HHS Public Access

Author manuscript

Biochim Biophys Acta. Author manuscript; available in PMC 2017 January 12.

Published in final edited form as:

Biochim Biophys Acta. 2016 May ; 1862(5): 860–868. doi:10.1016/j.bbadis.2015.12.015.

Vascular cognitive impairment and dementia

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Abstract

Vascular contributions to cognitive impairment are receiving heightened attention as potentially modifiable factors for dementias of later life. These factors have now been linked not only to vascular cognitive disorders but also Alzheimer's disease. In this chapter we review 3 related topics that address vascular contributions to cognitive impairment: 1. vascular pathogenesis and mechanisms; 2. neuropsychological and neuroimaging phenotypic manifestations of cerebrovascular disease; and 3. prospects for prevention of cognitive impairment of later life based on cardiovascular and stroke risk modification.[1]

Keywords

Stroke; Prevention; Vascular cognitive impairment; Pathophysiologic mechanisms

1. Introduction

Over 100 years ago, Dr. Alois Alzheimer and colleagues noted "arteriosclerosis of the small cerebral vessels" as a potential source of the dementia observed in his most famous patient, Auguste Deter. This view reflected the predominant theory of the day that dementia was caused by hardening of arteries in the brain [1]. Although Alzheimer's disease (AD) research has since become more focused on mechanisms of plaque and tangle pathology, emerging data show that cerebrovascular disease (CVD) dramatically increases the risk of developing dementing disorders such as AD and vascular cognitive impairment and

[1]This article is part of a Special Issue entitled: Vascular contributions to cognitive impairment and dementia edited by M. Paul Murphy, Roderick A. Corriveau and Donna M. Wilcock.

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Transparency document

The Transparency document associated with this article can be found in the online version.

dementia (VCID) [2], and likely contributes to mixed dementia cases that are often seen in clinical pathologic cohorts [3]. These observations have reinvigorated the field to gain a better understanding of how vascular brain lesions affect cognitive decline in the elderly. In this regard, significant associations have been established between incident dementia and hypercholesterolemia, atherosclerosis, diabetes, hypertension, lack of exercise, and obesity [4]. Epidemiology aside, there is a strong scientific rationale for linking CVD to cognitive impairment, as the link between age-related cerebrovascular changes and the dysregulation of cerebral perfusion, blood–brain barrier (BBB) function, and neurovascular coupling is now better appreciated [5,6].

In this chapter, we review three important and inter-related topics: 1. current thinking on CVD and VCID risk factors and prevention; 2. age-related cerebrovascular factors and pathological events that are believed to precipitate VCID as well as promote the progression of AD and mixed dementia; and 3. neuropsychological and neuroimaging manifestations of these cerebrovascular disorders. Given the rising prevalence of CVD and dementia with aging, interventional measures to prevent or forestall CVD in advancing age may be key factors in preventing the onset of cognitive decline in the elderly. In our discussion, the terms vascular cognitive impairment (VCI) and VCID may be used interchangeably.

2. Risk factors and prospects for prevention

2.1. Risk factors

Traditional risks for stroke and cardiovascular disease have long been thought to be risks for VCID [2,7]. For example, raised blood pressure, hyperglycemia, insulin resistance, metabolic syndrome, diabetes mellitus, hyperlipidemia, cigarette habit, obesity, lack of physical activity, poor dietary practices, and medical history of coronary artery disease, stroke, chronic renal disease, atrial fibrillation, peripheral arterial disease, and heart failure (low cardiac output) may be epidemiologically linked to VCID [2,7,8]. In addition, other factors include older age and lack of social support or social networking. Furthermore and more recently, it has become recognized that traditional cardiovascular risks are also risks for AD [9–11]. Based on population attributable risk (PAR) calculations, it has been estimated that approximately 50% of AD risk is explained by traditional cardiovascular risks [12]. Reduction of these risks could possibly lead to a substantial decrease in AD and cognitive decline. To date, these intriguing epidemiologic findings have not translated into successful treatment studies, perhaps because of the high cost of necessary long term experimental designs, and the lack of sensitive neuropsychological instruments as primary study endpoints.

The mechanistic linkage of traditional cardiovascular risks to cognitive impairment and dementias of later life has been the subject of considerable study and discussion. Hypertension and diabetes mellitus are two such factors that have been closely scrutinized. Raised blood pressure may be linked to cognitive impairment and dementia through the following mechanisms: 1. *functional* (e.g., endothelial dysfunction, impairment of hyperemic response, exaggerated blood pressure dipping or non-dipping, and reduced clearance of cerebral amyloid); 2. *structural* (e.g., presence of white matter disease, increase in the number of neuritic plaques and neurofibrillary tangles, and smaller brain size); 3.

systemic (e.g., alterations in the renin–angiotensin aldosterone system [RAAS]); 4. *stroke-related* (e.g., occurrence of strategic stroke [in the thalamus, angular gyrus, and caudate nucleus] and tissue loss associated with large and small strokes); and 5. *other* (e.g., presence of traditional cardiovascular risks with other metabolic factors that they are associated with) [13].

