Clinical management of cerebral small vessel disease: a call for a holistic approach

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Abstract

Cerebral small vessel disease (SVD) is a common global brain disease that causes cognitive impairment, ischemic or hemorrhagic stroke, problems with mobility, and neuropsychiatric symptoms. The brain damage, seen as focal white and deep grey matter lesions on brain magnetic resonance imaging (MRI) or computed tomography (CT), typically accumulates "covertly" and may reach an advanced state before being detected incidentally on brain scanning or causing symptoms. Patients have typically presented to different clinical services or been recruited into research focused on one clinical manifestation, perhaps explaining a lack of awareness, until recently, of the full range and complexity of SVD.

In this review, we discuss the varied clinical presentations, established and emerging risk factors, relationship to SVD features on MRI or CT, and the current state of knowledge on the effectiveness of a wide range of pharmacological and lifestyle interventions. The core message is that effective assessment and clinical management of patients with SVD, as well as future advances in diagnosis, care, and treatment, will require a more "joined-up"' approach. This approach should integrate clinical expertise in stroke neurology, cognitive, and physical dysfunctions. It requires more clinical trials in order to improve pharmacological interventions, lifestyle and dietary modifications. A deeper understanding of the pathophysiology of SVD is required to steer the identification of novel interventions. An essential prerequisite to accelerating clinical trials is to improve the consistency, and standardization of clinical, cognitive and neuroimaging endpoints.

Keywords: Dementia; Magnetic resonance imaging; Mild cognitive impairment; Risk factors; Small vessel disease; Stroke; Symptoms; Treatment

Introduction

Cerebral small vessel disease (SVD) is a global brain disease affecting multiple clinical domains by disrupting normal function of the perforating cerebral arterioles, capillaries, venules, and brain parenchyma, manifesting on magnetic resonance imaging (MRI) as white matter hyperintensities (WMH), small subcortical infarcts, microinfarcts, lacunes, enlarged perivascular spaces (PVS), microbleeds, superficial siderosis, intracerebral hemorrhage (ICH), and atrophy.[1,2] The core clinical manifestations include lacunar ischemic stroke, intracerebral hemorrhage and cognitive decline, including vascular cognitive impairment and amplification of pathological and cognitive Alzheimer's disease manifestations.[3-5] There is increasing recognition that its multidomain involvement extends beyond stroke and dementia [Figure 1] to include gait and balance dysfunction, behavioral and neuropsychiatric symptoms, and subtle, non-focal neurological features [Figure 2],[6-8] resulting in presentations to diverse general and specialist services [Table 1].

The onset of sporadic SVD typically occurs during mid to late life and although the disease, its associated risk factors, and clinical features such as gait dysfunction and cognitive decline are more prevalent with advancing age, these are not just inevitable consequences of ageing. SVD often arises on a background of other complex comorbidities, and untangling SVD symptoms from those attributable to other conditions requires careful clinical judgment including neuroimaging review. Adopting a more integrated, holistic approach to identifying early and intermediate

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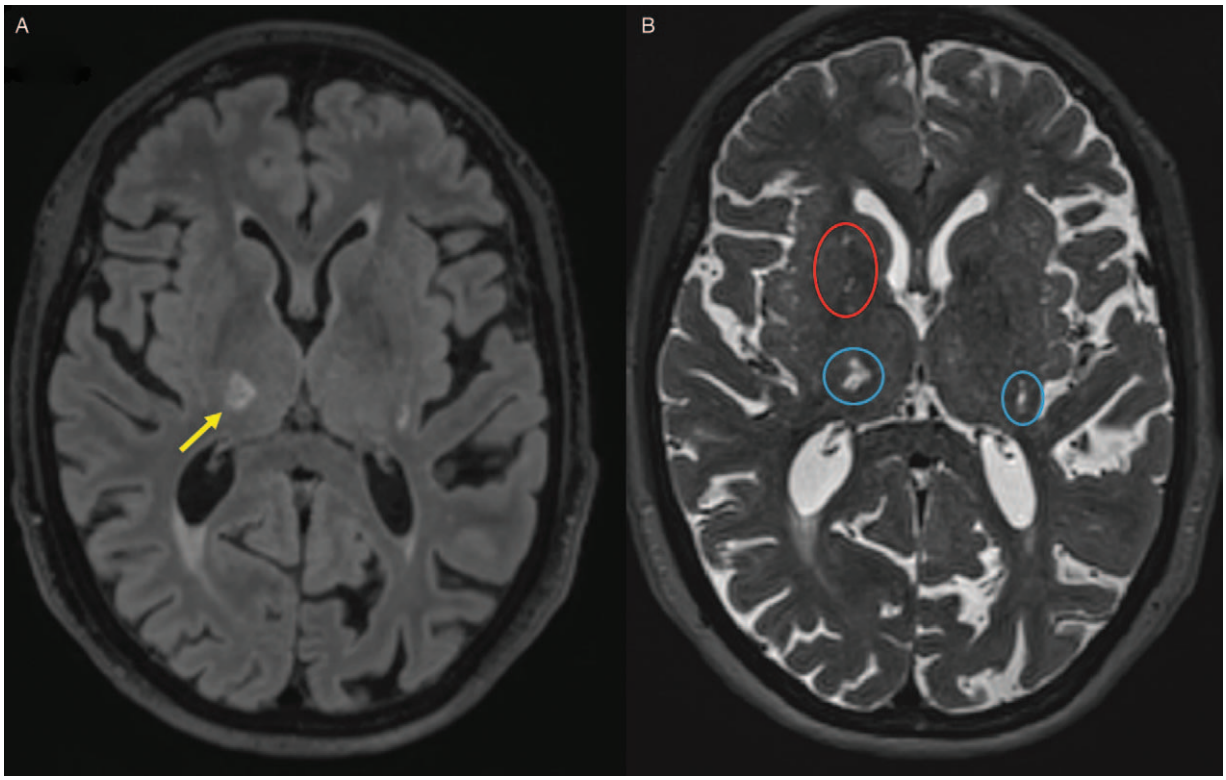

