Vascular cognitive impairment

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Abstract | The term vascular cognitive impairment (VCI) was introduced around the start of the new millennium and refers to the contribution of vascular pathology to any severity of cognitive impairment, ranging from subjective cognitive decline and mild cognitive impairment to dementia. Although vascular pathology is common in elderly individuals with cognitive decline, pure vascular dementia (that is, dementia caused solely by vascular pathology) is uncommon. Indeed, most patients with vascular dementia also have other types of pathology, the most common of which is Alzheimer disease (specifically, the diffuse accumulation of amyloid-β plaques and neurofibrillary tangles composed of tau). At present, the main treatment for VCI is prevention by treating vascular diseases and other risk factors for VCI, such as hypertension and diabetes mellitus. Despite the current paucity of disease-modifying pharmacological treatments, we foresee that eventually, we might be able to target specific brain diseases to prevent cognitive decline and dementia.

Vascular cognitive impairment (VCI) refers to the entire spectrum of vascular brain pathologies that contribute to any degree of cognitive impairment, ranging from subjective cognitive decline to dementia[1–3] (FIG. 1). Typically, patients with VCI have mental slowness and problems with executive function, including higher-order cognitive functions, such as planning, organizing and monitoring behaviour. Memory problems, behavioural symptoms and psychological symptoms, including apathy, anxiety and depression, are frequent. Other neurological signs and symptoms, including reflex asymmetry, dysarthria (difficulty with speech), parkinsonism, rigidity or urinary incontinence, often occur. The signs or symptoms that occur during the course of the disease depend on the type, extent and location of the underlying cerebrovascular pathology.

The main cerebrovascular pathologies in VCI are infarcts and white matter hyperintensities (WMHs) due to ischaemia[4,5]. Both in autopsy series and in clinical studies, a diagnosis of pure vascular dementia (that is, dementia due solely to cerebrovascular disease) is uncommon[6,7]. Indeed, vascular pathology alone probably accounts for only ≤10% of dementia cases[8]. This finding contrasts with the proportion of patients with dementia in whom vascular pathology contributes to cognitive decline[3] (BOX 1). Indeed, up to 75% of patients with dementia have evidence of vascular pathology at autopsy[9], and accordingly, mixed dementia (also known as dementia due to mixed pathology) is common, particularly at old age.

The state of the art in the VCI field was summarized in a scientific statement by the American Heart Association (AHA) and the American Stroke Association (ASA) in 2011 (REF. 4). Other terminologies used for VCI, such as the descriptive term vascular cognitive disorder, have been proposed[10]. This term overlaps with the nomenclature in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for mild and major vascular neurocognitive disorders[11]. However, the disadvantage of the term vascular neurocognitive disorder is that neurocognitive is a pleonasm, and therefore, the use of this term has not gained momentum in the field. In one Delphi consensus study that integrated opinions from more than 120 professionals in the field, only a small majority (56%) favoured using the term vascular dementia over the other proposed terminologies, and therefore, the consensus paper recommended replacing this term with mild and major VCI — which more easily aligns with the DSM-5 nomenclature[12]. Other terms include vascular mild cognitive impairment[4].

In this Primer, we discuss the spectrum of VCI from subjective cognitive decline to dementia, and from a clinical syndrome caused solely by vascular pathology to a syndrome in which vascular pathology is one contributor. As the term vascular dementia is used throughout the literature, we cannot avoid using both the terms vascular dementia and VCI. In addition, we briefly discuss Alzheimer disease due to the high prevalence of mixed cerebrovascular and Alzheimer disease pathology and as only limited data for VCI or vascular dementia are available for several topics of interest. We start by discussing VCI epidemiology and the underlying mechanisms and pathophysiology and then discuss diagnosis, practical recommendations in terms of prevention and disease

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management, and the quality of life (QOL) issues faced by patients and caregivers. We conclude with an outlook on future developments.

Epidemiology

In epidemiological literature, vascular dementia, rather than VCI, is the term most frequently used, and in general, these studies do not separate individuals with pure vascular dementia from those with vascular pathology as a contributor to dementia. Vascular dementia is claimed to be the second most common cause of dementia, accounting for ~15–30% of cases[13,14]; however, the criteria used to classify vascular dementia in most epidemiological studies are mainly based on a history of stroke and do not require neuroimaging evidence of cerebrovascular disease, which could inflate estimates[13,14]. If individuals with dementia due to mixed pathology and individuals with WMHs are included in estimates, VCI accounts for between 50% and 70% of dementias[8,15].

Demographic factors

Most dementias occur in individuals >80 years of age; this age group is estimated to increase from 120 million individuals in 2012 to 391 million individuals in 2050, worldwide[16,17]. Accordingly, the number of patients with dementia is expected to rise from 36 million in 2010 to 115 million in 2050 (REF. 16). Although the prevalence and incidence of vascular dementia increase with age, the increased risk of dementia due to cerebrovascular disease seems to decline at very old ages[18]. One reason for this change might be that other causes of dementia, including dementia due to mixed pathology, are more common at very old ages[19–21]. Patients with vascular dementia have reduced survival compared with individuals with Alzheimer disease[22–24]. Indeed, the median survival time from diagnosis ranges from 3 to 5 years in patients with vascular dementia and from 7 to 10 years in individuals with Alzheimer disease[22–24].

After 85 years of age, women have a higher risk for Alzheimer disease than men, whereas the contribution of cerebrovascular disease to dementia does not have a clear sex predilection[18,25]. In addition, there are no robust findings on whether vascular dementia is more common in certain geographical areas, although inhabitants of low-income and middle-income countries might have a higher risk than individuals in high-income countries owing to poor availability and affordability of treatments for vascular risk factors[26]. Previously, vascular dementia was reported to be more common than Alzheimer disease in East Asia, but more-recent studies in Japan[27,28] and China did not confirm this finding[29]. In China, the prevalence of dementia and vascular dementia increased from 1985–1990 to 2001–2005 (no data are available between 1990 and 2001), but the prevalence of vascular dementia decreased between 2006 and 2010 (REF. 29). In Japan, the prevalence and incidence of dementia and Alzheimer disease increased between 1985 and 2012, although the incidence of vascular dementia was unchanged[28].

Risk factors

Although the number of individuals with dementia is estimated to increase in the coming decades, recent studies indicated that the incidence and prevalence of dementia have declined in Europe and North America over the past 3–4 decades[30–32]. At the same time, although the incidence of stroke has decreased, survival after stroke has increased, thereby increasing the number of individuals with a history of stroke[33–35]. Indeed, stroke increases the risk of dementia three to six times, and the increased risk persists for several decades[20,36,37]. Thus, interestingly, the reduction in the incidence and prevalence of dementia in two studies[25,30] was primarily due to a decline in vascular dementia, which was due to a reduced risk of post-stroke dementia. This reduced risk might be due to better treatment of stroke or an increased cognitive reserve (owing to, for example, a higher level of education) in later birth cohorts[38] or a changing pattern in risk factors for cerebrovascular diseases, including a decrease in hypercholesterolaemia[35,39] and smoking[35]. Conversely, other risk factors such as diabetes mellitus[35,40] and overweight and/or obesity have increased[35,41] (TABLE 1). The prevalence and incidence of atrial fibrillation (another risk factor for stroke) have increased, although this might be due to increased ascertainment[42].

In addition, the prevalence of high systolic and high diastolic blood pressure — the main risk factors for stroke and WMHs and, consequently, for vascular dementia[43–45] — have decreased in most high-income countries, although the prevalence of these risk factors has increased in some low-income and middle-income countries and has remained high in countries in Eastern Europe[46]. The reduction in prevalence in high-income countries is only partly due to increased use of antihypertensives[47]. Although high diastolic blood pressure has been a treatment target since the 1960s, isolated high systolic blood pressure was not treated until the 1990s[47]. Whether alterations in blood pressure levels will further

decrease the incidence of vascular dementia in high-income countries and increase incidence in low-income and some middle-income countries remains to be seen.