In addition, classes of blood pressure lowering drugs have hypothesized positive and negative influences on cognitive outcomes [13]. These may be summarized by drug class: 1. *beta blockers* (neutral influence or possible negative cognitive outcome if adrenergic pathways in the brain are blunted); 2. *diuretics* (in the case of potassium-sparing diuretics, AD might be decreased); 3. *angiotensin* receptor blockers (inhibition of the AT-1 receptor allows access of Ang II to the neuroprotective AT-2 receptor); 4. *angiotensin converting enzyme inhibitors* (prevention of catabolism of brain enhancing peptides could result in a positive effect, however, there may be an increase in the long-term burden of brain β-amyloid with this class of agents); and 5. *calcium channel blockers* (may provide neuroprotection by maintenance of intracellular calcium homeostasis).

In relation to diabetes mellitus, there have been a number of hypothesized mechanisms whereby diabetes might be deleterious to cognitive outcomes. Key brain mechanistic pathways that may be influenced include that of insulin-degrading enzyme in relation to degradation of brain β-amyloid, abnormalities of insulin signaling, lower effective brain insulin levels, brain insulin resistance, inadequate production of acetylcholine, and presence of advanced glycation end-products [14]. There are a host of other cardiovascular risks which may be linked to cognitive impairment, however, specific discussion of hypothesized mechanisms is beyond the scope of this chapter and is reviewed elsewhere [14].

2.2. Prospects for prevention of cognitive impairment and dementia of later life

A 2010 US National Institutes of Health State-of-the-Science Conference addressing risk factors and preventive interventions for AD concluded that insufficient evidence existed to draw firm conclusions about the association of modifiable risks such as cardiovascular risks and the risk of AD [15]. The latter statement provided a sobering viewpoint and concluded that there were no proven preventives for AD. On the other hand, large epidemiologic prospective studies of the prevalence or incidence of cognitive decline or dementia over time have now shown that a reduction of the prevalence or incidence of cognitive impairment may be explained by protective mechanisms associated with better control of traditional cardiovascular risks and education [16]. Clearly, the challenge remains to better understand basic mechanisms that underlie vascular causes of cognitive impairment and the attendant clinical manifestations and outcomes. The challenges and next steps to better understand the process have been articulated by an expert group of scientists brought together by the Alzheimer's Association, National Institute of Neurological Disorders and Stroke, and the National Heart, Lung and Blood Institute of the US National Institutes of Health and are discussed in detail elsewhere [17].

A recent major statement on *cognitive aging*, a process that takes into account changes that occur for example in an individual's memory, decision making, processing speed, wisdom and learning over time, was released by the Institute of Medicine (IOM) [18]. The statement

was crafted by an expert committee with support from the McKnight Brain Research Foundation, the US National Institute on Aging, the National Institute of Neurological Disorders and Stroke, AARP, and the Retirement Research Foundation, under the auspices of the IOM. Committee members convened to scrutinize public health aspects of cognitive aging [18]. In relation to steps to reduce risks for cognitive impairment, the IOM-designated committee identified specific actions supported by scientific evidence to maintain cognitive health and possibly reduce the effects of cognitive aging. Specific actions to be taken by the public based on the committee report are listed in Table 1 [18]. In addition, the IOM group listed other actions where there is some scientific evidence to indicate positive benefits on cognitive health (see Table 1).

The IOM report emphasizes firstly the importance of physical exercise, cardiovascular risk factor control, and scrutiny of medications that might influence cognitive health [18]. Also and secondarily, the potential importance of social networking, continued learning, proper sleep hygiene, and avoidance of delirium, if hospitalized, is highlighted. While the effect of correcting these conditions on preventing neurocognitive deterioration has been inconsistent, the IOM statement may serve as a springboard for future brain health initiatives at the individual and population levels. At a minimum, control of traditional cardiovascular and stroke risks will result in reduction of stroke and heart disease [2]. An added benefit, therefore, might be the preservation of brain health and cognitive vitality. Implementation of additional scientific studies as outlined in a prior publication on vascular contributions to cognitive impairment and dementia, might help to further validate the value of cardiovascular and stroke risk control in relation to maintenance of cognitive function [2]. Moreover, basic and translational research efforts to elucidate the age- and disease-related factors underlying cerebrovascular lesions and their downstream pathological consequences will aid the identification of potential disease modifying modes of intervention.