Figure 1: Case vignette. A 75-year-old female presents to the acute medical assessment unit with recurrent falls. She has a past medical history of hypertension, hypercholesterolaemia and recent lacunar stroke 3 months ago. She is an ex-smoker of 40 pack-years. On examination her blood pressure is 169/85 mmHg, without postural hypotension, and pulse is regular. She is objectively apathetic and mildly bradyphrenic. She has a slow, shuffling gait, with preserved arm swing, and is unsteady on initiation and turning. She has mild dysarthria and a left pronator drift. She scores 22/30 on MoCA, with deficits in executive function, attention and abstraction. Her daughter reports progressive cognitive and functional decline over the past 2 years and subtle behavioural changes developing over the past month: she has become apathetic, finds it increasingly difficult to manage her finances, and is easily fatigued performing minor household tasks. Full blood count, urea and electrolytes, and C-reactive protein are normal, serum cholesterol is 5 mmol/L, HbA1c is 40 mmol/mol and electrocardiogram shows sinus rhythm, normal conduction intervals, and mild left ventricular hypertrophy. Brain MRI shows a subacute right thalamic small subcortical infarct, periventricular and deep white matter hyperintensities, enlarged perivascular spaces, and a chronic lacune: (A) Subacute small subcortical infarct in the right thalamus (yellow arrow, on FLAIR) relating to clinical lacunar stroke three months ago and white matter hyperintensities (hyperintense on FLAIR); (B) Lacunes and enlarged perivascular spaces (blue and red circles respectively, hyperintense on T2-weighted imaging. MoCA: Montreal cognitive assessment scale; MRI: Magnetic resonance imaging; FLAIR: Fluid-attenuated inversion recovery.

clinical brain damage markers is essential to permit prognostication, supportive management strategies, identification of patients for emerging treatment trials, and future refinement of targeted prevention and management strategies.

Here we present an evidence-based overview of the literature on clinical aspects of SVD, discussed in the context of our clinical and research experience of caring for these patients.

Methods for Searching, Identifying, Selecting, and synthesizing Data

We searched Ovid MEDLINE using the terms "Cerebral Small Vessel Diseases/" or "White matter hyperintens*" and "Clinical" from inception to April 3, 2020. We separately searched "Lacunar state" or "Binswanger". On risk factors for SVD and its progression, we searched Ovid MEDLINE using the terms "Cerebral small vessel disease" OR "White matter hyperintens*" AND "vascular risk factor" OR "risk factor" AND "disease progress*" OR "outcome" up to June 5th 2020. On therapeutic approaches to SVD, we searched Ovid MEDLINE using the terms "Cerebral small vessel disease" OR "White matter hyperintense*" OR "lacunar" OR "vascular cognitive impairment" up to 12th May 2020. We supplemented the electronic search with the authors' personal files and searched reference lists of identified papers. We screened 2169 papers for clinical diagnosis, 1094 for risk factors and progression, and 7695 for interventions in SVD, including the most relevant papers reporting SVD associations.

Defining the Natural History of Clinical Cerebral Small Vessel Disease

The earliest clinicopathological reports by Binswanger[9] in 1894, based on eight post-mortem cases, described "encephalitis subcorticalis chronica progressiva", characterized pathologically by pronounced white matter atrophy and cortical thinning and clinically by a progressive, fluctuating course, arising predominantly in males in their 50s, characterized by chronic cognitive and emotional symptoms, and occasionally punctuated by acute hemiplegic episodes.

