post-ischemic and hemorrhagic stroke [6], as well as the MarkVCID to validate biomarkers of VCI due to SVD [127, 128]. Similarly, other large-scale international collaborations such as STROKOG (Stroke and Cognition Consortium), SVDs@target (Small Vessel Diseases-At-Target), and the HBC (Heart-Brain Connection) are established to investigate the mechanisms of VCI [129], with STROKOG being the largest consortium with 18,000 individuals from 32 studies and representing 18 countries [130]. Thus, understanding and targeting the mechanism of VCI are a high priority for reducing the overall burden of cognitive impairment and dementia.

Diagnostic Criteria of Vascular Cognitive Impairment and Vascular Dementia

The concept of VCI was first outlined in 2006 by the NINDS in collaboration with the Canadian Stroke Network in a statement on harmonization of minimum, common, clinical, and research standards for the description, data collection, and study of VCI [131]. In the 2011, AHA-ASA had issued a scientific statement on vascular contributions to cognitive impairment and dementia to further capture the entire VCI spectrum associated with all forms of vascular brain injury, ranging from MCI to fully developed dementia [132], and proposed the term VCI for all forms of cognitive disorder associated with cerebrovascular disease regardless of the etiology (e.g., atherosclerotic, ischemic, hemorrhagic, cardioembolic, or genetic). Thus, VCI could range from the mild cognitive deficits, through the multifocal cognitive deficits to clinical vascular dementia that is severe enough to affect social or occupational function.

The 2011 AHA/ASA scientific statement defines VCI as “a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain.” Memory impairment is not a requirement for diagnosis of VCI as memory deficits like seen in AD are not suitable for VCI, in which memory-related structures (hippocampus, thalamus) may be intact and not causing memory impairment [133]. The need for continued development and refinement of cognitive batteries for VCI is emphasized as well as identification of imaging and soluble biomarkers of VCI.

Since the 1970s, there are a variety of vascular dementia (VaD) criteria, ranging from the clinical Hachinski Ischemic Score (HIS) and the National Institute for Neurological Diseases and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences

(NINDS-AIREN) criteria mostly used in research [134] to the AHA-ASA vascular cognitive impairment criteria in 2011, Diagnostic and Statistical Manual (DSM-III, IIIR, IV), the International Classification of Disease 10th and 11th revision (ICD-10, ICD-11), the California Alzheimer’s Disease Diagnostic and Treatment Centers (ADDDTC), and the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) criteria [135–139]. There is a considerable variability in the sensitivity of these different criteria when using pathology as a “gold standard” (ranging from 0.2 to 0.7). Specificity, however, ranges from 0.78 to 0.93; thus, most of these criteria emphasize specificity over sensitivity. Nevertheless, less than 50% of all individuals with moderately severe vascular pathology at autopsy are diagnosed during life as having VaD [140].

More recently, the international Vascular Impairment of Cognition Classification Consensus Study (VICCCS-1 and 2) has synthesized the conceptual framework, built the consensus, and harmonized diagnostic criteria for VCI and VaD into mild or major [141, 142]. In VICCCS-1 major VCI category, four VCI sub-types are defined: post-stroke dementia, subcortical ischemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementias (Fig. 2). VICCCS-2 further discusses VCI neuroimaging markers with MRI recommended as a gold standard requirement for a diagnosis of VCI.

Neuroimaging Correlates of Vascular Cognitive Impairment

Figure 3 briefly outlines MRI sequences with most typical imaging findings and their implication on cognition. The VICCCS-2 diagnostic guidelines [142] recommend the use of imaging in the diagnosis of VCI based on the MRI measures, including the number, size and location of infarcts, and hemorrhages, extent on a quantitative or validated semiquantitative scale of WMH volume, and measures of total brain (or ventricular) and hippocampal volumes. For research purposes, the NINDS-CSC VCI harmonization guidelines [131] recommend a minimal imaging dataset with MRI 3D T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and gradient echo (GRE) sequences. Diffusion-weighted images (for acute stroke), diffusion tensor imaging (DTI) for assessing the state of the white matter tracts where abnormal DTI (lower fractional anisotropy) in normal-appearing white matter as it has been associated with vascular risk factors and poorer executive function [143], PET for β -amyloid, and non-invasive assessment of the cerebral vasculature (carotid ultrasound preferably or MR angiography) are also suggested.