2.3. Factors associated with VCID, AD and mixed dementia

2.3.1. The neurovascular unit and age-related changes in the cerebrovasculature—

Neurons, astrocytes, oligodendrocytes, and vascular and perivascular cells that comprise the neurovascular unit operate through structurally interrelated and metabolically codependent pathways to couple blood supply with energy demand and maintain the homeostasis of the cerebral microenvironment [19]. Vasoregulatory signaling keeps cerebral blood flow (CBF) within a relatively constant range of perfusion pressure through a variety of spatiotemporal signaling mechanisms generated by synaptic and glial activity, including the regulation of ion channel activity, arachidonic acid metabolism, and nitric oxide, endothelin, and prostanoid production within the vascular endothelium [20,21]. Together, these signaling mediators coordinate vessel tone and neurovascular coupling, immune surveillance, and hemostasis following injury [22–24]. Cerebral endothelial cells also play a highly critical role in barrier function: tight junctions and transporters within these cells regulate the trafficking of molecules between blood and brain, thus comprising the BBB that allows influx of nutrients into the brain and the efflux of metabolic byproducts [25]. Together, these highly coordinated processes regulate the hemodynamic response of the cerebrovascular network and support neural activation and neuronal function.

The neurovascular unit is profoundly influenced by cerebrovascular aging processes that hasten CVD in the presence of cardiovascular risk factors and impact the onset of VCID [26]. Common elements of vascular aging include changes in large arterial structure and function over the life span that often correlates with silent cerebral small-vessel disease (SVD). These changes include vessel wall plaque deposition and increased vessel wall thickness (atherosclerosis) and increased vessel stiffness (e.g., hardening of the arteries, or arteriosclerosis) [27]. Although a number of over time, gradually increasing intima-media thickness by nearly three-fold between 20 and 90 years old [28]. Moreover, pathological factors that thicken vessel media such as hypertension and/or intima thickening in response to atherosclerotic risk factors can compound the severity of these age-related changes [28]. In this regard, ultrasound can be used to measure this thickness in the extracranial carotid arteries, and studies have reproducibly shown an association between increased artery thickness and poorer cognitive performance [29,30]. Arterial stiffness during aging is also associated with collagen and plaque buildup in the vessel wall in addition to pathways involved in the mechanical regulation of vascular structure, including integrins, proteoglycans, fibulin-1, and fascin [31]. Carotid-femoral pulse wave velocity is a reliable measure of arterial stiffness [27], and increased pulse wave velocity has been linked not only with cognitive decline, but also with white matter hyperintensities predictive of incident dementia [32,33].

Venous damage may also play a role in VCI. Venous collagenosis is associated with long-term hypertension in rats [34]. In humans, Gao and colleagues [35] noted a relationship between periventricular hyperintensities (PVH) and venulopathy in a sample of patients with AD compared to controls. They hypothesized that collagenosis dilates the veins, causing venous insufficiency and vessel leakage. Henry-Feugeas and Koskas [36] suggest that pulse wave encephalopathy may affect both capillaries and cerebral veins, leading to cerebrovascular pathology, stroke and dementia. Thus, both arterial and venous pathology are implicated in leukoaraiosis and VCI [37]. Vascular aging and the effects of cardiovascular risk factors on these processes likely play an important role in VCID and present multiple targets for disease modifying therapies administered early in the aging trajectory.

2.4. Vascular lesions associated with VCID

Age-related and pathologic arterial structural abnormalities can lead to cognitive dysfunction by downstream cerebrovascular events that cause macroscopic infarctions, discrete regions of brain parenchyma necrosis caused by insufficient blood flow. These events include thrombotic occlusion of large vessels with subsequent chronic cerebral hypoperfusion, cerebral embolism originating from carotid plaques, and blood pressure dysregulation affecting BBB integrity [2,38]. Moreover, lacunar infarcts, microinfarcts, hemorrhages, cerebral microbleeds, and white matter lesions can result from interior small vessel and microvascular disease, arising either from large vessel disorders or as an independent systemic process [39]. SVD, which also increases with age and is accelerated by vascular risk factors such as hypertension, results from thickening of the capillary basement membrane, vessel tortuosity, lipohyalinosis and other pathologic processes, eventually leading to endothelial leakage and microthrombi, systemic arteriolar dysfunction and local