Several risk factors for vascular dementia have changed over time and are considered risk factors for Alzheimer disease (TABLE 1). Importantly, many risk factors are amenable to prevention and treatment. For vascular dementia, no robust genetic risk factors have been identified[48–50]. However, familial genetic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), that predispose individuals to repeated stroke might give some insight into the pathogenesis of vascular dementia.

Mechanisms/pathophysiology

Several biological mechanisms might link vascular disease to cognitive impairment. Historically, vascular dementia was associated with large vessel infarcts; however, small vessel diseases can also lead to cognitive impairment and dementia. Due to the variability of cerebrovascular disease, common comorbid pathologies and diverse clinical phenotypes of VCI, no widely accepted criteria defining the neuropathological threshold of this disorder are available[51,52]. One prospective screening study showed that seven pathologies, including large infarcts, lacunar infarcts, microinfarcts, myelin loss, arteriolosclerosis, leptomeningeal cerebral amyloid angiopathy (CAA) and perivascular space dilation, predicted cognitive impairment[53]. Vessel wall modifications, such as arteriolosclerosis, atherosclerosis and CAA, have been suggested to be very common and of key importance in VCI, suggesting that all of these disorders should be routinely incorporated into the neuropathological assessment of dementia[54,55]. In addition, other pathophysiological processes are likely to have roles in VCI. These include possible interactive injury with Alzheimer disease and other neuropathological processes, including α-synucleinopathy, tau pathology, TAR DNA-binding protein 43 pathology and microglial reactions, in addition to local tissue injury or dysfunction, including innate immune processes and disruption of the neurovascular unit leading to blood–brain barrier alterations[56,57] (FIG. 2).

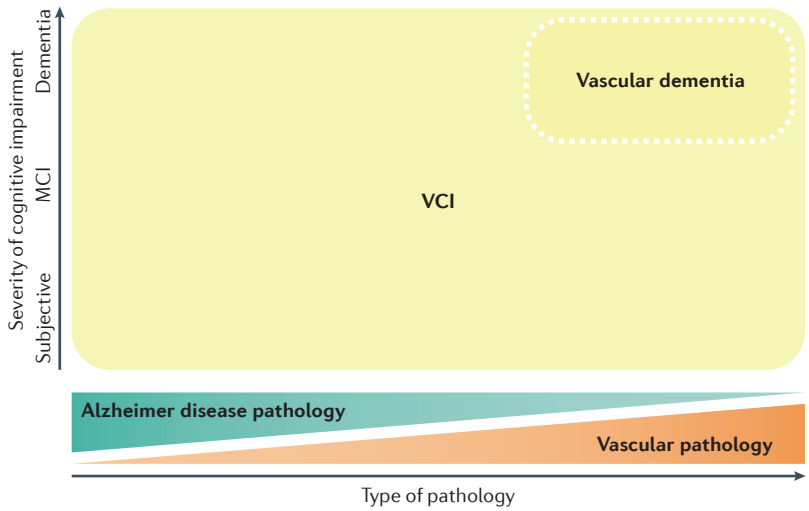

Figure 1 | **Relationship between VCI and vascular dementia.** Vascular cognitive impairment (VCI) refers to any degree of cognitive impairment that is associated with any severity of vascular pathology[1–3]. As such, VCI can refer to subjective cognitive impairment, mild cognitive impairment (MCI) and dementia. In addition, VCI can refer to a clinical syndrome that is entirely caused by cerebrovascular pathology or a syndrome whereby any degree of cerebrovascular pathology has, to some extent, contributed to cognitive impairment. Vascular dementia refers to a subgroup of patients who have dementia that is largely attributable to cerebrovascular pathology.

Direct tissue injury

VCI is most commonly attributed to direct ischaemic tissue injury, such as multiple or strategically located macroscopic infarcts (regions of tissue loss caused by ischaemic injury and/or haemorrhages; FIG. 3). Microinfarcts and white matter injuries are also associated with cognitive impairment. Macroscopic infarcts are found in approximately one-third of individuals who died after 80 years of age[8,58–60]. Depending on sampling techniques, cohort characteristics and other factors, microinfarcts are found in 20–40% of individuals who died after 80 years of age, and macroscopic infarcts and/or microinfarcts are found in >50% of older persons who died after 90 years of age[61,62].

Intracranial vessel diseases, including atherosclerosis, arteriolosclerosis and CAA, are associated with microinfarcts and haemorrhages. However, not all older individuals with cerebral infarcts have intracranial vessel disease, suggesting that other cardiac factors (for example, myocardial infarction or atrial fibrillation) or systemic factors (such as carotid atherosclerosis or clotting abnormalities) have a role in infarct formation[55]. In addition, these vessel diseases are independently associated with the risk of VCI after other vascular risk factors and infarcts are controlled for (see Vessel diseases)[63].

The number, location and size of macroscopic infarcts affects the likelihood that they will be associated with cognitive impairment; in general, multiple infarcts, larger infarcts and infarcts in cortical regions are more likely to be associated with dementia[59]. Although dementia can be caused by multiple infarcts (which explains the old term of multi-infarct dementia), single infarcts in specific brain regions can also substantially influence cognitive function. These so-called strategic infarcts have been described in the thalamus, the cortical regions of the parietal and temporal lobes and the genu of the internal capsule. Small subcortical (lacunar) infarcts, particularly if several occur or are present in individuals with other subcortical vascular diseases such as arteriolosclerosis or white matter disease, increase the risk of dementia; this pathology has been referred to as Binswanger disease, subcortical dementia or subcortical vascular ischaemic disease[64] and might be the result of concomitant small vessel disease[64] and/or Alzheimer disease pathology[65].

Microinfarcts can also lead to VCI[61,66,67] (FIG. 3). Microinfarcts are very small infarcts that are defined in terms of pathology as infarcts that cannot be observed by the eye but that can be observed using microscopy[68]. One study suggested that the presence of few microinfarcts detected using microscopy indicates that hundreds to thousands of microinfarcts are actually present

throughout the brain[69]. Microinfarcts can look similar to macroscopic infarcts and have cavitation and macrophage infiltration[68]. Alternatively, microinfarcts might have incomplete tissue injury or puckering or scarring of the tissue[70]. Notably, the definition of microinfarcts differs in pathology studies and neuroimaging studies. In pathology studies, the size of microinfarcts ranges from 85 μm to >2.9 mm, with an average diameter of between 0.2 and 1 mm[69–71]; the upper size limit varies depending on the definition and the method of tissue preparation used. By contrast, traditional neuroimaging techniques only reliably capture infarcts that are ≥3 mm in diameter, and consequently, lesions <3 mm are considered microinfarcts. High-resolution neuroimaging (for example, 7T MRI) can identify microinfarcts <1 mm in diameter, although, these infarcts are among the largest microinfarcts detected in pathology studies[72–75]. The mechanism by which microinfarcts promote cognitive impairment and dementia is unclear. Some studies have suggested that multiple cortical microinfarcts are most strongly associated with dementia, but microinfarcts with a subcortical location might also affect cognition[61]. Other studies have suggested that local reactions such as innate and adaptive immune responses[76–78] and impaired protein clearance[79,80] are important mechanisms for tissue injury and cognitive impairment.

Macroscopic haemorrhages and microbleeds, if sufficient, can also result in cognitive impairment. Owing to the imaging characteristics of haemosiderin (which can be detected in the brain following haemorrhage), microbleeds can be detected more readily using neuroimaging than using pathological analysis[72]. Indeed, the number and location (for example, lobar) of microbleeds detected using neuroimaging have been associated with cognitive impairment and an increased risk of stroke and mortality[81–83].

Box 1 | **Dementia due to mixed pathology**

Over the past 2 decades, accumulating evidence suggests that vascular pathology is very common in individuals >65 years of age but also has an important, additive role when combined with Alzheimer disease pathology. Vascular pathology might occur before, after or at the same time as the development of Alzheimer disease or other neurodegenerative pathologies. Vascular changes, such as infarcts (including macroscopic infarcts and microinfarcts), atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy (CAA), have independent, additive effects on the risk of dementia and reduced cognitive function[63]. Although most individuals with probable Alzheimer disease have a confirmed diagnosis following autopsy, pure Alzheimer disease pathology is uncommon, as most individuals have a mixed pathology, the most common of which is vascular pathology[62,65,67]. It is well accepted that vascular pathology lowers the threshold for a clinical diagnosis of Alzheimer disease.

