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Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management

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Purpose of review
We present recent developments in the field of small vessel disease (SVD)-related vascular cognitive impairment, including pathological mechanisms, updated diagnostic criteria, cognitive profile, neuroimaging markers and risk factors. We further address available management and therapeutic strategies.

Recent findings
Vascular and neurodegenerative pathologies often co-occur and share similar risk factors. The updated consensus criteria aim to standardize vascular cognitive impairment (VCI) diagnosis, relying strongly on cognitive profile and MRI findings. Aggressive blood pressure control and multidomain lifestyle interventions are associated with decreased risk of cognitive impairment, but disease-modifying treatments are still lacking. Recent research has led to a better understanding of mechanisms leading to SVD-related cognitive decline, such as blood-brain barrier dysfunction, reduced cerebrovascular reactivity and impaired perivascular clearance.

Summary
SVD is the leading cause of VCI and is associated with substantial morbidity. Tackling cardiovascular risk factors is currently the most effective approach to prevent cognitive decline in the elderly. Advanced imaging techniques provide tools for early diagnosis and may play an important role as surrogate markers for cognitive endpoints in clinical trials. Designing and testing disease-modifying interventions for VCI remains a key priority in healthcare.

Keywords
imaging, small vessel disease, vascular cognitive impairment, vascular dementia, vascular risk factors

INTRODUCTION

Vascular cognitive impairment (VCI) refers to conditions in which cerebrovascular diseases contribute to decline in mental abilities [1,2▪▪]. Although these diseases can independently lead to cognitive deficits and account for 15–30% of dementia cases, second only to Alzheimer's disease, they rarely occur in isolation [2▪▪,3▪]. Importantly, age-related cognitive impairment is typically driven by co-occurring vascular and neurodegenerative pathologies [4]. In a recent clinical–pathologic populational study, the majority of participants (~78%) had at least two concomitant neuropathologies at the time of death, most commonly neurodegenerative and vascular diseases [3▪].

Among the multiple mechanisms involved in VCI, cerebral small vessel disease (SVD) is arguably the most prevalent one [5], contributing to cognitive impairment irrespective of stroke [2▪▪]. SVD is characterized by abnormalities that affect the structure and function of small vessels of the brain, with multiple neuroimaging and neurological manifestations,

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KEY POINTS

- VICCCS's recent guideline for diagnosing mild and major vascular cognitive impairment relies on neuropsychological evaluations of core domains, functional assessment (IADLs/ADLs) and MRI findings.
- Recent discoveries on complex pathological mechanisms underlying SVD, such as blood brain barrier dysfunction, reduced cerebrovascular reactivity and impaired perivascular clearance of solutes, have provided new potential targets for the development of future therapeutic interventions.
- Although conventional neuroimaging markers of SVD are widely available and incorporated into clinical practice, advanced techniques, such as DTI, enable early diagnosis and offer stronger and more consistent associations with cognition.
- Vascular risk factor control and healthy lifestyle interventions are associated with reduced risk of dementia and are key to slowing down SVD progression and cognitive decline.
- Lowering blood pressure control to the standard target (<140/80 mmHg) is the primary modifiable prevention strategy, but a more aggressive blood pressure target (SBP < 120 mmHg) and reduction of blood pressure variability may be beneficial in selected middle-aged and elderly patients.

including cognitive decline [6▪▪]. Rather than a homogeneous disorder, SVD encompasses different sporadic and inherited diseases, resulting from a complex mix of genetic and vascular risk factors. The prevalence of SVD increases with age, and the two most common sporadic types are arteriolosclerosis, also referred to as hypertensive arteriopathy or deep perforator arteriopathy, and cerebral amyloid angiopathy (CAA) [7]. Arteriolosclerosis has been traditionally linked to hypertension and type II diabetes [8]. In pathology, arteriosclerosis is characterized by abnormal thickening of arteriolar walls, preferentially located in the deep grey nuclei and deep white matter, observed in >80% of individuals over 80 years of age, according to autopsy studies [8]. CAA is defined by pathological deposition of amyloid-β in the walls of cortical and leptomeningeal arterioles and capillaries. Moreover, CAA is known to commonly co-occur with Alzheimer's disease [9▪▪].

In this narrative review, we focus on the latest advances in the management of sporadic SVD-related VCI, with an update on diagnostic criteria, neuroimaging markers and cognitive profile. We further address the current state of prevention and therapeutic approaches.