hypoperfusion [6]. SVD first appears in arteries of the basal ganglia and then expands into the peripheral white matter and leptomeningeal arteries, as well as into thalamic, cerebellar and brainstem vessels, but neocortical vessels are typically spared [40]. Finally, the deposition of the β-amyloid peptides in cerebral vessels, a pathologic event termed cerebral amyloid angiopathy (CAA), is a disorder that most frequently involves neocortical arteries, veins, and capillaries [41]. Notably, β-amyloid is the chief component of extracellular senile plaque pathology in AD. CAA is prominent in AD and, to a lesser extent, VCID, and is associated with lobar micro-hemorrhages and microbleeds [42] and microinfacts [43]. Clusters of families carrying distinct familial mutations in the amyloid precursor protein (APP), from which β-amyloid derives, suffer from prominent CAA [44,45], providing a valuable patient resource for better understanding the effects of CAA on VCID.

In clinical–pathological studies, the number and volume of macroscopic infarcts are associated with an increased likelihood of dementia [3,46]. However, determining a threshold number or volume of infarcts necessary for VCID has been elusive, likely because the impact of these macroscopic lesions are influenced by neuroanatomical location and distribution that differentially affect neural circuits underlying higher order cognitive behaviors [39]. For instance, cortical relay regions such as the thalamus and basal ganglia may be more likely than other regions to result in cognitive impairment. However, multiple microscopic infarcts have also been related to dementia independent of macroscopic infarcts, likely due to local hypoxia, inflammation, and BBB breakdown in key gray and white matter regions [47–49]. By contrast, SVD (e.g., arteriole stenosis) in the deep white matter can contribute to cognitive decline via gliosis, axon demyelination, and axon loss [50]. A recent imaging study showed that lobar, but not deep or infratentorial microbleeds were also associated with worse performance on neuropsychological tests after adjustments for vascular risk factors and other imaging markers of SVD [51].

Three broad subclassifications of VCID can be defined with respect to this spectrum of underlying neuropathology: multi-infarct dementia, strategic infarct dementia, and subcortical vascular encephalopathy. Multi-infarct dementia is the most common VCID subtype as it is not linked to any specific age-related vessel disorder or pathologic lesion, but rather includes cases comprising multifarious large, lacunar, and microinfarcts, as well as age-related vessel disorders across multiple, predominantly gray matter regions such as cingulate and temporal neocortex. By contrast, strategic infarct dementia is characterized by single infarcts in discrete subcortical regions mediating cognitive function such as the hippocampus [52], thalamus [53] or the anterior limb of the internal capsule [54]. Subcortical vascular encephalopathy (also known as Binswanger’s disease) is characterized by confluent central and peripheral white matter lesions associated with demyelination and axon loss [39,40]. This pattern of degeneration is similar to Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), an inherited, relatively early onset disorder which is linked to a mutation in the Notch 3 gene. The disease primarily affects small blood vessels in the white matter and its clinical course is characterized by multiple lacunar infarcts and white matter lesions progressing to dementia and psychiatric problems [52]. CARASIL, which is an autosomal recessive arteriopathy associated with mutations in the HTRA1 serine peptidase gene, presents with similar cognitive deficits and small vessel disease [55]. Recently, other heterogeneous autosomal

dominant disorders have been associated with heterozygous HTRA1 gene mutations [56]. Hippocampal sclerosis has also been suggested to reflect vascular damage, and a recent neuropathological examination revealed a strong correlation between this disorder and arteriolosclerosis in multiple regions outside of the hippocampus (e.g., frontal cortex) [57]. Hence, VCID and even mixed dementia subclassifications will likely undergo refinement as clinical pathologic studies reveal new VCID subtypes that reflect the spatiotemporal and pathological heterogeneity of CVD lesions found in the general population.