White matter hyperintensities (WMHs) are often seen on FLAIR or T2 MRI sequences, increasingly with age and

VCI				
Mild VCI	Major VCI			
Impairment in at least one cognitive domain, and none to mild impairment in activities of daily living (ADLs)	Clinically significant deficits in at least one cognitive domain and severe disruption to ADLs			
	Post-stroke dementia	Subcortical ischemic vascular dementia	Multi-infarct dementia	Mixed dementia
	Immediate and/or delayed cognitive decline within 6 months after stroke and does not reverse	Small-vessel disease (lacunar infarcts, white matter lesions) mainly located subcortically	Presence of multiple cortical infarcts and their contribution to the dementia	Combination of vascular and degenerative disease (VCI-AD, VCI-Lewy body dementia, etc.)

Fig. 2 Vascular cognitive impairment (VCI) diagnostic criteria

in the setting of vascular risk factors. They are associated with cerebral SVD, though they can be seen in other neurological conditions and in the appropriate clinical setting (e.g., multiple sclerosis). While often heterogenous in size, distribution, and quantity, their presence is noteworthy when considering vascular etiology of cognitive impairment in clinical practice. The presence of WMHs is associated with global cognitive dysfunction [144, 145], both associated

with brain atrophy [146–148] and independent of atrophy [65]. Increased WMH burden has also been associated with functional decline [149]. Still, many questions remain unanswered about the cognitive implications of specific characteristics of WMH, such as asymmetry of distribution [150], impact of the underlying histopathology [151], or location (e.g., peri-ventricular vs. sub-cortical) [152]. WMHs may also be implicated in AD and AD-related dementia, though

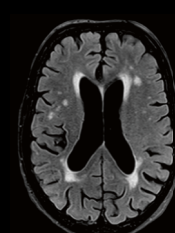
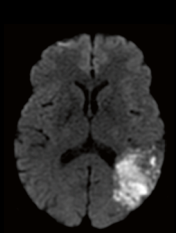
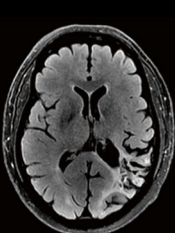
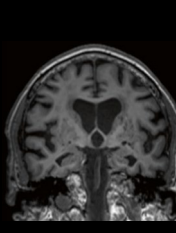
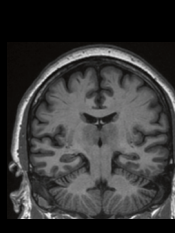
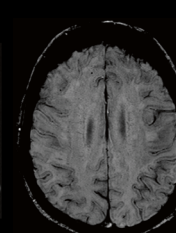
MRI Finding	White matter hyperintensities	Infarct		Atrophy	PVS*	Hemorrhagic/Microbleeds
		Acute	Chronic			
MRI Sequence	T2 or FLAIR**	DWI***	T2 or FLAIR	T1	T1	SWI/GRE****
						
Implication on Cognition	Increased risk of cognitive deficit	Strategic-infarct dementia, increased stroke burden	Infarct number and volume correlate with poorer outcomes; frontal-subcortical processes affected	Predicts global cognitive impairment	Presence and number associated with decline in global cognition, increased risk of stroke/dementia	Presence associated with global cognitive impairment and dementia
<p>* PVS = Perivascular Spaces ** FLAIR = Fluid-Attenuated Inversion Recovery *** DWI = Diffusion-Weighted Imaging ****SWI/GRE = Susceptibility Weighted Imaging/Gradient Echo</p>						