What is less clear is whether vascular pathology has a synergistic effect with the pathologies of Alzheimer disease or other neurodegenerative diseases. In a classic study, individuals with subcortical infarcts and Alzheimer disease pathology were more likely to have dementia than individuals with either type of pathology alone[65]. However, subsequent studies demonstrated additive rather than synergistic effects[51,60,63,67]. Similarly, the severity of atherosclerosis has been associated with increased amyloid-β load[214,215], although conflicting findings have been reported[216]. A more direct role for amyloid-β clearance has been suggested for CAA[217],whereby cerebral vascular pathologies might result in altered amyloid-β distribution, favouring the development of CAA[152]. Other proposed mechanisms for the interaction between Alzheimer and vascular pathology include hypotension or low blood flow, inflammatory cascades and perivascular clearance.

Tissue injury is also commonly observed in the white matter of older individuals and individuals with vascular risk factors and disease, and is related to an increased likelihood of cognitive impairment. Although not specific for vascular diseases, white matter injuries commonly co-occur with vascular disease and are often presumed to be vascular in origin. White matter injuries that can be detected using MRI include WMHs, loss of integrity and volume loss. The specific tissue injury underlying these imaging observations is related to ischaemia and myelin loss, but the exact mechanisms and consequences are not well understood and are of great interest to researchers[84]. Speculated mechanisms include alterations of the blood–brain barrier, altered vascular reactivity, hypoperfusion and inflammation[78,85,86].

Vessel diseases

Intracranial small vessel diseases (such as arteriolosclerosis and CAA) and large vessel diseases (such as atherosclerosis) are common in the ageing brain. As previously mentioned, although one mechanism by which these diseases result in cognitive impairment is through direct tissue injury, atherosclerosis and arteriolosclerosis are also independently related to VCI after controlling for macroscopic infarcts, microinfarcts and vascular risk factors[63]. CAA is associated with intracranial haemorrhage, microinfarcts and cognitive decline[87], although the presence and severity of CAA is more related to Alzheimer disease pathology than to ischaemic vessel disease[88] and is not commonly recognized as being related to other typical vascular risk factors. However, CAA is also an independent contributor to the decline in cognitive function in the decade before death[87]. Indeed, more than 50% of individuals >65 years of age with a pathological diagnosis of Alzheimer disease have no or mild CAA pathology, and ~20% of individuals with moderate to severe CAA pathology do not have a pathological diagnosis of Alzheimer disease[88].

Small and large vessel cerebrovascular disease are speculated to lead to cognitive impairment through hypoperfusion. Other mechanisms might include ischaemic neuronal injury and/or tissue injury without a focal, well-delineated region of tissue infarction. Indeed, cortical volume loss, white matter volume loss and WMHs are related to vascular disease[89]. Of these, WMHs are often considered the most sensitive marker of ischaemic injury in brains of older individuals. However, although common in individuals with vascular disease, WMHs are nonspecific and can be observed in neurodegenerative diseases, particularly in individuals with Alzheimer disease[89,90]. Wallerian degeneration (that is, axonal loss) with or without comorbid unrecognized vessel disease and myelin loss is postulated to cause WMHs in Alzheimer disease[91–94].

Other pathophysiological processes

Several mechanisms of tissue injury might be important in the cascade through which vascular disease (with or without concomitant Alzheimer disease pathology) promotes injury and cognitive impairment. Histopathological studies have demonstrated neuronal

Table 1 | **Established risk factors for vascular dementia**

Risk factor	Modifiable?	Time trend	Suggested risk factor for Alzheimer disease?
Demographic factors			
Age	No	↑	Yes
Female sex	No	NA	Yes
Low education	Yes	↓	Yes
Low social class	No	NA	Yes
Chronic disorders			
Hypertension	Yes	↓	Yes
Diabetes mellitus	Yes	↑	Yes
Myocardial infarction, angina pectoris	Yes	↓	Not clear
Atrial fibrillation	Yes	↑	Yes
Ischaemic heart failure	Yes	↓	Not clear
Stroke*	Yes	↓ incidence and ↑ prevalence	Not clear
Hypercholesterolaemia	Yes	↓	Yes
Depression	Yes	No clear change	Yes
Overweight	Yes	↑	Yes
Lifestyle factors			
Smoking	Yes	↓	Not clear
Reduced physical activity	Yes	↓	Yes

*Part of the diagnostic criteria for vascular dementia. ↑ denotes increasing trend over time; ↓ denotes decreasing trend over time. NA, not applicable. Produced from data in[35,39–42,46,47].

atrophy and white matter oligodendrocyte and astrocyte changes[95], and imaging studies have demonstrated hippocampal and global brain volume loss and atrophy due to vessel disease[96].

Local inflammation due to ischaemia is important in vascular-associated tissue injury and cognitive impairment, although systemic inflammatory responses might also have a role. The involvement of systemic inflammatory responses is supported by findings of brain dysfunction and altered reperfusion in the setting of systemic inflammation in humans[97–99]. Indeed, data from animal models suggest that inflammation is a key process associated with the development of microhaemorrhages and that microhaemorrhages, hypertension and vascular fibrosis might lead to CAA[100,101]. The neurovascular unit is essential for maintaining brain health[102] and is composed of several cell types, including neurons, astroglia, endothelial cells and pericytes. Immune cells and inflammatory mediators might interact with components of the neurovascular unit to propagate injury[76]. Indeed, leakage of the blood–brain barrier led to the activation of angiotensin receptors on the surface of perivascular macrophages and the release of reactive oxygen species in a mouse model of hypertension, which could contribute to tissue damage[103]. In addition, pericyte degeneration leading to blood–brain barrier impairment in the hippocampus early in disease states has been reported[104]. Pericytes are also involved in contractility to control blood flow. Impaired lymphatic clearance (including perivascular and paravascular drainage) might occur in vascular disease and ageing, which might impair the removal of toxins and interstitial proteins from the brain and alter signalling[105]. Changes in astrocytes have been observed in several VCI models and might link to lymphatic drainage to provide crosstalk between VCI and Alzheimer disease[106]. In addition to the role of the innate immune response in both vascular and Alzheimer disease pathophysiology, the adaptive immune response has also been hypothesized to have a role[76,107,108].

Diagnosis, screening and prevention

Most patients with VCI present for clinical evaluation owing to the presence of cognitive deficits. Although memory deficits are only part of these problems, many patients and their families report problems with memory, as memory is often used as a denominator of any cognitive and behavioural issues. Other symptoms, such as behavioural and psychological issues, are also commonly observed in VCI. In addition, some patients seek clinical evaluation due to the presence of motor and/or gait deficits (for example, vascular parkinsonism) and are only diagnosed with VCI after neuropsychological and functional assessments have revealed cognitive impairment. Finally, some patients present with cognitive impairment after they have a stroke.