2.5. Molecular mechanisms of VCID

Oxidative stress and inflammation in cerebral vessels are currently thought to be key, interrelated pathogenic factors linking CVD pathology with neurovascular dysfunction and VCID [26]. For instance, patients with hypertension exhibit deficits in the capacity to autoregulate cerebral perfusion in response to changes in blood pressure. This leads to aberrant signaling of the vasoactive peptide angiotensin II, which mediates vascular remodeling in response to blood pressure dysregulation [58]. Angiotensin II activation in this context has been linked both to pro-inflammatory effects through activation of leukocytes, cell adhesion molecules, and inflammatory cytokines [59], as well as the stimulation of NADPH oxidase, which has emerged as an important source in vascular oxidative stress and reactive oxygen species (e.g., superoxide) production [60]. In addition, several studies indicate that experimental hypoperfusion (e.g., ischemia/reperfusion models) results in NADPH oxidase-induced reactive oxygen species that can signal the commencement of inflammatory pathways through Toll-like receptors. Inflammation, in turn, enhances oxidative stress by down-regulating antioxidant defenses [61]. BBB breakdown also appears to play a role in this inflammation-oxidative stress loop, as proteins such as plasma-borne complement and intracerebral β-amyloid are potent activators of inflammation and free radical production [62]. Regardless of the source, continued vascular damage from oxidative and inflammatory insults likely interferes with neurovascular coupling and exacerbates tissue hypoxia, compromising neuronal and white matter function. Oxidative stress reduces endothelial production of brain-derived neurotrophic factor [63], which provides an important source of neuroprotective signal transduction via TrkB receptors on the neuronal membrane [64]. Finally, vascular oxidative stress and inflammation from CVD risk factors and BBB breakdown also impede the proliferation, migration, and differentiation of oligodendrocyte progenitor cells and compromise repair of the damaged white matter, contributing to demyelination and local hypoxia [65]. Taken together, these diverse pathways likely represent key mechanisms whereby the progression of CVD pathology contributes to the clinical expression of VCID.

2.6. Animal models of VCID

Over the past several decades, a variety of animal models have been developed to replicate vascular pathology associated with VCID. Here, we highlight a few of these models. Several excellent review articles can be consulted for more detailed information [66–68]. The most commonly used experimental paradigm induces ischemia and global hypoperfusion via surgical ligation of the common carotid arteries in the rat, which results in central cholinergic dysfunction and increased oxidative damage, white matter pathologies (e.g., demyelination), hippocampal cell loss, atherosclerotic changes, and impaired learning and

memory on behavioral tasks [69]. The electron cycler methylene blue was shown to reverse cognitive deficits following this lesion, suggesting a therapeutic role of augmented mitochondrial respiration to combat hypoperfusion [70]. More recently, new methods of less acute common carotid artery stenosis using microcoils or ameroid constrictors have been shown to gradually reduce CBF, resulting in arterial remodeling, subcortical infarctions, and cognitive impairment. These mice replicate the natural history of CVD pathology more closely than acute global hypoperfusion and may prove more efficacious for preclinical drug testing for VCID [71,72]. Focal hypoperfusion can also be induced in rats by occluding the middle cerebral artery, resulting in cortical, striatal, and subcortical white matter lesions, as well as spatial memory impairment [73,74]. While these models of ischemia are valuable in studying the pathogenic sequel following infarction, models replicating risk factors for CVD and VCID may be more valuable for testing preclinical strategies for disease modification. For instance, the angiotension II infusion mouse model of hypertension reduces CBF and results in increased leukocyte adhesion, superoxide-mediated oxidative stress, BBB permeability and vessel amyloid accumulation, and behavioral deficits [75,76]. Spontaneously hypertensive rats exhibit strokes, predominantly in the neocortex and basal ganglia [77], and chronic cerebral artery remodeling that can be attenuated by treatments that deplete macrophages, detoxify superoxide, or inhibit matrix metalloproteases [78–80]. Several transgenic mouse models of atherosclerosis have also been developed, most notably those based on null mutations in the ApoE or LDLR genes. In particular, apoE−/− mice display reduced CBF, BBB breakdown, and arterial remodeling concomitant with inflammatory cytokine production, leukocyte infiltration, gliosis, and spatial memory impairments [81–83]. ApoE−/− mice showed behavioral improvement with targeted replacement of human apoE3, but not apoE4 [84]. Given that the apoE4 allele is the greatest genetic risk factor for AD [83], these data suggest that apoE may influence AD pathophysiology through its role in modulating vascular health. Finally, mouse models of AD engineered by overexpressing mutant APP have been found to serve as suitable models for CAA, as APP-derived β-amyloid accumulates in the cerebrovasculature of these mice in addition to brain parenchyma (see [68]). Among these strains, the Tg2576 mouse has been the most thoroughly characterized for CAA pathology [85–88]. This mouse expresses human APP bearing the Swedish (K670M/N671L) mutation driven by a prion protein promoter [89]. With respect to CAA, in vivo imaging [85,87,88] and neuropathologic analysis [86,88,90] of these mice reveal the initiation of cerebrovascular deposition of β-amyloid starting from 9 months old and rapidly progressing to involve most arterioles by 18 months.

Taken together, these and future VCID models will be valuable preclinical tools for understanding and treating the vessel lesions and perfusion factors related to cognitive impairment. Given the accumulating evidence that vascular dysfunction and hypoperfusion influence the progression of AD, these models will also be key for understanding the role of CVD in AD and mixed dementia.