Fig. 3 Vascular MR imaging phenotypes associated with vascular cognitive impairment

the extent of this association remains to be established [153]. Additional work demonstrates an association of WMHs with amyloid deposition, but not with tau [154]. Some suggest the increased risk from WMHs may be independent of the vascular contribution [155]. In fact, WMHs have been associated with processing speed dysfunction via direct and indirect effects on AD-specific radiographic signatures [156]. Ischemic strokes are likewise associated with VCI. The clinical cognitive outcome associated with prior infarction is impairment of frontal-subcortical functions, such as perceptual speed [55]. In addition to the cumulative effect of prior infarcts, one or more strategic infarcts in select anatomic areas associated with cognitive processes may trigger direct cognitive consequences — these are known as strategic infarcts, or single-stroke dementia. Some studies have correlated certain white matter tract lacunar infarcts to specific cognitive domain dysfunction, but concede that making cognitive outcome predictions based on location of stroke is not yet possible [54, 55]. In fact, most studies report a diversity of anatomic locations that have been associated with this VCI phenotype. The presence of more than one infarction was most strongly associated with perceptual speed and other frontal-subcortical functions [157]. Brain atrophy is measured by employing volumetric analysis of CSF (e.g., sulcal and ventricular CSF volumes) and cortical thickness (e.g., medial temporal lobe thickness). Such atrophy denotes disease progression in the context of cerebrovascular disease. Perivascular spaces on CT or MRI are visible as parenchymal hyperintensities on MRI T2-weighted images (or hypointensities on T1/FLAIR) as either linear, if run along the image plane, or round, if they are perpendicular to the image plane [158]. They are common in elderly and visible on MRI in 50–100% of individuals, depending on the imaging methods, scanner resolution, and criteria used for PVS assessment. Most commonly, PVS are seen in the basal ganglia and the centrum semiovale, and less in the hippocampus, the midbrain, the pons, and very rarely in the cerebellum [159]. The exact anatomy, structure, and the function of PVS and their role in cognitive dysfunction and risk of dementia are still unclear. Novel imaging technology to measure cerebrovascular injury is emerging and will inform future VCI research and definitions, particularly imaging of blood–brain barrier (BBB) integrity using gadolinium-enhanced MRI [160]. It measures contrast agent leakage from the blood plasma to the brain interstitial space over time and allows the detection of subtle leakage values in aging, SVD, MCI, AD, and VaD [161]. However, whether BBB leakage is associated with the variation in age-related cognitive decline remains to be investigated. The additional imaging of vascular dysfunction and BBB disruption has been recently suggested to the AD “ATN” (amyloid, tau, neurodegeneration) biomarker research framework [162, 163].

The harmonization of neuroimaging markers of cerebrovascular injury for the diagnosis of VCI is underway. The Harmonizing Brain Imaging Methods for Vascular Contributions to Neurodegeneration (HARNES) initiative provides resources to reduce variability in measurement in MRI studies of SVD and has made available MRI protocols and analysis tools for research use [164]. This initiative complements the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria that suggests harmonized definitions of common cerebrovascular pathologies [158]. Similarly, the NIH-funded MarkVCID is established to validate both neuroimaging and serum- or fluid-based biomarkers for VCI [127, 128]. Most recently, the NIH has awarded the INDEED study (clinical significance of incidental white matter lesions on MRI among a diverse population of cognitive complaints) to investigate the role of MRI-quantified white matter lesions on cognition and health outcomes [165]. There is a great expectation that this research will soon translate the use of multiple neuroimaging biomarkers of VCI into clinical practice.

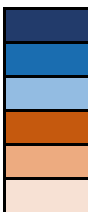
Vascular Risk Factors and Vascular Cognitive Impairment

Evidence accumulated over the past several decades suggests a significant contribution of vascular risk factors to VCI [166] and AD [167, 168]. Although age remains the most significant risk factor for VCI and all-cause dementia [169], vascular risk factors come in second with strongest evidence supporting an effect of hypertension, hyperglycemia, and diabetes [25]. The evidence for the associations of deleterious and resilience factors with VCI as well as for therapeutic approaches to VCI is summarized in Fig. 4.