POTENTIAL PATHOLOGICAL MECHANISMS LINKING SMALL VESSEL DISEASE TO COGNITIVE IMPAIRMENT

Interactions between ageing [10], environmental risk factors [11▪▪] and genetic variants [12,13] are thought to contribute to the development of sporadic SVD (Fig. 1a). In the early pathogenic stages, damage to functional units composed of neurons, endothelial cells, astrocytes and pericytes (neurovascular units) may lead to impaired regulation of blood flow, vascular permeability, immune trafficking and waste clearance [6▪▪,16]. A cascade of events may arise, including blood–brain barrier (BBB) leakage, deficient cerebrovascular reactivity (CVR), inflammation, vessel wall thickening and remodelling, as well as luminal narrowing (Fig. 1b) [6▪▪,8]. Together, these processes contribute to the broad spectrum of SVD-related brain parenchymal injury, including haemorrhagic and nonhaemorrhagic (presumably ischemic) lesions (Fig. 1c). Through impaired vasomotion and reduced vasoreactivity, it has been hypothesized that SVD might compromise the drainage of solutes along the vessels [9▪▪,17,18▪▪], potentially facilitating interstitial and perivascular accumulation of proteins, including amyloid-β. Such aggregation, could contribute to secondary neuronal degeneration and loss of vascular smooth muscle cells [9▪▪]. This potential interactive pathway is thought to play a critical role in comorbid CAA and Alzheimer's disease [9▪▪] and may lead to a self-reinforcing cycle in which neurodegenerative and vascular pathologies intensify and aggravate each other [9▪▪]. Furthermore, sleep has been found to act as an important modulator of perivascular clearance and may also play a relevant role in age-related cognitive decline [18▪▪,19].

Evidence suggests that SVD-related brain lesions affect cognition also by disrupting structural and functional networks, causing a disconnection syndrome [14]. The strategic anatomical locations of some lesions play an important role and help explain VCI's heterogeneous neuropsychological manifestations [14,20,21]. In addition, subcortical lesions may further contribute to functional decline by triggering secondary degeneration of affected white matter tracts, leading to remote abnormalities such as white matter atrophy and cortical thinning (Fig. 1d) [6▪▪,14].

CLINICAL CLASSIFICATION

Several classification systems have been proposed over the years to guide clinical diagnosis of VCI, reflecting methodological and diagnostic challenges [5,22–27]. When using these classifications, it is