The clinical diagnosis of VCI rests on clinical judgement that is preferably corroborated by neuropsychological testing, together with evidence of vascular pathology, such as lacunar infarcts, WMHs or microbleeds, detected using neuroimaging. In everyday practice,

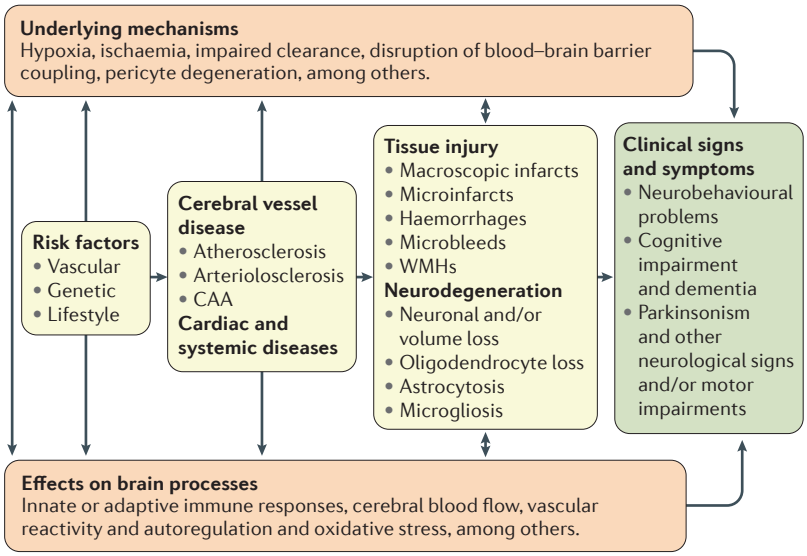

Figure 2 | **Mechanisms of VCI.** Several biological mechanisms might link vascular disease to cognitive impairment, although the order in which these processes occur is difficult to identify. The underlying mechanisms of vascular cognitive impairment (VCI) and the effects of these mechanisms on brain processes is variable between patients. Risk factors, some types of cerebral vessel diseases and tissue injuries interact with these mechanisms and brain processes, each leading by itself or in combination to cognitive impairment and dementia, and the other clinical signs and symptoms of VCI. CAA. cerebral amyloid angiopathy; WMHs, white matter hyperintensities.

many clinicians diagnose VCI, including vascular dementia, when they have excluded other causes of cognitive impairment and found evidence of vascular pathology, but this approach lacks standardization[109]. The differential diagnosis of VCI includes other types of dementia, including Alzheimer disease, dementia with Lewy bodies and frontotemporal dementia, as well as psychiatric disorders such as depression. One of the major challenges is identifying coexisting pathologies, particularly Alzheimer disease pathology, which can be challenging without the use of specific biomarkers that are not always available in clinical practice. Despite the overlapping risk factors for VCI and Alzheimer disease, a specific diagnosis of VCI is clinically relevant, as prognosis, treatment and prevention are different for each disorder.

Diagnostic criteria

Depending on the setting or study type (for example, care settings or research settings, and for clinical research or epidemiological studies), different diagnostic criteria might be used, each of which have disparate levels of evidence and agreement. The first set of criteria for vascular dementia (that is, the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (NINDS-AIREN)) was proposed after the introduction of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS–ADRDA) criteria for Alzheimer disease and was constructed in a similar way[5,110]. When these criteria were developed, memory impairment was considered the main symptom of dementia, and consequently, the screening tools used for Alzheimer disease that often rely on memory function were proposed for vascular dementia. However, although this clinical characterization is globally acceptable for Alzheimer disease, it is now recognized that memory is often not the leading cognitive disturbance in individuals with VCI[4]. Other diagnostic criteria for VCI are available, including the DSM-5 criteria and the AHA/ASA criteria. The different criteria identify different patients because they define distinct core features of VCI. These features commonly include a stepwise cognitive deterioration, a patchy or unequal distribution of cognitive deficits, focal neurological signs and symptoms, a history of multiple ischaemic stroke, evidence of cerebrovascular disease and an association with aetiology, in addition to a temporal relationship between cerebrovascular disease and dementia[5,111–114]. As most patients with vascular dementia or VCI have small vessel disease rather than large vessel disease, deterioration can be slow and gradual; stepwise deterioration and focal cognitive deficits are often not observed[115]. Focal neurological deficits are not always clearly present in patients with vascular dementia or VCI, and the specific deficits depend on the type and location of vascular disease[116]. A temporal relationship between cerebrovascular disease and dementia is often not apparent, particularly in patients with small vessel disease or silent infarcts[117]. For this reason, criteria for what is considered the most common and homogeneous subtype of vascular dementia (that is, subcortical vascular dementia) were introduced in 2000 by Erkinjuntti and colleagues[117].

The heterogeneity of the underlying cerebrovascular pathology and clinical manifestations of vascular dementia have made it difficult to produce a validated and broadly applicable set of criteria. Most criteria describe subtypes of vascular dementia, although this is arbitrary because subtypes overlap. For example, post-stroke dementia can be caused by small vessel disease or by ≥1 large vessel infarct. Thus, a major limitation of the criteria for vascular dementia is the lack of specificity for subtypes that can differ in their clinical and neuroimaging features[116,118,119]. Indeed, vascular dementia has been definitively broadened to include different subtypes and mild forms of cognitive impairment that do not meet the criteria for dementia (which are captured under the term VCI)[3,12,120]. A further step has been made by the Vascular Impairment of Cognition Classification Consensus Study, which proposed new standardized VCI-associated terminology[12,121] (BOX 2).

Here, we briefly discuss two recent sets of diagnostic criteria for VCI. The AHA/ASA criteria uses a definition of VCI based on the traditional construct that first recognizes cognitive impairment (ranging from mild cognitive impairment to dementia) and then recognizes the presence of vascular disease and the relationship with cognitive decline[4] (BOX 3). The DSM-5 criteria for vascular neurocognitive disorders exceed previous approaches, as impairment in any cognitive domain (including executive function) is sufficient for diagnosis, and the memory domain is no longer hierarchically prominent. DSM-5 criteria further distinguish between mild and major neurocognitive disorders; mild neurocognitive disorder

is in line with the term mild cognitive impairment, and major neurocognitive disorder is in line with the term dementia (BOX 4). Other collaborative efforts to improve the understanding of the vascular contributions to cognitive decline and dementia are currently underway, particularly those related to small vessel disease, with the intention of arriving at new diagnostic criteria[122,123].

Diagnostic work up

Neuroimaging. Neuroimaging is an essential part of the workup of patients presenting for the first time with cognitive decline and can exclude any underlying causes of cognitive impairment that might be amenable to treatment; however, these causes are quite rare. In patients with suspected VCI, neuroimaging should be used to assess the extent, location and type of vascular lesions (FIG. 4). MRI should include T1-weighted imaging to detect atrophy, T2-weighted imaging to detect lacunar infarcts and fluid-attenuated inversion recovery (FLAIR) sequences to detect WMHs[124]. In addition, susceptibility-weighted imaging is useful for detecting microbleeds and superficial siderosis. MRI is the first-choice neuroimaging technique for the evaluation of patients with suspected vascular dementia, although CT can be used to detect atrophy and some vascular lesions (TABLE 2). In addition, diffusion tensor imaging (DTI) can detect microinfarcts and changes in the white matter tracts; however, these advanced MRI techniques are not routine in clinical practice and are only used in research settings. The neuroimaging field is rapidly advancing, and more sophisticated MRI techniques could be available for clinical application in the future.

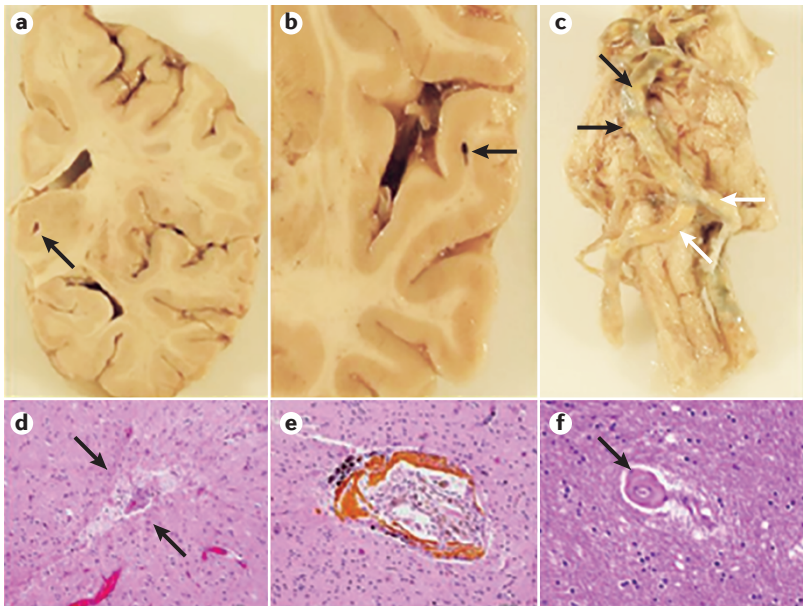

Figure 3 | **Macroscopic and microscopic vascular pathology at autopsy.** **a** | Macroscopic aspect of a lacunar infarct in the thalamus (arrow). **b** | Small haemorrhage in the subcortical white matter of the superior temporal gyrus (arrow), which could appear as a microbleed when detected using neuroimaging. **c** | Atherosclerosis at the circle of Willis, including atherosclerotic plaques in the vertebral artery (white arrows) and the basilar artery (black arrows). In addition, atherosclerosis in what seems to be the posterior cerebral and posterior communicating arteries can be observed. **d** | Microscopic aspect of microinfarct. **e** | Microhaemorrhage. **f** | Arteriolosclerosis.