Deleterious Factors

Hypertension is strongly and negatively associated with cognitive function. Hypertension has been consistently associated with poor performance in executive function [170]; greater rate of cognitive decline [171]; increased risk for MCI [171]; dementia — particularly vascular dementia (VaD) [172]; and structural and functional brain changes [173]. When uncontrolled, hypertension may lead to regional patterns of gray matter atrophy associated with white matter lesions and with worse cognitive performance [174]. In the Honolulu-Asia Aging Study, midlife systolic blood pressure (SBP) of ≥ 120 mmHg was associated with an increased risk of late-life dementia and VaD, with the latter risk being reduced with antihypertensive treatment for SBP but not DBP [175]. In NOMAS, the inverse association of SBP with processing speed/visual motor integration function was non-significant when antihypertension treatment

Fig. 4 Evidence for VCI preventive and therapeutic strategies

		Evidence
Strong evidence as prevention strategy Insufficient evidence No evidence Strong evidence as prevention strategy Insufficient evidence No evidence		
Deleterious Factors	Hypertension	
	Obesity	
	Vascular disease	
	Diabetes/hyperglycemia	
	Hypercholesterolemia	
	Heavy alcohol intake	
	Smoking	
	Homocystine	
Resilience Factors	Physical activity	
	Education	
	Diet	
	Social network	
Pharmalogical Therapies	Donepezil	
	Galantamine	
	Rivastigmine	
	Mematine	
Non-Pharmalogical Approaches	Behavioral control	
	Psychological approach	
	Caregiver support	

was accounted for, in a support of the effect of hypertension control on maintenance of cognitive function [176]. The evidence of increased risk of VaD [177] is particularly strong for midlife rather than late-life hypertension [178], while for AD this relationship is less clear [179]. Furthermore, the relationship between hypertension and cognition appears to be U-shaped, with both higher and lower BP associated with worse cognitive outcomes in older adults [180]. Data pooled across 5 large cohorts suggest that racial disparities in late-life cognitive decline may be explained at least in part by higher BP levels in Black compared to white participants [181].

Obesity has been consistently linked to an increased risk of future dementia when measured in midlife, while after the age of 65, obesity appears to protect against dementia [182]. Newer evidence from a study of 39 cohorts totaling over 1.3 million dementia-free individuals suggests that the positive effect in later life may in fact be confounded by weight loss during the preclinical dementia phase, while the negative effect of midlife BMI is less likely

impacted by preclinical changes and may better capture its direct effect on dementia risk [183]. Several mechanisms have been proposed to explain the link between obesity and cognitive function, including chronic low grade systemic inflammation and oxidative stress in obese individuals [184], increased permeability of the BBB [185], and increased insulin resistance leading to declines in glucose metabolism, all of which contribute to neurodegeneration and neuronal death [186]. In addition, obesity may play a significant role in the development of VCI by promoting arterial stiffness and development of atherosclerosis and SVD [187] via endothelial dysfunction [188]. Weight control is currently considered a reasonable (class IIb/level B evidence) preventive strategy for individuals at risk for VCI [132].

Diabetes and high glucose levels are consistently linked to poor cognitive performance [189], increased risk of dementia [190] and VCI [191]. Individuals < 65 years of age [192] and those with undiagnosed diabetes [189] are at particular high risk. Poor glycemic control in middle-aged

patients with type 2 diabetes mellitus was found to significantly increase rate of decline in memory and reasoning in the Whitehall II cohort study [193]. These effects are supported by a strong relationship of hyperglycemia, diabetes, and insulin resistance with brain vascular changes [191, 194], alterations in cerebral flow [195], AD and non-AD pathology [196], brain infarcts [197], and changes in BBB permeability, all of which play a role in the development of VCI. Metabolic syndrome, a clustering of vascular risk factors, has been negatively linked to cognitive function across global measures [198] and cognitive domains [199] and with increased risk of MCI and its progression [200].