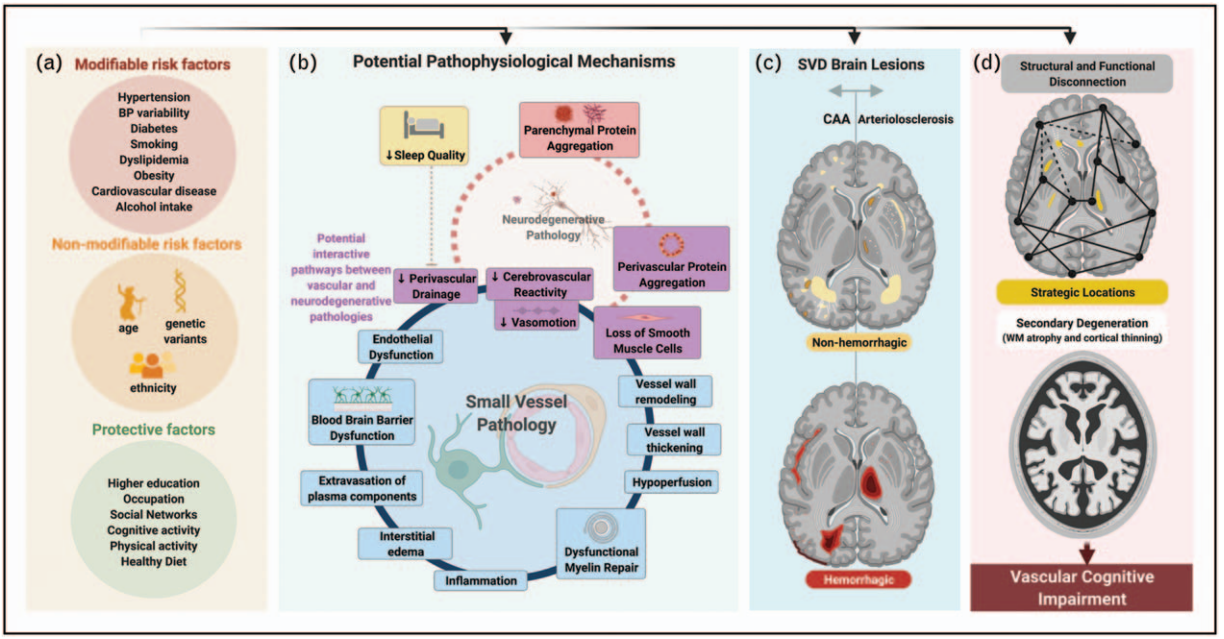

FIGURE 1. Schematic overview of potential mechanisms leading to vascular cognitive impairment. (a) Risk factors associated with SVD and related cognitive decline. (b) Potential pathophysiological mechanisms of SVD. Dysfunctional NVUs have an important role in early SVD pathology. Several effects are described around the blue circle, the order of which is not yet established. Combined, these effects are thought to contribute to exacerbate tissue injury. (c) Typical brain lesions associated with sporadic SVD: CAA (left) and arteriolosclerosis (right) patterns. The hemorrhagic lesions (bottom figure) include: CMB, cSS, SAH and ICH. The non-hemorrhagic lesions (upper figure) include WMH, lacunes, PVS, small acute subcortical infarcts and cortical CMI. (d) Potential mechanisms involved in SVD-related cognitive decline: impairment of structural and functional connectivity (upper figure) and secondary degeneration (lower figure). AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CMI, cerebral microinfarcts; cSS, cortical superficial siderosis; ICH, intracerebral hemorrhage; NVU, neurovascular unit; PVS, perivascular spaces; SAH, subarachnoid hemorrhage; SVD, small vessel disease; WMH, white matter hyperintensity. Adapted from [5,11▪▪,14,15]. Created with BioRender.com.

important to be aware of the broad overlap between neurodegenerative and vascular diseases in clinical [28▪] and pathological levels [3▪], acknowledging the great heterogeneity in the cognitive impact of such diseases at an individual level [3▪].

The clinical diagnosis of VCI relies strongly on cognitive profile and neuroimaging findings. According to the most recent diagnostic guidelines, from the Vascular Impairment of Cognition Classification Consensus Study (VICCCS), VCI's definition aligns with the terminology of DSM-V and encompasses a broad clinical spectrum that ranges from mild to major VCI, and incorporates mixed-disease cases (Table 1) [24,25]. Subcortical ischemic vascular dementia (SIVaD) refers to cases in which SVD is the primary mechanism underlying cognitive decline, and the most common brain lesions are white matter hyperintensities (WMH) and lacunar infarcts [24,25]. Importantly, according to VICCCS guidelines, individuals with neuroimaging signs of SVD may qualify for SIVaD, post-stroke dementia or mixed-dementia, depending on temporal associations and comorbidities.

Cognitive profile

Cognitive decline linked to cerebrovascular diseases, including SVD, is thought to typically present in a stepwise and gradual pattern, progressing slowly and affecting processing speed, complex attention and frontal-executive functions [5,26]. Disturbances in the frontal-executive domain are considered more likely to be present in mild VCI than in Alzheimer's disease related mild cognitive impairment (MCI), in which decline in episodic memory is the most prominent feature [29].

This observed predilection for impairment of frontal-executive functions is thought to result from the disruptive effect of SVD lesions on the brain's structural and functional connectivity [14]. Neuroimaging studies have shown that the degree of structural network disruption is associated with the burden and extent of SVD lesions [30,31] and, at least in part, mediates their association with cognitive decline [32,33]. Also, functional networks associated with attention and executive functions have been found to be predominantly affected in SVD patients [14].

Table 1. Summary of the Vascular Impairment of Cognition Classification Consensus Study criteria

Definition	VCI is defined as impairment in at least one cognitive domain and in IADL/ADLs independent of the motor/sensory sequelae of the vascular event: Mild VCI: at least one cognitive domain affected and mild to no impairment in IADL/ADLs. Major VCI (vascular dementia): clinically significant deficits of sufficient severity in at least one cognitive domain and severe disruption of IADL/ADLs.
Evaluation	Cognitive assessment should include five core domains: executive function and processing speed, attention, memory, language, and visuospatial domains. The full-length protocol takes 60 min to complete but can be shortened to 30 or even 5 min using Montreal Cognitive Assessment (MoCA) [22].
Imaging	MRI is considered the 'gold-standard' imaging method for the clinical diagnosis of VCI.
Certainty of evidence	Probable VCI: if (1) only CT imaging is available or (2) aphasia is present after vascular event, but normal cognition was documented (e.g. annual cognitive evaluations) before the clinical event. Possible VCI: if neither MRI nor CT is available, but VCI is suspected clinically.
Major VCI subtypes	Post-stroke dementia: a clear temporal relationship (within 6 months) of irreversible cognitive decline following the vascular event. Subcortical ischemic vascular dementia (SIVaD): small vessel disease is the main vascular cause, including lacunar infarcts and white matter hyperintensities are the main lesions. Multi-infarct (cortical) dementia: large cortical infarcts contributing to dementia. Mixed pathology: VCI-AD, AD-VCI or VCI-DLB, VCI-* depending on probable contribution.
Exclusion criteria	Drug/alcohol abuse/dependence within the last 3 months, other causes of sustained impairment (e.g. depression, vitamin D deficiency, other vitamin or hormonal deficiencies).