2.7. Neuroimaging and neuropsychological considerations in VCID

Neuroimaging and neuropsychology often go hand-in-hand in VCID. If neuroimaging provides the “picture” of stroke and cerebrovascular disease, neuropsychology interprets the

picture. That is, cognitive and behavioral markers show the relationship of cerebrovascular pathology to cognitive and behavioral decline. Advances in both neuroimaging and neuropsychology techniques provide a more complete understanding of VCI.

2.8. Advances in neuroimaging and VCID

The primary role of neuroimaging in the study of VCID is descriptive rather than diagnostic, as there are no pathognomonic radiographic features in VCID and both cerebrovascular and degenerative conditions often co-exist [3]. A challenge to accurate comparisons across imaging studies was the variations in techniques used by different imaging teams. The VCI Harmonization Conference [91] attempted to establish similar methods across study teams. They recommended MRI over CT when possible and required that the MRI protocol consist of 3-D T1, T2 weighted fluid-attenuated inversion recovery (FLAIR) and gradient echo sequences, and images acquired parallel to the AC–PC line. In addition, they recommended diffusion-weighted images and the quantification of the apparent diffusion coefficient (ADC) to provide information about acute ischemic stroke. Using this protocol, the following factors for study were mandated: brain atrophy, white matter hyperintensities, infarction volume, hemorrhage volume, and other measures, including the presence of mass lesions, AVMs, and extra-axial fluid collections that may complicate CVD assessment. The recommended methods to achieve these MRI measures are detailed in Table 2. The committee preferred quantitative measurement of the mandated factors but recognized that some investigators were limited to rating scales. For WMH, they noted as acceptable the Age-Related White Matter Changes Scale [92] and the White Matter Hyperintensity Scale from the Cardiovascular Health Study [93]. Other rating scales in widespread use include Schelten's Scale [94] and the Fazekas Scale [95]. A potential complication when measuring microinfarcts are that lesions <3 mm may either be microinfarcts or perivascular spaces, as noted by studies which compare MRI to pathology. Future studies using 7 T may differentiate the two more reliably than can be done at 3 T [96,97].

The harmonization imaging protocol has been used to produce a wealth of information about the relationship of CVD to both cognitive and functional impairment. A recent example of this is a study by Chaudhari et al. [98], who examined 102 stroke patients for six months to assess risk factors for VCI incidence. They found a 45% VCI rate in their sample. Neuroimaging-related factors associated with VCI included age-related white matter changes and strategic site lesions, defined as strokes in the areas of thalamus, angular gyrus, caudate, globus pallidus, basal forebrain, cingulate gyrus, genu or anterior limb of the internal capsule or hippocampus. Of interest, they did not find that left hemisphere strokes were a risk factor for VCI, unlike some previous studies [99,100]. The authors note that the 45% rate of VCI included 18% with vascular dementia, while 27% were classified with vascular cognitive impairment, no dementia (VCIND). This inclusion of non-demented persons with VCI is consistent with new guidelines from the American Heart Association/ American Stroke Association, which posit that VCI should include the entire spectrum of cognitive impairment associated with stroke and CVD [2].

In addition to standard MRI protocols, investigators have used less conventional MR techniques these techniques is diffusion tensor imaging (DTI), which measures the

movement of hydrogen in at least six non-collinear directions. This allows for an examination of the extent of directional diffusion. Relatively high directional diffusion is found in non-damaged white matter fibers, while non-directional diffusion occurs more frequently in damaged areas, where there are less consistent barriers to diffusivity. A primary DTI measure is fractional anisotropy (FA), which ranges from 0 to 1. Scores closer to 1 indicate greater directional diffusivity. FA scores are lower in areas of leukoaraiosis due to white matter damage in patients with lacunar infarctions [101], CADASIL [102], or non-CADASIL, ischemic subcortical vascular disease patients [103]. Of note, lower FA scores have also been found in the subcortical gray matter structures, such as thalamus, of patients with CVD [104]. More recent studies have used diffusion tensor tractography to identify the effects of small vessel ischemic disease on major white matter fiber tracts [105] and the relationships between subcortical infarcts and cortical thinning in connected cortical regions [106]. Other studies have focused on relationships between DTI measures and cognitive function, with an inverse relationship found between FA scores and measures of executive function, attention, memory or psychomotor ability [107,108].

Magnetic resonance spectroscopy techniques are used to examine the neurochemical underpinnings of primarily subcortical CVD. The metabolite N-acetylaspartate (NAA) is only found in neurons and is identified as a measure of general neuronal health. Capizzano et al. [109] found lower NAA in the cerebral cortices of patients with dementia and lacunar infarctions compared with healthy, age-matched controls. Lower NAA–creatinine (NAA:Cr) ratios have also been found in patients with CADASIL [110]. A relationship between absolute NAA (absolute levels or ratios) and measures of cognitive function have been found in some [111] but not all [109] studies.