Lipids are the basic components of cell membranes. In the brain, long-chain polyunsaturated fatty acids (PUFAs) account for about 30% of total fatty acids including docosahexaenoic acid (DHA) and arachidonic acid [201] and are implicated in the maintenance of membrane permeability and the interaction between lipids and proteins, therefore promoting brain neurogenesis and modulating inflammation [202]. Reduction in PUFAs has been linked to lipid rafts, particularly in the frontal cortex [203], which may promote aggregation of beta amyloid and hyperphosphorylated tau [204]. Large observational studies support a link between high *cholesterol* particularly in midlife and cognitive impairment and development of AD and VaD in later life, independently of other vascular risk factors including hypertension and diabetes [205]. These findings are supported by a slower progression of cognitive decline in individuals taking statins, particularly among homozygous ApoE4 carriers [206]. The evidence on the effect of long-chain PUFA enriched diets on cognitive performance in older adults is conflicting, with some showing improvement in memory and executive function [207, 208] while others reporting no effects [209–211]. These conflicting results are a consequence of methodological limitations related to lack of uniform biomarkers and sufficient duration of intervention. Trials that address these limitations may help further our understanding of the effect of lipids on cognitive function in older adults and elucidate mechanisms of action [212].

Elevated homocysteine, a risk factor for vascular damage, has been linked to cognitive impairment and a greater likelihood of dementia and VaD [213], findings supported by an evidence of increased neuropathological burden in individuals with high homocysteine levels [214]. Although earlier meta-analyses did not find supporting evidence that lowering homocysteine helps prevent cognitive decline and dementia [215–217], findings from clinical trials of sufficient duration [218] and in participants already cognitively impaired [219] support a beneficial effect of lowering homocysteine with vitamin B supplementation. This positive effect was found on cognitive performance [218] and on the slower rate of brain atrophy in individuals with MCI and particularly in those with total plasma homocysteine levels $> 13 \mu\text{mol/L}$

[219]. However, the benefits of lowering homocysteine on VCI prevention or progression are yet to be determined [214, 220].

Active smoking has detrimental effects on brain health. Early work had shown that nicotine, known for its short-term effects on the neuronal cholinergic system, may have potential benefits in terms of enhanced cognitive performance particularly on memory, cognitive functions that require sustained attention [221], and dementia risk [222], likely through inhibition of amyloid formation [223] and a modulation of choroid plexus function [224]. However, nicotine is just one among the thousands of compounds in tobacco smoke, with many having toxic effects on cardiovascular and pulmonary systems and the brain. The first longitudinal study to assess the impact of smoking on cognitive performance found smoking to increase the risk of cognitive impairment over a 20-year period [225], finding letter supported by subsequent studies showing greater cognitive declines in memory and executive function [226, 227] and a greater risk for dementia [228]. Smoking appears to have a greater impact on cognition in women as compared to men [229], while its relationship to VCI is unclear, although there is some evidence for a greater risk in smokers [230]. Smoking cessation is currently recommended as a reasonable (class IIa/level A) strategy for the prevention of VCI [132].

Due to a lack of homogeneity in the definition of alcohol intake, the use of reference groups, and outcomes, the impact of alcohol use on cognition is unclear [132]. However, there is reasonable evidence from large longitudinal prospective studies that drinking alcohol in moderation may have benefits in terms of a slower rate of decline in cognition [231] and reduced risk of dementia, AD, and VaD [232], potentially through a reduction in the accumulation of neuropathologic changes among individuals with a lifetime history of moderate alcohol intake [233]. In contrast, heavy drinking as well as abstinence have been linked to an increased risk for cognitive impairment [132] and dementia [232]. These reports support a modest benefit (class IIb/level B) of moderate alcohol consumption in older adults and particularly in those at risk for VCI and is therefore considered a reasonable preventative approach [132].

Resilience Risk Factors

Education is positively associated with cognitive performance. Older adults with higher education perform better on global and domain-specific measures of cognition such as working memory and reasoning [234], have a lower risk of dementia [235], and a lower risk of developing post-stroke dementia [236]. While education may not protect against vascular and other neurodegenerative pathologies [220], it may buffer the impact of the neurodegenerative pathology on clinical symptoms [237]. However, issues of confounding of

the education-VCI relationship by various factors including quality of schooling, socioeconomic status, and acculturation have been raised [132], which together with a lack of its ability to prevent development of neuropathology suggest that educational interventions may not be very effective preventative approach for VCI.