(VICCCS) diagnosis guidelines. AD, Alzheimer's disease; ADL, activities of daily living; CT, computed tomography; DLB, dementia with Lewy bodies; IADL, instrumental activities of daily living; VCI, vascular cognitive impairment.
*Other possible disease.
Adapted from Vascular Impairment of Cognition Classification Consensus Study [24].

Traditionally, a history of early onset of memory deficit and worsening of cortical functions (aphasia, apraxia, agnosia), in the absence of corresponding vascular brain imaging lesions, can be suggestive of Alzheimer's disease as primary diagnosis [26]. Nonetheless, episodic and semantic memory can also be affected in cognitive impairment of presumably vascular origin [34–36].

Importantly, there is much overlap in cognitive profiles across dementia types [37], possibly related to the multifactorial nature of age-related cognitive decline combined with patient-specific factors related to cognitive reserve and spatial distribution of vascular lesions.

Accordingly, recent findings support a much more heterogeneous spectrum of cognitive impairment related to SVD. This suggests that multiple domains can be affected, owing not only to overlapping diseases but also to close interdependence of executive function and processing speed to perform fluid cognitive tasks [38]. Interestingly, in severe CAA cases [39], visuospatial dysfunction has also been reported [40], hypothesized to relate to a posterior predominance of amyloid disease.

Psychiatric, behavioural and other manifestations

Additional features of VCI, depending on lesion localization and severity, may include personality and mood alterations (apathy, depression, emotional incontinence) [41,42], disturbed sleep [42], motor and gait disturbances (frequent falls, small-step parkinsonian gait) [43], early urinary incontinence and pseudobulbar palsy due to lacunes in basal ganglia or pons [26,27]. VCI is often associated with psychiatric and behavioural symptoms underlined by lesions in thalamocortical, striatocortical and prefrontal-basal ganglia pathways [44] and are often amenable to therapy (reviewed in detail elsewhere [45▪▪]). Although depression often manifests with a reversible decline in cognitive function, late-life occurrence can also be an early sign of dementia [46].

A distinct form of SVD is CAA-related inflammation (CAA-ri), characterized by an autoimmune reaction to cerebrovascular amyloid-β deposits [47], and clinical presentation may include subacute cognitive dysfunction [47,48]. Early identification is critical, as neurological deficits can be reversible with early immunosuppressive treatment [49▪].

NEUROIMAGING EVALUATION

In the context of cognitive impairment, detection of underlying microvascular disease relies strongly on neuroimaging [26], for which MRI is considered the 'gold-standard' [24,50▪▪]. Many SVD features are visible and detectable almost exclusively through MRI, but none are considered pathognomonic and,

hence, must be interpreted in light of clinical findings [26]. Neuroimaging also helps to distinguish etiological subtypes of SVD. The modified Boston criteria [51] and the Edinburgh criteria [52] enable in-vivo diagnosis of CAA, with the former providing high positive predictive values even in the absence of intracerebral haemorrhage (ICH), thus facilitating CAA diagnosis in memory-clinic patients [53]. The likelihood of underlying arteriolosclerosis or CAA can be further inferred based on the distribution pattern of several MRI-visible lesions (Fig. 1c; Fig. 2) [54–57]. Arteriolosclerosis has been found to more commonly present with deep cerebral and cerebellar microbleeds (CMB) [56], deep lacunes [57], perivascular spaces (PVS) visible in the basal ganglia [55], deep ICH and peri-basal ganglia WMH [54] (Fig. 1c, Fig. 2). In contrast, evidence suggests that CAA more typically presents with cortical CMB [53,56], cortical cerebral microinfarcts (CMI) [58], lobar lacunes [57], PVS visible in the centrum semiovale [55], cortical superficial siderosis (cSS) [51], convexity subarachnoid hemorrhage (cSAH) [59,60], lobar ICH and WMH foci distributed as multiple subcortical spots [54] (Fig. 1c, Fig. 2). This distinction is particularly important because CAA frequently overlaps with Alzheimer's disease, and confers higher risk of haemorrhagic complications, influencing decision-making on antithrombotic treatment [61▪▪]. Importantly, detection of SVD MRI lesions in young individuals without significant risk factors should prompt investigation of monogenic SVD [62].

Conventional neuroimaging markers in small vessel disease-related cognitive impairment

MRI-visible lesions represent only a small portion of the spectrum of brain injury related to SVD and probably reflect late and irreversible steps in this pathological process [15]. Established SVD markers include WMH, lacunes, PVS, recent small subcortical infarcts, CMB, cSS, ICH and atrophy (Fig. 2). More recently, CMI and cSAH have been associated with SVD, especially with CAA (Fig. 2) [58–60]. Even though these markers are useful for the diagnosis of SVD, their relevance as predictors of cognitive impairment and dementia is less evident.