Finally, functional MRI (fMRI) techniques are used to describe relationships between areas of CVD and cerebral activation, as defined by changes in the paramagnetic state of oxygenated and deoxygenated cerebral blood. A common use for fMRI in patients with stroke has been to examine for cortical activation changes in patients with or without specified rehabilitative techniques [110]. These studies appear to show a post-stroke shift in activation to the non-affected hemisphere [111] and/or within the affected motor cortex [112]. Other studies have shown an apparent inverse relationship between subcortical ischemic vascular disease, such as white matter hyperintensities, and fMRI-defined activation [113,114].

As noted above, standardization and harmonization of neuroimaging protocols is important to allow for comparison of results across studies. A position paper, STandards for Reporting Vascular changes on nEuroimaging (STRIVE), was developed by an expert group to standardize terminology and definitions for imaging analysis in cerebral SVD [115]. For example, over 50 different terms have been used for neuroimaging findings of white matter disease related to stroke. STRIVE investigators provide both MRI brain- and CT head-based definitions for this disorder under the rubric of white matter hyperintensities of presumed vascular origin.

3. Advances in vascular cognitive impairment classification

The classification of cerebrovascular-related cognitive impairment has gone through many permutations and descriptive titles, including multi-infarct dementia (MID) and vascular dementia (VaD). The fifth edition of the Diagnostic and Statistical Manual from the American Psychiatric Association (DSM-5) [116] has done away with the term “dementia,” choosing instead to classify patients as showing major or minor cognitive impairment. CVD is one potential cause for cognitive impairment. VCI is defined as, “a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain” [2]. The construct of VCI is an advance from previous diagnostic systems, as it includes all levels of cognitive severity, from vascular-based mild cognitive impairment (VaMCI), to full blown vascular dementia. This VCI umbrella also includes both “pure” vascular-based impairment and “mixed” pathologies, such as a combination of AD and CVD [2]. In another break from some prior diagnostic systems, such as the NINDS–AIREN criteria, VCI criteria do not require memory impairment or any other specified cognitive domain to be present for the diagnosis. This broadens the scope of VCI and frees it from potential a priori categorization biases.

4. Advances in neuropsychological protocols

The VCI Harmonization Conference provided guidance for neuropsychological assessment of persons with suspected VCI in much the same manner as it provided neuroimaging protocol guidelines [91]. At this conference, the neuropsychology committee recommended tests that showed acceptable psychometrics, a track record of use in patients with CVD, relatively low cost, and receptiveness to examination of patients in many different languages and cultures. The tests used in the recommended 60 Minute Protocol are listed in Table 3.

4.1. Screening examinations

The Mini-Mental State Examination (MMSE), while brief, may not be as sensitive to VCI as newer screening measures, such as the Montreal Cognitive Assessment Test (MoCA) [117]. Several studies have shown the MoCA to possess superior sensitivity to cerebrovascular-related cognitive impairment than the MMSE [e.g. 118]. Some have questioned whether this increased sensitivity has come at the cost of specificity [119], especially in patients with limited educational attainment. The Five Minute protocol from the VCI Harmonization Conference has also been shown to be sensitive to the effects of CVD [120].

4.2. Executive domain tests

Speeded tests of executive function are especially sensitive to cognitive deficits of patients with suspected VCI [121]. Several such speeded tests are included in the Harmonization protocol, such as the Digit Symbol Substitution Test from the WAIS-III, a phonemic fluency task, a semantic fluency task, and the Trailmaking test. Non-speeded executive function tests, such as the Wisconsin Card Sorting Test, are not as sensitive in this population [122].

4.3. Memory domain tests

Memory deficits are especially noted in patients with suspected AD. However, patients with CVD often show memory deficits as well. This may be because of difficulties in learning new information due to attention or focus problems, rather than because of rapid forgetting of newly learned information [121]. The VCI Harmonization Committee recommended both the Hopkins Verbal Learning Test (HVLT) and the California Verbal Learning test (CVLT). Which test is chosen is dependent on the time available to complete the assessment. Both tests have been shown to be sensitive to patients with suspected VCI [123,124].