Physical activity has been consistently linked to better performance on cognitive testing including global cognition [238] and executive function [239] and to a reduced risk of cognitive decline and dementia including VaD [220]. These effects may result from exercise-induced increases in expression of neurotrophic factors including brain-derived neurotrophic factor (BDNF) that promote neuro- and synaptogenesis and improve brain perfusion [132]. Other mechanisms include attenuation of age-related myelin reduction [240] and maintenance of white matter integrity [241]. The AHA/ASA guidelines gave physical activity class IIb/level B evidence as a reasonable prevention strategy for individuals at risk for VCI [132].

A *healthy diet* is another potential cognitively protective factor with evidence in support of the Mediterranean diet [242]. With its focus on fruits, vegetables, fish, nuts, whole grains, and monounsaturated oils, the Mediterranean diet provides adequate intake of antioxidants such as vitamins E and B12, folate, and n-3 fatty acids, the consumption of which either as part of diet or as supplements was linked to better cognitive function [220] and reduced risk of cognitive impairment [243]. These findings are however inconsistent. Several studies reported no cognitive benefit for antioxidants [244, 245] and fatty acids [246], while Mediterranean diet was not assessed specifically for VCI risk [132]. Higher circulatory levels of vitamin D have also been linked to better cognitive function and may protect against cardiovascular disease and stroke [247], although the evidence is inconsistent [248]. Finally, intake of folic acid and vitamins B6 and B12 may provide protection against cognitive decline by increasing production and metabolism of homocysteine [249]. The AHA/ASA guidelines place diet at class III/level A evidence and do not recommend diet for the prevention of cognitive impairment including VCI.

Although having an active *social network* and *social support* have been linked to better cognitive function [250] and may reduce risk of dementia [251], the quality of social support can have differential effects. While positive social support from the immediate family has been linked to reduced risk of dementia, negative social support has the opposite effect increasing the risk [252]. In addition, being married, having contact with friends, engagement in paid work, and participation in community groups may reduce the risk of incident dementia [253]. Testing these relationships in randomized clinical trials and specifically in relation to VCI is needed before a recommendation for social support as a VCI preventative strategy can be made [132].

The Impact of Combinations of Risk Factors on VCI

While individual risk factors are important to consider when assessing risk of dementia and VCI, the combined effect of risk factors within an individual is a stronger predictor of cognitive decline than independent risk factors. A higher number of vascular risk factors within an individual were associated with greater impairment in executive function and processing speed [254]. In contrast, an increasing number of ideal cardiovascular health factors may protect against decline in processing speed, executive function, and memory [255]. The Cardiovascular Risk Factors, Aging and Dementia (CAIDE), a midlife composite vascular risk score that does not require labs and better reflects the age and education distribution of the study population, was associated with greater cognitive decline [256] and found to predict dementia risk 20 years [257] and even 40 years later [258]. In addition, a higher CAIDE risk score was linked to lower performance on global and domain-specific cognitive tests and helped discriminate cognitive impairment from normal cognition, MCI and dementia cases, and particularly VCI cases from controls [259]. Other vascular risk scores such as the NOMAS GVRs (Global Vascular Risk Score) were found to be inversely associated with level of global cognition and shown to better predict declines in processing speed and memory compared to CAIDE, likely because of an additional inclusion of smoking and glucose levels [260], further supporting the idea that a higher number of vascular risk factors within an individual better predicts cognitive decline.

Strategies for VCI Prevention

One strategy for the prevention of dementia and VCI is to address modifiable vascular risk factors, with particular interest in multimodal interventions.