CMB's occurrence, number and topographical distribution reflect the presence, severity and cause of the underlying SVD and correlate with increased mortality and a higher risk of haemorrhagic and ischemic stroke [63▪▪,64]. However, although there is some evidence linking CMB to cognitive impairment, studies have yielded conflicting results and small effect sizes [63▪▪,64,65], possibly because CMB do not cause significant disruption of adjacent tissues [65]. Similarly, cSS contributes to in-vivo diagnosis of CAA and is strongly associated with recurrent lobar ICH [66], but there are insufficient data supporting an independent association with cognition [67].

In contrast, nonhaemorrhagic markers, in general, are more strongly associated with cognition [65]. WMH is one of the earliest and most established markers of SVD, associated with increased risk of stroke and mortality [63▪▪]. Recent meta-analyses support a strong link between WMH and VCI and indicate that extensive baseline burden, progression and periventricular distribution of WMH are associated with an increased risk of dementia [63▪▪,68]. Likewise, incident lacunes have been associated with dementia, worse executive function and psychomotor speed [69]. Although the burden of cortical CMI is underestimated on MRI, they are considered the most widespread form of brain infarct, associated with CAA and highly prevalent in cognitively impaired individuals [58]. In contrast with CMB, they are strongly associated with cognitive endpoints [70,71▪], affecting performance potentially by disrupting adjacent tracts, with secondary perilesional and remote degeneration [58]. Although brain atrophy has been frequently associated with SVD, it reflects the final converging effects of aging and several other pathologies, including neurodegenerative diseases [72▪,73]. Several studies link smaller brain volumes with cognitive impairment, yet none of them controlled for co-occurring Alzheimer's disease, limiting causal inferences [74]. Increased visibility of PVS has also been associated with worse cognitive performance [72▪], but overall results are still conflicting, and its usefulness as a biomarker for cognition remains largely unknown [75].

Finally, in an attempt, to capture the overall burden of SVD, sum scores have been developed based on visual ratings of several aforementioned MRI-visible lesions [76,77]. In population-based and patient cohorts, higher scores were associated with cognitive decline and increased risk of dementia [78–81].

Advanced neuroimaging markers in small vessel disease-related cognitive impairment

Although conventional MRI markers are appealing for being widely available and easily evaluated, advanced MRI techniques offer stronger cognitive associations in general, likely as a result of their sensitivity to microstructural abnormalities and disruption of network connections.

Diffusion tensor imaging (DTI) is considered one of the most promising MRI techniques in the fields of VCI and SVD. Diffusion properties of the