Cognitive testing. Although neuropsychological testing is necessary for identifying the extent of cognitive deficits and the affected cognitive domains in patients with suspected VCI, this testing is not standardized and different research groups and clinical centres use different protocols. The VCI harmonization standards document produced by the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network has proposed different protocols that can be used based on the time available and in different settings; other groups have proposed other protocols[120,125]. The cognitive evaluation should include an extensive investigation of executive functions and memory, and given the heterogeneity in dementia-associated lesions and cognitive deficits, other domains, such as language, visuospatial functioning, attention and mental speed[120,125]. One screening tool that is increasingly used in the context of cerebrovascular disease is the Montreal Cognitive Assessment (MoCA), which assesses cognitive domains that are more prominently affected in patients with VCI (for example, attention, psychomotor speed and executive tasks)[126]. Because of the more prominent involvement of subtasks that rely on executive function, the MoCA is able to detect more-subtle declines in cognitive function than, for example, the Mini-Mental State Examination.

Laboratory testing. No specific laboratory test is available for VCI. For other types of dementia, some routine blood tests might exclude comorbidities and identify potential risk factors or other causes of cognitive decline, although their role is limited[127]. Assessment of levels of vitamin B_{12}, folate, thyroid-stimulating hormone, calcium and glucose is recommended, in addition to a complete blood cell count and assessment of abnormalities in renal and liver function. Concentrations of amyloid-β 1–42, tau and phospho-tau in the cerebrospinal fluid can be used to identify comorbid Alzheimer disease[128]. Specific markers for vascular injury are not yet available[129].

Pathology-confirmed diagnosis. Although neuropathology is presented as the basis for the definite diagnosis of VCI, accepted and validated criteria are not available. Neuropathology can be used to detect vascular lesions but cannot connect syndrome to disease and is performed post-mortem, hence years after the occurrence of symptoms[130]. Several types of vascular lesions should be evaluated for, including lesions in the parenchyma (such as infarcts and white matter changes) and alterations in blood vessels (such as arteriolosclerosis and CAA)[120,131]. One issue is the frequent coexistence of vascular and degenerative pathologies; although this syndrome has been traditionally referred to as dementia due to mixed pathology, this term reflects the inability to precisely attribute the relative weight of pathological lesions of different aetiologies in dementia, and clear criteria for mixed pathology are entirely lacking. This issue is further complicated by findings that abnormalities that were typically considered as neurodegenerative pathology, such as atrophy of the medial temporal lobe (including the hippocampus), can also be caused

Box 2 | **Definitions and diagnosis of VCI according to the VICCCS2***

- Mild vascular cognitive impairment (VCI): impairment in at least one cognitive domain and mild to no impairment in instrumental activities of daily living
- Major VCI (vascular dementia): clinically significant deficits of sufficient severity in at least one cognitive domain and severe disruption to Activities of Daily Living or Instrumental Activities of Daily Living (ADLs/IADLs)
- Core domains include executive function, attention, memory, language and visuospatial function
- MRI is a gold standard requirement for a clinical diagnosis of VCI
- Patients given a diagnosis of major VCI are subcategorized according to the underlying pathology:
  - Post-stroke dementia
  - Dementia due to mixed pathology (for example, VCI–Alzheimer disease)
  - Subcortical ischaemic vascular dementia (incorporates the overlapping clinical entities of Binswanger disease and lacunar state)
  - Multi-infarct dementia
- Exclusions from diagnosis: drug or alcohol abuse or dependence within the last 3 months of first recognition of impairment or delirium

*Vascular Impairment of Cognition Classification Consensus Study[121].

by vascular pathology[132]. The development of predictive neuropathological models to attribute vascular pathology to cognitive impairment is underway[53].

Prevention

Most risk factors for VCI are modifiable, therefore, targeting these risk factors might reduce the incidence of VCI. Patients who have vascular risk factors without cognitive deficits comprise the so-called brain-at-risk population. Possible approaches to prevent the development of VCI in this population include improving control of vascular risk factors and cardiovascular diseases; in this regard, focusing on individuals at high risk (such as individuals with diabetes mellitus) might be particularly useful. Pharmacological therapies or lifestyle modifications, including exercise can be used to control vascular risk factors and diseases.

Based on analysis of large data sets and computer models, elimination of the seven most common modifiable risk factors for vascular dementia (obesity, hypertension, diabetes mellitus, high cholesterol, smoking, low level of education and cardiovascular disease) has been estimated to lead to a reduction of approximately one-third of dementia cases, particularly of vascular dementia[133,134]. Indeed, initial data from the Framingham study support this estimate, as a reduced incidence of vascular dementia was reported between the late 1970s and the early 2000s, potentially due to improved management of cardiovascular risk factors[30]. By contrast, intervention studies that aim to rigorously control the vascular risk factors for vascular dementia, with a focus on the treatment of hypertension, in individuals >70 years of age have been largely unsuccessful[135]. However, randomized preventive trials have several methodological limitations that might explain the insufficient evidence for the prevention of VCI[136]. Nonetheless, a multimodal intervention simultaneously targeting dietary modification, physical exercise, cognitive training and the control of vascular risk factors would probably be the best approach to prevent vascular dementia and is the intervention most likely to produce effects in at-risk individuals[137].

Management

Management of VCI should include an assessment of the severity of cognitive impairment and should take the presence of comorbidities and the needs of caregivers into account. Treatment should aim to prevent further cognitive decline, improve cognitive symptoms, behavioural symptoms and daily functioning, reduce mortality and manage any other disabilities associated with underlying cerebrovascular disease or stroke, as well as provide education and support for patients and their caregivers (BOX 5). Although small vessel disease is very common in elderly patients, no randomized controlled trials targeting the prevention of stroke in individuals with silent cerebrovascular disease have been carried out. A working group produced by the Stroke Council of the AHA concluded that primary stroke prevention is indicated in patients with silent brain infarcts, WMHs or microbleeds[38].

Secondary prevention

Several strategies for secondary prevention (that is, treatments and therapeutic strategies aiming to counteract the effects of cerebrovascular disease) are available, including improving control of vascular risk factors in patients with a mild degree of cognitive impairment who are at high risk of vascular dementia (such as patients with signs of small vessel disease detected using neuroimaging) and implementing intervention measures to halt or slow progression of cognitive decline in patients with vascular mild cognitive impairment.

Prevention of stroke and post-stroke cognitive impairment. The current guidelines for the prevention of recurrent stroke should be followed for individuals with a history of stroke and might include the use of antithrombotics, antihypertensives and lipid-lowering agents, as well as non-pharmacological interventions, such as exercise and diet modification (for example, low sodium intake and adherence to a Mediterranean diet)[139]. Although the prevention of recurrent stroke should, in theory, prevent further stroke-related cognitive decline and mortality, whether conventional preventive therapies actually prevent cognitive decline is controversial[140,141].

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) demonstrated a reduction in the risk of recurrent stroke-associated incident dementia and cognitive decline by lowering blood pressure using angiotensin-converting enzyme inhibitors and diuretics, compared with placebo[142]. However, trials investigating the use of other antiplatelet and blood pressure-lowering regimes failed to prevent cognitive decline following stroke[143,144], although the sample sizes and study durations (usually 2–3 years) might not be adequate to yield positive results in individuals with a low risk of cognitive decline[145]. One prospective population-based register (the South London Stroke Register) study demonstrated a protective effect of the appropriate implementation of conventional

secondary stroke preventive strategies on cognitive function, up to 10 years after the first stroke[146]. However, in the preDIVA study, blood pressure-lowering strategies did not prevent dementia. This discrepancy might be because the participants in the preDIVA study had a low cardiovascular burden, and only ~10% had a history of stroke or transient ischaemic attack[135,146]. An ongoing study (the SPRINT-MIND, or Systolic Blood Pressure Intervention Trial) is assessing whether a more-aggressive systolic blood pressure target of <120 mmHg is associated with a slower rate of cognitive decline in individuals with increased cardiovascular risk[147,148]. However, whether the results of this study can be extrapolated to older individuals with vascular dementia is uncertain, as low blood pressure in elderly individuals with dementia might worsen cognitive function[149].