Several large clinical trials have assessed the impact of *antihypertensive medications* on cognitive outcomes including risk of dementia and VCI in patient populations with various risk conditions. One of the first and most compelling studies is the Dementia Study of the Systolic Hypertension Europe (Syst-Eur), which randomized 2418 dementia-free 60+ years adults with seated SBP between 160 and 219 mmHg and DBP < 95 mmHg to either an active treatment receiving nitrendipine (a dihydropyridine) combined or replaced by enalapril (an ACE inhibitor) and/or hydrochlorothiazide (a diuretic) or a control group [261]. After an average of 2 years of follow-up, a 50% reduction in the incidence of dementia was reported for the active treatment group. In an open-label follow-up study, a significant reduction in both AD and VaD was reported for the active treatment group [262]. The Dementia Study of the Systolic

Blood Pressure Intervention Trial (SPRINT–MIND) randomized 9361 50+ years patients with SBP between 130 and 180 mmHg and increased cardiovascular risk to an intensive BP lowering regimen (< 120 mmHg) or the standard regimen of < 140 mmHg [263]. A significant 20% reduction in the risk of MCI and 15% in a composite outcome of MCI or probable dementia was reported, as well as a smaller increase in cerebral white matter lesion volume in the intensive treatment group was observed [264]. In the Dementia study of the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS), another large trial comparing 2 antiplatelet treatments (ASA + dipyridamole vs. clopidogrel and telmisartan) in 20,332 patients with prior stroke, there was no difference in the rates of cognitive decline between the 2 treatment groups, which also did not differ in risk of recurring stroke or major vascular events that were the primary outcomes [265, 266]. Additional support for a benefit of lowering BP on cognition comes from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in which 6105 older adults with a history of cerebrovascular events were randomized to either perindopril (ACE inhibitor) and indapamide (diuretic) vs. placebo [267]. Receiving the BP lowering treatment was associated with significant reductions in the risk of dementia and cognitive decline in patients with recurrent stroke and delayed progression of WMHs [268] in addition to substantial reductions in stroke risk [269]. The AHA/ASA guidelines gave class I/level A evidence to BP lowering as a preventative strategy in people at risk for VCI [132].

Existing evidence points to a negative contribution of midlife *hypercholesterolemia* to cognitive function and increased risk of dementia and VCI. Early statin trials, however, failed to demonstrate an effect on cognitive decline. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) reported no differences between a pravastatin and a control group in rates of decline in cognitive tests during the 3-year follow-up [270]. This was in line with data from the Heart Protection Study, which found no benefit of simvastatin on cognition [245]. Some evidence for a benefit for atorvastatin in improving cognitive function in older adults with dementia was reported in a small trial [271]; however, other statin clinical trials in patients with mild to moderate AD did not show cognitive benefits [272]. A benefit of simvastatin in preserving white matter microstructure was reported in cognitively normal middle-aged adults, suggesting a potential for VCI prevention [273]. Larger trials are however needed to establish a clinical benefit for statins in preventing or treating VCI. Nevertheless, maintenance of normal plasma cholesterol levels remains an important health promotion strategy. Treatment for hypercholesterolemia is currently recommended as a reasonable preventative modality for individuals at risk for VCI (class IIb/level B evidence) [132].

There was some initial evidence of an effect of *diabetes treatments* on cognition in small trials [274]; larger trials have been largely negative. Intensive glucose lowering in the ACCORD study in participants with type 2 diabetes mellitus (T2DM) did not significantly reduce major cardiovascular events over a period of 3.5 years and was found to increase mortality [275]. In the ACCORD MIND sub-study, intensive lowering of lipid and BP levels did not affect cognitive decline and was associated with greater decline in brain volume compared to standard therapy [276]. The latter finding could be explained by compromised brain perfusion and impaired autoregulation during intensive BP lowering, suggesting that intensive lowering of BP in older adults with T2DM may not be safe or beneficial [277]. In the largest study to date testing the efficacy of low-dose pioglitazone in delaying onset of MCI, there was no effect on delaying onset of MCI due to AD [278]. A recent meta-analysis of T2DM randomized clinical trials also found no robust evidence that T2DM treatment prevents or delays cognitive impairment [279]. Trials to assess impact of diabetes control on cognitive decline are needed in middle-aged individuals at risk for VCI as they may be able to assess benefits in preventing development of VCI. Treatment of hyperglycemia is currently considered a reasonable preventative strategy for individuals at risk for VCI (class IIb/level C of evidence) [132].