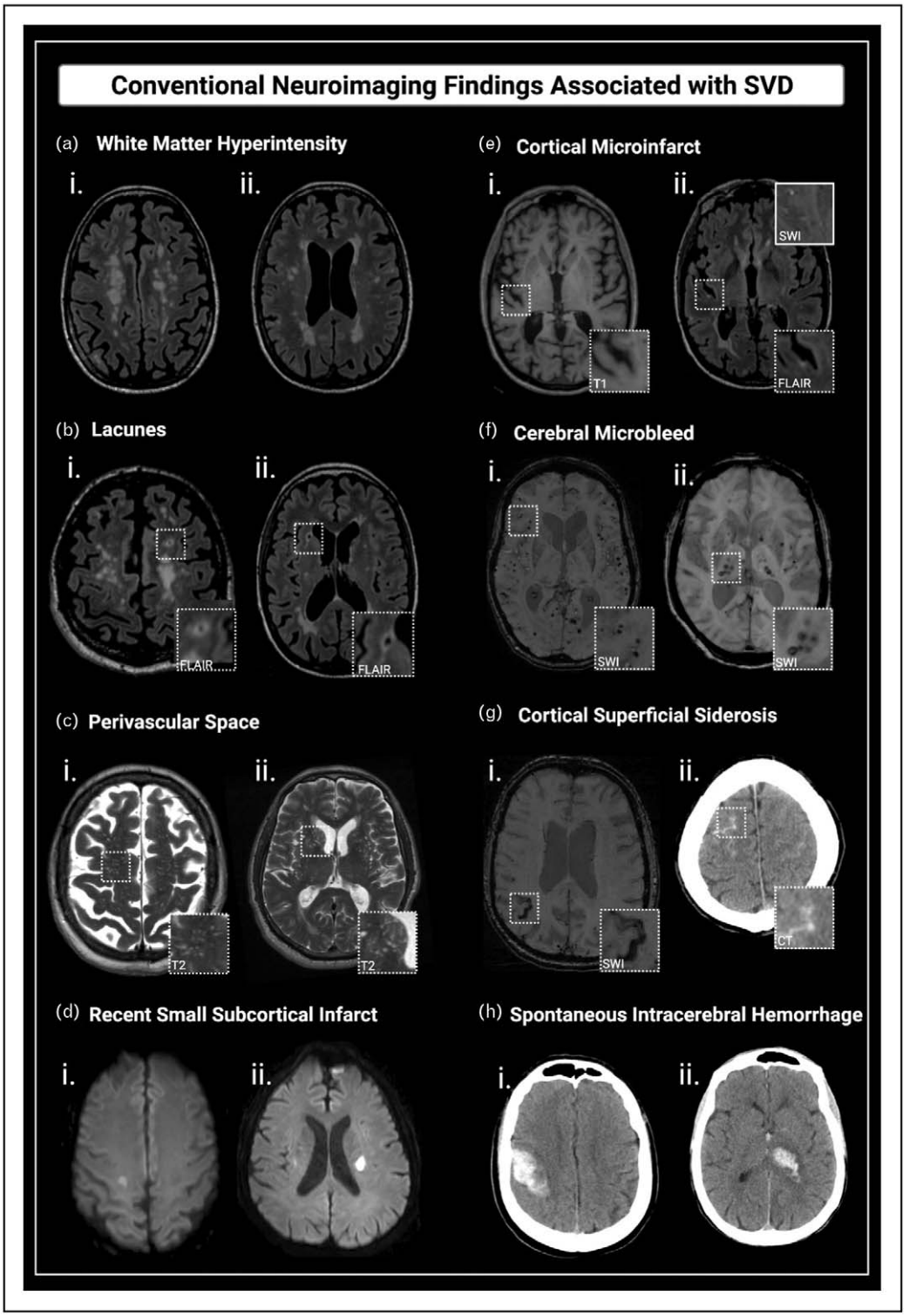

FIGURE 2. Conventional neuroimaging findings associated with SVD. (a) WMH: confluent hyperintensity foci visible on FLAIR (i and ii). (b) Lacunes: fluid-filled subcortical cavities, 3–15 mm, isointense to CSF, often with hyperintense rims on FLAIR (i - lobar lacune; ii - deep lacune). (c) PVS: linear, ovoid or round-shaped fluid-filled spaces, following the course of vessels (i - predominating in the centrum semiovale; ii - affecting the basal ganglia). (d) Recent small subcortical infarcts: hyperintense foci on DWI (i and ii). (e) Cortical CMIs: intracortical lesions $\leq$ 4 mm, hypointense on T1 (i) and hyper or isointense on FLAIR (ii). (f) CMBs: foci of hemosiderin deposition, with very low signal intensity on SWI (lobar CMBs (i), and deep CMBs (ii)). (g) cSS: linear hypointense foci with gyriform pattern over the cerebral cortex on SWI (i). The acute form of superficial bleeding is cSAH, seen as linear hyperdensities on CT (ii) or as hyperintensity on FLAIR. (h) Spontaneous ICH: nontraumatic

water molecules reflect microstructural integrity and correlate with relevant histopathological changes [82]. DTI markers are sensitive to early and widespread abnormalities that go undetected on conventional MRI [14] and outperform MRI-visible lesions [83,84▪] by explaining more cognitive variance [14,85]. Furthermore, diffusion changes seem to be predominantly driven by SVD in comparison to Alzheimer's disease pathology [86▪]. To overcome challenges imposed by highly complex and time-consuming postprocessing techniques, novel automated DTI-based markers, such as peak width of skeletonized mean diffusivity (PSMD), have been developed. PSMD reflects the heterogeneity of diffusivity across the main white matter tracts [85]. It shows consistent cognitive associations in SVD and ageing populations [85,87–91] and is considered a promising biomarker to be applied in future clinical trials in the field of VCI. Furthermore, through the combination of tractography and graph-theory analysis, valuable metrics of structural connectivity can be derived from diffusion images and have been found to predict cognitive decline [84▪,92], conversion to dementia [93] and even all-cause mortality [92] in SVD populations.

Other advanced imaging techniques evaluating functional connectivity status [14,94] and pathological changes in perfusion, vascular permeability and vasoreactivity [95,96] are still under investigation.

Despite their relevance in the research field, the aforementioned modalities require further validation before they can be applied in clinical practice.

MANAGEMENT OF VASCULAR COGNITIVE IMPAIRMENT

Currently, management of VCI is centred on preventing and controlling vascular risk factors such as hypertension, obesity, smoking and diabetes (Fig. 1) [45▪▪,97,98]. Together, they account for 25–40% of dementia cases [2▪▪,45▪▪]. Better control of these factors is partly responsible for the decreasing incidence of dementia observed in high-income countries [45▪▪,99], mostly driven by lower rates of vascular dementia, considered the most preventable component of age-related cognitive decline [4,97,98]. Known protective factors include markers of increased cognitive reserve, such as higher education, occupation, social networks, cognitive and physical activity [11▪▪,100].