Concerns have been raised regarding the use of antithrombotics for the prevention of ischaemic stroke in patients with Alzheimer disease, as an increased risk of intracerebral haemorrhage has been reported, particularly in individuals with cerebral microbleeds[82,150–152]. Consequently, the decision to administer antithrombotics to individuals with a clear indication (for example, those with ischaemic stroke) but who also have multiple cerebral microbleeds (for example, ≥5) remains difficult[153]. However, the evidence supporting positive effects of the use of antithrombotics in individuals with microbleeds seems to outweigh the evidence of adverse effects. Of further note, one observational study demonstrated a reduced risk of stroke, bleeds and dementia with newer oral anticoagulants in patients receiving long-term anticoagulation, compared with warfarin[154]. Close monitoring of anticoagulant compliance in individuals with cognitive impairment is important to prevent adverse events related to overdosage and underdosage.

With respect to non-pharmacological strategies, the ASPIS trial did not demonstrate a benefit of a 24-month multidomain intervention (including improved compliance with prescribed evidence-based medication, regular blood pressure measurements, healthy diet, regular physical activity and cognitive training) on the incidence of post-stroke cognitive decline over one year, compared with standard stroke care[155]. However, as the incidence of cognitive decline was low during the course of the study (~10%), the sample size and study duration might not have been adequate to detect a significant difference between the treatment groups. Despite the negative findings of the ASPIS study, a healthy lifestyle as recommended in stroke prevention guidelines should be adhered to for recurrent stroke prevention[139].

Prevention of WMH progression. Given that detecting a clinical efficacy in preventive trials for vascular dementia might require large sample sizes and/or long durations, the use of surrogate outcome measures, such as changes in the volume of WMHs, has been proposed[156,157]. Indeed, the presence and progression of WMHs and lacunes (small subcortical ischaemic infarcts resulting from occlusion of a small perforating artery) are associated with cognitive decline[145,158–161]. In the PROGRESS MRI substudy, lowering blood pressure using perindopril and indapamide was associated with less progression in WMH volume in individuals with cerebrovascular disease, compared with placebo[162]. The largest effect was observed in individuals with severe WMHs at baseline[162], although the incidence of new lacunes was unaffected[163]. The optimal blood pressure target in individuals with WMHs is uncertain, as a U-shaped association between blood pressure levels and the severity of WMHs has been reported[164]. In the Regression Of Cerebral Artery Stenosis study (ROCAS), the use of statins by patients with diabetes was associated with a reduced incidence of lacunes and reduced progression of WMHs, particularly in those with severe WMHs at baseline, compared with

Box 3 | **AHA/ASA criteria for vascular dementia**

Diagnostic criteria for vascular dementia according to the American Heart Association (AHA) and the American Stroke Association (ASA) scientific statement on Vascular Contributions to Cognitive Impairment and Dementia[4].

Dementia

- The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in at least two cognitive domains that are of sufficient severity to affect the individual's activities of daily living
- The diagnosis of dementia must be based on cognitive testing, and a minimum of four cognitive domains should be assessed: executive or attention; memory; language; and visuospatial functions
- The deficits in activities of daily living are independent of the motor or sensory sequelae of the vascular event

Probable vascular dementia

- Cognitive impairment and imaging evidence of cerebrovascular disease are present, and:
  - A clear temporal relationship exists between a vascular event (for example, clinical stroke) and onset of cognitive deficits; or
  - A clear relationship exists between the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (for example, as in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL))
- No history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder

Possible vascular dementia

Cognitive impairment and imaging evidence of cerebrovascular disease are present, but

- No clear relationship (temporal, severity or cognitive pattern) exists between the vascular disease (for example, silent infarcts, subcortical small vessel disease) and the cognitive impairment
- Insufficient information is available for the diagnosis of vascular dementia (for example, clinical symptoms suggest the presence of vascular disease, but no CT or MRI studies are available)
- Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (for example, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable vascular dementia
- Evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition is available, such as:
  - A history of other neurodegenerative disorders (for example, Parkinson disease, progressive supranuclear palsy or dementia with Lewy bodies);
  - The presence of Alzheimer disease biology is confirmed by biomarkers (for example, PET, cerebrospinal fluid, amyloid ligands) or genetic studies (for example, mutations in *PS1*); or
  - A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function

placebo[165,166]. In patients with severe WMHs after stroke, the use of statins was associated with reduced WMH progression and less decline in executive function[167]. However, statins failed to attenuate WMH progression in elderly individuals with a history of, or risk factors for, vascular disease in the Prospective Study of Pravastatin in the Elderly (PROSPER)[168]. Overall, as most patients with vascular dementia have a history of vascular risk factors and/or stroke, blood pressure and lipid-lowering therapies are administered irrespective of their potential benefits on attenuating the progression of WMHs.

Some trials are also evaluating other treatments, aside from the conventional stroke preventive treatments, on WMH progression. The Vitamins to Prevent Stroke (VITATOPS) MRI substudy demonstrated that reducing homocysteine levels (using vitamin B supplementation) slowed down WMH progression only in individuals with severe small vessel disease at baseline[169]. This finding is consistent with the main study that showed a reduction in recurrent vascular events only in individuals with stroke associated with small vessel disease[170]. In another study, treatment with vitamin E tocotrienols was associated with less progression of WMHs in individuals with cardiovascular risk factors and WMHs detected using MRI, compared with placebo[171]. In the Evaluation of Vascular Care in AD (EVA) study, multicomponent vascular care, including lifestyle interventions (such as weight loss, dietary advice, exercise and smoking cessation) and the use of medications (such as low dose aspirin, pyridoxine and folic acid), was associated with reduced progression of WMHs in patients with Alzheimer disease and evidence of cerebrovascular disease on MRI, compared with standard care by a general practitioner[172]. Two ongoing trials are investigating the effects of cilostazol (which has antiplatelet and vasodilating properties) on progression of WMHs in individuals with extensive WMHs at baseline (CUHK_CCT00430 and NCT01932203). In addition, another trial is assessing the effect of aerobic exercise on WMH progression and cerebral blood flow in patients with mild VCI[173,174]. Of note, MRI-based markers of other small vessel disease that are based on white matter tracts and diffusion histograms (derived from DTI) could be more sensitive for detecting clinical change than WMH volume[175].

Alterations in cognitive performance was not reported in the studies described above. Accordingly, treatments that can improve surrogate markers, such as

Box 4 | **DSM-5 criteria***

Major neurocognitive disorder

- Evidence of significant cognitive decline from a previous level of performance in at least one cognitive domain (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on:
  - Concern of the individual, a knowledgeable informant or the clinician that there has been a significant decline in cognitive function; and
  - A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
- The cognitive deficits interfere with independence in everyday activities
- The cognitive deficits do not occur exclusively in the context of a delirium
- The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia)

Specify whether due to one of the following pathologies:

- Alzheimer disease
- Frontotemporal lobar degeneration
- Lewy body disease
- Vascular disease
- Traumatic brain injury

Mild neurocognitive disorder

- Evidence of modest cognitive decline from a previous level of performance in at least one cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on:
  - Concern of the individual, a knowledgeable informant or the clinician that there has been a mild decline in cognitive function; and
  - A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
- The cognitive deficits do not interfere with capacity for independence in everyday activities
- The cognitive deficits do not occur exclusively in the context of a delirium
- The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia)

Vascular neurocognitive disorder

- Criteria are met for major or mild neurocognitive disorder
- The clinical features are consistent with a vascular aetiology, as suggested by either of the following:
  - Onset of the cognitive deficits is temporally related to one or more cerebrovascular events;
  - Evidence for decline is prominent in complex attention (including processing speed) and frontal executive function
- Evidence of cerebrovascular disease from history, physical examination, and/or neuroimaging that is considered sufficient to account for the neurocognitive deficits
- The symptoms are not better explained by another brain disease or systemic disorder