Multimodal interventions such as in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a 2-year multicenter RCT that enrolled 1260 adults 60–77 years of age into an intervention including diet, exercise, cognitive training, and vascular risk monitoring or a control group, provided strong evidence for positive cognitive change and potential for prevention of AD and VCI [280]. The FINGER model with multiple vascular risk factors control seems to be most promising brain health strategy and currently is being tested in diverse populations worldwide.

Strategies for Symptomatic Treatment

Symptomatic treatment for VCI requires a multifaceted approach that involves pharmacological therapies to directly address cognitive and behavioral symptoms as well as non-pharmacological modalities that focus on optimizing quality of life for both patients and caregivers [281].

Several clinical trials had tested the effect of *cholinesterase inhibitors* and *NMDA receptor antagonists* on cognition, global and physical functions with modest support for their efficacy in VCI [132]. The first 2 large trials of *donepezil* reported benefits on cognition and to a lesser extent on global function and activities of daily living outcomes, with similar side effects as observed in AD [282, 283]. A meta-analysis of 12 studies provided support for the efficacy of

donepezil in improving cognitive function [284], although the improvements failed to reach clinical significance [285]. *Galantamine* in comparison to placebo did not show clinical significance, but showed some benefits on cognition, improved functionality measures, and reduced behavioral symptoms in mixed AD/VaD, not in pure VaD [286]. A trial that included only patients with pure VaD reported improvement in cognition, with 40% of participants in the galantamine group having a clinically significant change in ADAS-Cog score of ≤ -4 points versus 27% in the placebo group [287]. Evidence for *rivastigmine* and *memantine* is even less robust, with two studies showing a slight improvement in executive function and behavior for rivastigmine in patients with subcortical VaD [288], in executive function in VCI patients [289], and in cognition for memantine in mild to moderate VaD patients [290, 291], although these improvements were not clinically significant. A recent meta-analysis found moderate to high evidence that donepezil has the greatest effect on cognition followed by galantamine, although effects were not of clinical significance [292]. Despite its slight effects and in the absence of other treatments, this meta-analysis supports the use of donepezil in people with VCI, which is in line with the AHA/ASA recommendations regarding the use of donepezil for cognitive enhancement in VCI [132].

Caregivers need a *support system* to address the challenges posed by a dementia diagnosis and clinicians are well positioned to guide them as they learn to navigate the formal care system, identify community resources to address challenges in various aspects of health, assess transportation needs, plan for future care needs including placement and palliative care, and help in the management of psychological symptoms and neurobehavioral complications [132]. Another important goal is to reduce caregiving-related stress, burden, and strain, and improve their quality of life. As caregiver and patient experiences with dementia care and their impact on health are closely related and often reinforce each other, reducing caregiver stress, addressing their support needs, and improving their coping skills have the potential to elicit positive effects in VCI patient outcomes [293] and delays in nursing home placement [294].

Concluding Thoughts

Vascular cognitive impairment (VCI) includes the whole spectrum of cognitive impairment ranging from clinical mild cognitive difficulties that are evident only on cognitive testing to MCI and clinical dementia. The neuropathology of cognitive impairment in later life is often a mixture of vascular, AD, and other neurodegenerative pathology, which overlap and increase risk of cognitive impairment. Determining the contribution of vascular disease to VCI is greatly

facilitated by neuroimaging, particularly by novel MRI techniques and advancements in magnetic field strength. Cerebrovascular risk factors are common among older adults and are major contributors to VCI. Currently, no specific treatments for VCI exist, but standard stroke preventive measures are recommended. Multimodality interventions that include the modifications of vascular risk factors and lifestyle are currently most promising VCI treatment and prevention strategy. VCI has been increasingly recognized as most prominent concept of vascular and mixed dementias and has received major attention worldwide with the opportunities for collaborative actions. VCI clinical and scientific framework that accounts for complexity of vascular factors and overlaying diagnoses will help drive translational research for improved understanding and ultimately lead to effective prevention and treatment of VCI in clinical practice.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13311-021-01170-y>.

Required Author Forms [Disclosure forms](#) provided by the authors are available with the online version of this article.

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