Vascular risk factor control

High blood pressure (BP) represents the primary modifiable risk factor involved in SVD progression and VCI [50▪▪]. Hypertension affects more than 75% of individuals over 65 years, of whom nearly 53% are inadequately controlled [101]. Although both mid-life and late-life hypertension are associated with WMH progression, lower brain volume in later life [102] and disruption of white matter microstructure [103,104], mid-life hypertension is more strongly linked to dementia, as BP begins to fall 5 years before diagnosis [105]. Likewise, systolic BP (SBP) of more than 130 mmHg at age 50, but not later in life, was associated with an increased risk of dementia [106]. Adding to the complexity, decline in BP in late life was associated with cerebral (micro)infarcts, with hypoperfusion being a potential culprit [107]. Interestingly, the effect of elevated BP on cognitive decline appears to be mediated by both vascular pathology as well as neuritic plaques and neurofibrillary tangles, suggesting that managing BP can alleviate both vascular and neurodegenerative pathways [107–109]. Beyond elevated mean BP, fluctuations of BP over a period of hours, days and years have been increasingly found to influence brain health [110,111▪,112▪▪]. Emerging evidence suggests a link between BP variability, SVD progression and dementia risk [111▪,113]. More insights are needed to define this complex relationship between BP profile in ageing and cognitive impairment.

Findings from clinical trials support that interventions may lower the risk of VCI progression. In the SPRINT-MIND study, middle-aged individuals (>50 years) and the elderly (mean age 68 years) with an increased vascular risk submitted to intensive BP management (SBP goal <120 mmHg) showed reduced WMH progression [114▪] and smaller incidence of MCI in comparison to the control group (SBP goal <140 mmHg) [115▪▪]. The ACCORD-MIND substudy and the INFINITY study also supported that intensive BP control might help slow down WMH progression, with varying effects on cognition [116,117]. Of importance, after ICH, inadequate BP control is associated with increased risk of lobar and nonlobar ICH recurrence [118].

lobar (i) and deep (ii) hemorrhages, depicted as focal hyperdense lesions on CT. CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CMI, cerebral microinfarcts; cSAH, convexity subarachnoid hemorrhage; CSF, cerebrospinal fluid; cSS, cortical superficial siderosis; CT, computed tomography; DWI, diffusion weighted image; FLAIR, Fluid-attenuated inversion recovery; ICH, intracerebral hemorrhage; PVS, perivascular space; SVD, small vessel disease; SWI, susceptibility weighted imaging; WMH, white matter hyperintensity. Adapted from [14]. Created with BioRender.com.

For patients with VCI, expert's consensus advocates that antihypertensive therapy should be initiated when BP is ≥140/90 mmHg and should aim to achieve a BP treatment target of <130/80 mmHg (<140/80 mmHg in elderly patients) [50▪▪,119]. New evidence suggest, that in eligible middle-aged and in the elderly with vascular risk factors, targeting SBP less than 120 mmHg with careful side effect monitoring may prevent development of MCI when compared with standard therapy [50▪▪,115▪▪] There is a lack of convincing data, on the choice of antihypertensive medications, but despite limited evidence [120], calcium-channel blockers and angiotensin receptor blockers may be preferred treatments [50▪▪,121].

Diabetes is an established risk factor for future dementia [122▪] and has been associated with poorer processing speed and executive function, likely by contributing to SVD-related disruption of structural and functional connectivity [103,122▪]. There is conflicting evidence regarding whether intensive glycaemic control in diabetic individuals could reduce micro/macrovascular complications [123,124], and no evidence insofar has been found for a protective effect on SVD progression or cognitive decline [116,125,126]. The focus should be on preventing hyperglycaemia and repetitive hypoglycaemia, as both have been linked to dementia [45▪▪,125].

Although the effects of hypertension and diabetes on cognition appear to be driven mainly by vascular disease, evidence suggests that dyslipidaemia contributes more to Alzheimer's disease related degeneration [103,127]. For instance, midlife dyslipidaemia has been associated with amyloid and tau deposition later in life [127,128]. Although these findings imply a potential benefit of lipid-lowering therapy on cognition, clinical trials have not yet shown encouraging results [129,130]. Moreover, a large prospective study, including 96 043 participants, suggested that lowering LDL cholesterol below 70 mg/dl may increase the risk of ICH [131▪]. Further research should evaluate the benefit/risk ratio of lipid-lowering therapy in patients at a higher risk of haemorrhagic complications, such as CAA cases [61▪▪].

Mid-life obesity is another emerging risk factor for dementia in later life [132]. Weight-loss of at least 2 kg was associated with improved attention and memory [133]. Not surprisingly, heavy midlife smoking has also been linked to increased risk of cognitive decline [45▪▪]. Smoking appears to contribute in a dose-dependent way to increase WMH burden and to disrupt microstructural integrity, effects that may be partly reversible after cessation [134,135].