4.4. Language and visuospatial domain tests

Other than in patients with focal lesions to the dominant hemisphere for language, tests of language functions may not be as sensitive as tests in the executive function or memory domains [122]. Similarly, other than in patients with focal non-language dominant (usually right) hemisphere, fronto-parietal lesions, tests of spatial functions are also relatively insensitive to CVD [122]. For completeness, the Harmonization Committee chose a 15 item version of the Boston Naming Test and the Rey Complex Figure to be included in the 60 Minute Protocol.

4.5. VCI-related behavioral or mood disturbance

Depression is the most common post-stroke psychiatric disorder, with an estimated one-third of all stroke patients experiencing depression during the months following stroke [125]. Depression scales that have been shown to be sensitive to stroke-related mood disturbance include the Beck Depression Inventory and the Center for Epidemiologic Studies Depression Scale (CES-D) [126,127]. The Frontal Systems Behavior Scale (FrSBe) examines for the presence of dysexecutive, disinhibitive and apathetic behaviors both before and after a stroke, and has been found to be useful in this population [128], as has the Neuropsychiatric Inventory [129]. Both scales utilize a collateral source who knows the patient well as an informant for behavioral change and/or mood disturbance.

In summary, this review highlights the progress made in understanding the relationships between CVD and VCID risk factors and the pathological events that precipitate VCID, the development of more sensitive neuropsychological and neuroimaging diagnostic and prognostic tools, and new modes of intervention for disease prevention. Given the rising prevalence of CVD and dementia with aging, the advancement of these major fields of study will be critical for elucidating and modifying VCID pathophysiology to mitigate the personal and socioeconomic impact of cognitive decline in the elderly.

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Table 1

Institute of medicine actions to take to maintain cognitive health [18].

3 actions supported by scientific evidence	
1	Be physically active
2	Prevent and treat cardiovascular risk factors (hypertension, diabetes mellitus, smoking)
3	Regularly review with your health care provider health conditions and medications that might influence brain health
Actions for which there is some scientific evidence for maintenance of cognitive health	
1	Be socially and intellectually engaged and continue learning activities
2	Aim for adequate sleep and treat sleep disorders as appropriate
3	Avoid risk of cognitive changes associated with delirium, if hospitalized

Table 2

Imaging: MRI measures.

Feature	Recommended MRI measure	Acceptable MRI measure
Brain atrophy	Quantitative measurement of brain volume normalized for head size	Estimates of atrophy and ventricular size using the CHS scale Estimates of medial temporal lobe atrophy using Schelten's Scale
White matter hyperintensities	Quantitative measurement of WMH normalized for head size Anatomical mapping also encouraged	Preferred: ARWMC scale Also acceptable: CHS WMH scale
Infarction	All infarcts should be localized using a standard approach to generate quantitative measures of volume and location. Ideally, identified infarcts would also be mapped to a common stereotatic space	Number and size at specified locations Size (largest diameter): Large N1.0 cm Small 3 mm–10 mm Location: Anatomical locations Supratentorial Hemisphere Cortical (may include subcortical)
	All infarcts should be further differentiated from perivascular spaces by CHS criterion independent of method to determine size and location	Exclusively subcortical white matter Exclusively subcortical gray matter Infratentorial
Hemorrhage	All lesions should be localized using a standard approach to generate quantitative measures of volume and location. Ideally, identified lesions would also be mapped to a common stereotatic space	Number and size in each location Size (largest diameter): Large hemorrhage N1 cm Microhemorrhage b1 cm Must report lower size limit cut-off, field strength Location: same as infarcts
Other	Mass lesions, AVMs, extra-axial collections, malformations, dysplasia or any other lesion that might complicate assessment of cerebrovascular disease	

Notes: CHS — Cardiovascular Health Study; ARWMC — Age-Related White Matter Changes Scale; WMH — white matter hyperintensity; AVM — arteriovenous malformation. Copied with permission from [91], page 2226.

Table 3

Sixty-minute protocol test list.

Executive activation: Animal naming (semantic fluency); Controlled Oral Word Association Test; WAIS-III Digit Symbol–Coding; Trailmaking Test; List Learning Strategies; Future Use: Simple and Choice Reaction Time
Language/Lexical Retrieval: Boston Naming Test, 2nd Edition, short form
Visuospatial: Rey–Osterrieth Complex Figure — Copy; Supplemental: Complex Figure Memory
Memory: Hopkins Verbal Learning Test — Revised; Alternate: California Verbal Learning Test — 2; Supplemental: Boston Naming Test Recognition; Digit Symbol–Coding Incidental Learning
Neuropsychiatric/Depressive Symptoms: Neuropsychiatric Inventory, Questionnaire Version; Center for Epidemiological Studies — Depression Scale
Other: Informant Questionnaire for Cognitive Decline in the Elderly, Short Form; MMSE

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