Probable vascular neurocognitive disorder

Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise, a possible vascular neurocognitive disorder should be diagnosed:

- Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (which is supported by neuroimaging)
- Neurocognitive syndrome is temporally related to one or more documented cerebrovascular events
- Both clinical and genetic (for example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)) evidence of cerebrovascular disease is present

Possible vascular neurocognitive disorder

Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met, but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established

* Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition[11]

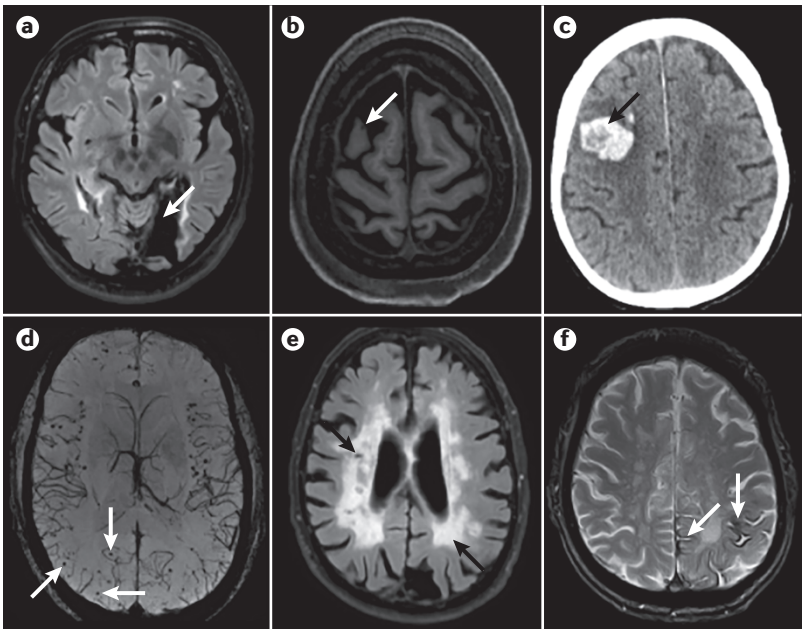

Figure 4 | **MRI manifestations of cerebrovascular disease. a** | Large vessel infarct detected using fluid-attenuated inversion recovery (FLAIR) sequences. **b** | Microinfarct detected using T1-weighted MRI. **c** | Macroscopic haemorrhage detected using CT. **d** | Multiple microbleeds indicative of cerebral amyloid angiopathy detected using susceptibility-weighted imaging (arrows point to three representative microbleeds). **e** | Extensive white matter hyperintensities (WMHs) detected using FLAIR sequences (arrows point to representative WMHs). **f** | Superficial siderosis detected using susceptibility-weighted imaging (arrows point to representative areas of superficial siderosis). Part **b** courtesy of Susanne van Veluw, Massachusetts General Hospital, USA.

WMHs and lacunes, should be further tested in larger clinical trials with longer durations that use cognitive performance as the primary outcome measure.

Treatment of dementia due to mixed pathology

Recent studies using *in vivo* amyloid-β PET demonstrated that ~30% of individuals with post-stroke dementia or subcortical vascular dementia have substantial concurrent Alzheimer disease pathology[140,176,177], and the presence of this pathology was associated with more rapid cognitive decline[178]. Accordingly, when disease-modifying preventive treatments for Alzheimer disease become available, the efficacy and safety of these therapies should be assessed in individuals with VCI and concomitant Alzheimer disease[179,180].

Symptomatic treatment

To date, the US FDA and the European Medicines Agency have not approved any symptomatic pharmacological treatments for VCI (including for vascular dementia). Several clinical trials have evaluated the use of acetylcholinesterase inhibitors and memantine (an *N*-methyl-D-aspartate receptor antagonist) in individuals with vascular dementia, both of which are established symptomatic treatments for Alzheimer disease. However, although one meta-analysis demonstrated a small improvement in cognitive performance in patients with vascular dementia after treatment for 6 months, this response was not associated with apparent functional or behavioural benefits in daily life[181]. Subgroup analyses suggested that acetylcholinesterase inhibitors have greater benefits in individuals with (multiple) cortical lesions and hippocampal atrophy compared with patients without hippocampal atrophy[181,182], and memantine was more effective in individuals with subcortical vascular dementia than in individuals with other dementias[183].

Other symptomatic therapies evaluated in patients with VCI include cerebrolysin, actovegin and nimodipine. Cerebrolysin (a combination of neurotrophic factors that were initially isolated from pig brains) and actovegin (which can promote glucose transport) might have neurotrophic and neuroprotective properties in individuals with mild to moderate vascular dementia or post-stroke cognitive impairment[184,185]. Indeed, one meta-analysis demonstrated a beneficial effect of cerebrolysin treatment on cognitive performance and global function in individuals with vascular dementia[185]. However, cerebrolysin treatment requires regular intravenous infusion, and therefore, widespread use of this drug for vascular dementia would be challenging. Actovegin treatment for 6 months improved cognitive function in individuals with post-stroke mild cognitive impairment compared with placebo[184], warranting further clinical trials. Nimodipine (a calcium channel blocker with potential vasoactive and neuroprotective properties) failed to show an overall benefit in global cognitive, behavioural and functional performance in individuals with subcortical vascular dementia over a 52-week period, compared with placebo[186]. However, post hoc analysis suggested an association with improved performance in an executive function test.

Therapies based on nutritional components, such as dl-3-n-butylphthalide and gingko biloba extract, have been assessed in individuals with vascular dementia. Indeed, dl-3-n-butylphthalide (which has antiplatelet and antioxidant properties and can improve microcirculation) treatment was associated with improvements in cognitive performance over a 6-month period in individuals with mild cognitive impairment associated with small vessel disease[187]. Given the promising results from this trial, further studies aiming to confirm the clinical benefits and explore whether dl-3-n-butylphthalide can prevent progression of small vessel disease and cognitive decline over a longer period are warranted. Some trials investigating an extract of gingko biloba (EGb 761) in individuals with dementia have included patients with vascular dementia. Subgroup analyses suggested that use of gingko biloba improved cognitive symptoms, activities of daily living and neuropsychiatric symptoms in individuals with vascular dementia[188,189]. An overview of systematic reviews of gingko biloba suggested that only a high dose of ≥200 mg/day for ≥5 months has benefits in individuals with dementia, although the quality of evidence was modest at best, illustrating the need for further rigorously executed trials[190].

To date, evidence supporting the use of cognitive training for VCI is lacking but this therapy is being investigated in an ongoing trial[191]. Given the potential benefits of noninvasive brain stimulation (for example, repetitive transcranial magnetic stimulation) in recovery

Table 2 | **Neuroimaging in VCI**

Lesion	Detectable by CT?	MRI sequences used for detection	Superiority of each method
Large infarcts	Yes	T2	MRI = CT
Small and lacunar infarcts	Yes	T1, T2 and/or FLAIR	MRI > CT
White matter lesions	Yes	FLAIR	MRI > CT
Microbleeds	No	SWI	MRI only
Enlarged perivascular spaces	Yes	T2	MRI > CT
Global atrophy	Yes	T1 and/or FLAIR	MRI = CT
Structural integrity of the white matter	No	DTI	MRI only; should be considered in research setting only
Cortical microinfarcts	No	DWI	3T MRI only; should be considered in research setting only

MRI > CT denotes MRI is superior to CT; MRI = CT denotes MRI and CT have similar performance. DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging; T1, T1-weighted images; T2, T2-weighted images.

from stroke and Alzheimer disease, this modality also warrants further investigation[192,193]. Regenerative therapy, such as the use of induced pluripotent stem cells (iPSCs), has been explored for the treatment of stroke[194,195]. Although the efficacy of iPSC transplantation in patients with stroke was inconsistent in early clinical studies, this treatment modality was feasible. Given that stroke-related brain damage and degeneration are associated with VCI, iPSC transplantation might hold promise for this disorder.