As expected, in addition to SVD, other cerebrovascular diseases play a major role in the pathogenesis of vascular cognitive impairment. Stroke itself is a powerful risk factor for dementia, increasing the risk two-fold [136]. The postevent conversion rate to dementia at 1 year is estimated at 34.4% in patients with severe stroke, 8.2% in minor stroke and 5.2% in those with TIA [137▪▪]. The variability in the incidence and temporality of poststroke dementia suggests that other factors, such as SVD, may influence poststroke outcomes [138]. Accordingly, atrial fibrillation is considered a potent risk factor for cognitive decline [139]. In a large registry study, incident dementia risk was reduced by 48% in patients with atrial fibrillation on oral anticoagulation vs. no anticoagulation [139]. Lastly, haemorrhagic stroke, accounting for highest burden of stroke-related morbidity and mortality, confer an increased risk of dementia, particularly high in lobar ICH cases, in which CAA disease plays an important role [61▪▪,140]. All things considered, strategies to prevent ischaemic and haemorrhagic stroke hold the potential to significantly reduce the burden of cognitive impairment in the population.

Symptomatic treatment

Acetylsalicylic acid is considered a reasonable therapy in patients with MCI or dementia presenting covert brain infarcts on imaging, yet confirmatory trials are still missing [50▪▪]. In contrast, aspirin is not recommended for patients presenting with VCI attributable to confluent WMH only, without other evidence-based indications [50▪▪]. Of note, the recent ASPREE trial did not show aspirin treatment to be beneficial in terms of cognitive outcomes in the general elderly population (>70 years) [141]. The question still remains if prophylactic antithrombotic treatment can benefit patients with underlying moderate to severe vascular disease.

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and N-methyl D-aspartate antagonist memantine may be considered for symptomatic treatment in selected patients with dementia and SVD [23,50▪▪]. Only donepezil has shown a modest clinically appreciable effect on cognition in trials that evaluated demented patients with vascular component [142]. Galantamine can be considered for treatment in patients with mixed neurodegenerative and SVD pathology [23]. Because cholinesterase inhibitors and memantine in VCI are considered off-label by FDA, the decision to administer these drugs should be taken with caution and discussed with patients in light of the risk of adverse events. Finally, extracts of *ginkgo biloba* (EGb761)

were reported to have some effect on cognition and ADLs [143].

Protective lifestyle factors

Maintaining cognitive activity in late-life plays a major role in improving and maintaining brain structure and function [100,144]. Evidence suggests that low levels of education contribute to cognitive impairment [38], whereas physical activity in the elderly decreases the risk of developing dementia [145,146]. Interestingly, the preventive effect of exercise and cultural activities on cognition is enhanced when conducted in company, reinforcing the importance of social networks [147]. Furthermore, Mediterranean diet is generally recommended to reduce the risk of cognitive decline [148,149], and both Mediterranean and vegetarian diets were shown to be associated with stroke risk reduction [150,151▪].

Combining different interventions is a promising approach. The Finish FINGER trial found improved cognitive performance in at-risk elderly individuals receiving a multidomain lifestyle intervention that included nutritional guidance, exercise, cognitive training and management of vascular risk factors [152].

Novel insights into sleep and cognition [18▪▪,19] suggest that short night sleep (<5 h), poor quality sleep and hypnotics use are associated with an increased risk of dementia in healthy adults [153,154]. Accordingly, moderate to severe sleep apnoea is linked to WMH and silent brain infarctions [155,156▪]. Recent findings on the influence of non-REM-sleep in perivascular clearance of metabolites from the brain, with potential impact on neurodegenerative and vascular pathways [19], raise questions as to whether interventions focused on improving sleep quality could prevent or reverse age-related cognitive decline. Further research is required to clarify associations between sleep quality and cognitive decline.

CONCLUSION AND FUTURE DIRECTIONS

Recent research has taught us that cognitive decline in the elderly is driven by interacting neurodegenerative and vascular pathways, with significant contribution from SVD. Reports of declining incidence of dementia in high-income countries, together with recent positive trials on multifactorial interventions and BP control, are encouraging and highlight the importance of further investigating the impact of vascular risk-factors on cognition. Although there is a challenging path ahead in the quest for disease-modifying interventions, a better understanding of pathological mechanisms underlying SVD could lead to identifying new potential therapeutic targets. Novel neuroimaging markers are promising tools for clinical trials in the field and may act as surrogate markers for cognitive endpoints [72▪,157]. As vascular disease is considered the most preventable component of cognitive decline in the elderly, tackling cardiovascular risk-factors remains the cornerstone therapeutic approach.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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