Other management issues

Given the risk of metabolic syndrome and mortality associated with the use of some antipsychotics (for example, haloperidol and risperidone)[196,197], these drugs should be used cautiously for the management of agitation, psychosis or aggression in patients with vascular dementia. For individuals with comorbid major depression, selective serotonin reuptake inhibitors are preferred over tricyclic antidepressants, owing to better tolerability in elderly individuals and fewer cardiovascular adverse effects[198]. Moreover, the close monitoring of parkinsonian features and the risk of falling or aspiration pneumonia is warranted, particularly in patients using antipsychotics and in those with coexisting parkinsonian features[199]. In patients with VCI and disabling parkinsonism, levodopa therapy should be considered[200]. Given the multiple comorbidities that can be associated with VCI, a team of health professionals is required for patient management (for example, nurses, physiotherapists, occupational therapists and psychologists), and appropriate and adequate education, training and support for relatives and caregivers are essential.

Quality of life

Measuring the effect of disease and therapeutic interventions must include not only clinical outcomes but also the quality of the physical, mental and social domains of life. Indeed, QOL is affected not only by physical health and psychological state but also by personal beliefs, social relationships and environmental factors[201]. Given that health-related QOL is a complex concept, many scales for measuring this concept have been developed and utilized, including scales for dementia.

A review of dementia QOL assessment scales identified 16 measures that varied in several areas: conceptual basis, whether patient or proxy reports were used, range of subscales and items, scoring systems and types of patients assessed[202]. The Quality of Life in Alzheimer Disease (QOL-AD)[203], Dementia Quality of Life (DQOL)[204], Quality of Life in Late-Stage Dementia (QUALID)[205] and QUALIDEM[206] measures have the highest quality evidence of overall validity, but their general and cross-cultural applicability and predictive validity are unknown owing to testing on selective samples. One important note is the lack of studies focusing on VCI, as the patient populations studied were predominantly those with Alzheimer disease. Although VCI and Alzheimer disease have common features, important differences also occur (such as VCI-specific symptoms, including mental slowness, depression and apathy) that might affect the measurement of QOL. In addition, the consequences of stroke might require separate assessments of QOL, such as the stroke-specific quality of life (SS-QOL) measure[207]. However, stroke-related QOL measures mostly do not focus on cognitive symptoms. As QOL is important as a measure of health and as an outcome in clinical trials and for cost-effectiveness analysis, it is essential to have valid QOL measures for VCI. The ideal QOL tool for VCI should be based on the sound concepts described in this section, have specificity for VCI and reflect the views and priorities of patients. Moreover, the QOL measure should be practical to minimize the burden on patients and healthcare workers and must be widely accessible as VCI is a global problem, especially in developing countries.

Four dimensions that contribute to QOL in patients with dementia have been identified: psychological well-being in terms of emotional state and mood; behavioural competence as assessed by cognitive and functional abilities; physical and social environment as ascertained by caregivers and the living situation; and perceived QOL[208]. Perceived QOL might be difficult to measure, given that patients with dementia might have impaired communication or might not have insight into their condition, especially in patients with severe dementia. Nevertheless, the preserved ability to experience positive emotions, the absence of depression or anxiety, a sense of belonging and enjoyment of activities in individuals with dementia are important for QOL. Several factors influence the effect of caregiving experience on a patient's QOL, such as gender, relationship to the patient, culture and personal characteristics[209]. In addition, a caregiver's QOL is correlated to the patient's QOL, the presence of behavioural disorders in patients, how the disease evolved (including the rate of progression and nature of symptoms) and the caregiver's gender[210]. Data for VCI are sparse, but in one trial assessing the use of a multicomponent intervention in patients with dementia, the

Box 5 | **Management of VCI**

Preventive

- Follow the latest management guidelines for primary (for individuals without stroke) or secondary (for patients with stroke) stroke prevention
- Target concurrent sporadic small vessel disease (for example, white matter hyperintensities (WMHs) or lacunes) and/or other dementing brain pathologies (for example, Alzheimer disease) once effective preventive therapies are available

Symptomatic

- Acetylcholinesterase inhibitors can be used, particularly in individuals with cortical infarcts, hippocampal atrophy and concurrent Alzheimer disease
- Memantine can be used, particularly in individuals with small vessel disease and concurrent Alzheimer disease
- Gingko biloba extract (EGb 761) and cerebrolysin can be considered

Other management issues

- Multidisciplinary approach for treating comorbidities (such as, motor, behavioural and sphincter) and caregivers' needs
- Clinicians should be aware of the following risks:
  - Cognitive decline with aggressive blood pressure-lowering in elderly individuals (for example, >80 years of age), individuals with severe WMHs or widespread severe atherosclerosis
  - Intracerebral haemorrhage with use of antithrombotics in individuals with lobar or ≥5 subcortical microbleeds
  - Metabolic syndrome or parkinsonism with use of antipsychotics

QOL of caregivers (measured by caregiver depression, burden, self-care and social support) and problem behaviours in patients improved[211]. In addition, community occupational therapy improved the QOL of both patients with dementia and caregivers[212].

Outlook

The so-called clinical-radiological paradox is typical for VCI; one individual might have extensive WMHs and lacunes detected by neuroimaging but function independently without cognitive impairment, whereas another individual with the same vascular damage might have severe dementia. Although the type, severity and location of cerebrovascular pathology can determine the severity of cognitive impairment[51,52], other factors must also have a role and might include cognitive reserve or brain reserve. Variation in brain atrophy could also be important for the relationship between cerebrovascular pathology and cognitive impairment. In addition, interest is increasing in the role of microscopic vascular pathology (such as microinfarcts and microbleeds) in the clinical manifestation of VCI. Novel, quantitative imaging methods, such as DTI to capture structural integrity of the white matter and arterial spin labelling to measure regional cerebral blood flow, can add further specificity to the diagnosis. The neurovascular unit, including the blood–brain barrier, is receiving increasing attention in the pathophysiology of VCI. In addition, how progression of the disease takes place is unclear. Progression is variable between patients; for example, progression of vascular dementia might be caused by recurrent strokes in one patient, but a single lacunar infarct or WMH might add up to an ongoing neurodegenerative process in another patient[65].

In addition to our current inability to capture and measure the full range of vascular pathology, one other factor in VCI is the presence of comorbidities. Indeed, as previously mentioned, most patients with VCI have co-occurring Alzheimer disease or Lewy body pathology, which might overshadow the effect of vascular pathology because of their stronger effects on cognitive function and behaviour. An infarct in an otherwise healthy brain might not lead to cognitive defects, but a small infarct in an individual with pre-existent, but subclinical, Alzheimer disease pathology might lead to dementia[65,213]. The current sets of diagnostic criteria for VCI or for Alzheimer disease do not have guidelines for mixed pathology. In the future, we expect a change from syndrome-based diagnosis to a more specific, mechanism-based diagnosis. In this scenario, syndrome diagnosis (that is, dementia, mild cognitive impairment or normal cognition), would be carried out first to judge the level of cognitive impairment. The syndrome diagnosis would direct therapy in terms of care and, to some extent, for alleviating symptoms. Second, a specialist at a memory clinic would determine the types of brain pathology contributing to the cognitive impairment. Imaging (MRI, PET, dopamine transporter (DAT)-SPECT) and biomarkers in cerebrospinal fluid (and, hopefully, in the future in blood) can determine the extent of vascular pathology, Alzheimer disease pathology and Lewy body pathology, among others. Identifying the exact combinations of pathologies will then allow for precise or personalized pharmacological treatments. To date, disease-modifying treatments for most of these neurodegenerative diseases are not yet available. Yet, it is conceivable to think of a future where we will be able to target specific brain diseases to cure, stop or even prevent cognitive decline and dementia.

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Author contributions

Introduction (W.M.v.d.F.); Epidemiology (I.S.); Mechanisms/pathophysiology (J.A.S.); Diagnosis, screening and prevention (L.P. and P.S.); Management (V.M.); Quality of life (C.L.H.C.); Outlook (All); Overview of Primer (W.M.v.d.F. and P.S.).

Competing interests

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