In 1901, Marie[10] described 'l'*é*tat lacunaire' or "the lacunar state", involving one or more lacunes on neuropathology, characterized by progressive neurological

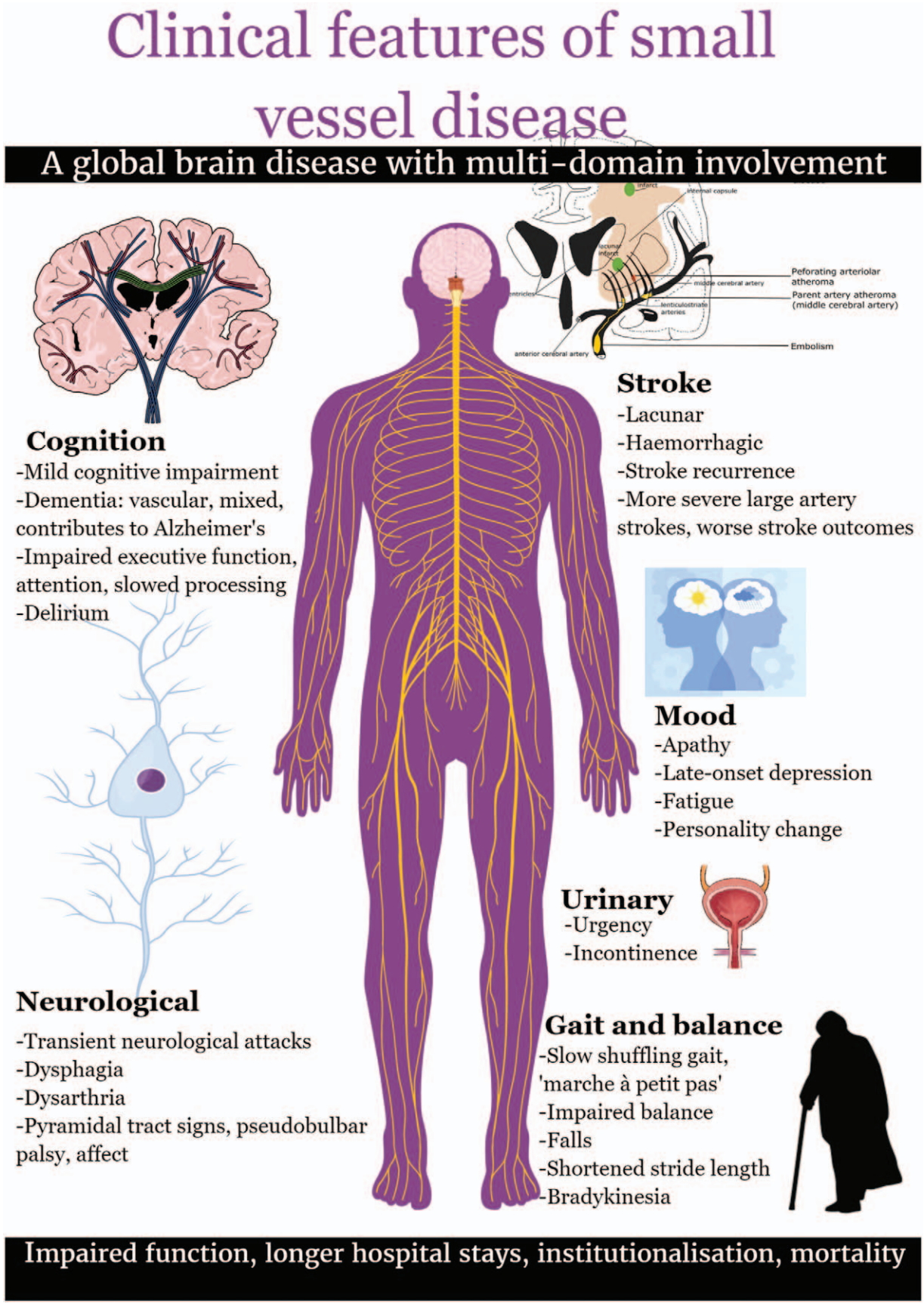

Figure 2: Clinical features of small vessel disease.

Table 1: Diverse presentations: clinical small vessel disease encounters with general and specialist services.

Clinical service	Presenting symptoms
General practitioner	All below presentations + informant reports of altered behavior, deteriorating cognition and function
Physiotherapist	Deteriorating mobility, falls
Speech and language therapist	Dysphagia, dysarthria
Occupational therapist	Functional decline requiring social support
Geriatric medicine service*	Inpatient admissions including unexplained falls, gait deterioration, delirium +/– obvious precipitant, stroke, functional and cognitive decline
	Falls clinics
	Parkinson's disease clinics
	Day hospital and rehabilitation
	Dementia clinics
	Residential and nursing home assessments
Stroke service*	Stroke, transient ischaemic attacks, transient neurological attacks
Neurology service*	Stroke, transient neurological attacks, cognitive assessment clinics, referrals for declining mobility, Parkinson's disease, pseudobulbar palsy
Psychiatry service*	Dementia clinics: cognitive impairment diagnosis, management of behavioral and psychological symptoms of dementia
	Mood and personality changes
	Severe or persistent unexplained delirium
Urology/gynecology	Urinary symptoms
Accident and Emergency*	Falls, delirium, acute neurological symptoms including stroke
Acute medical assessment unit and General internal medicine*	Acute neurological symptoms including stroke, falls, delirium
Orthopedic service Osteoporosis service	Falls resulting in fractures

* Services with readily available access to neuroimaging investigations.

decline, episodes of mild hemiparesis, and later, dysarthria, marche *à* petit pas (gait with little steps), imbalance, incontinence, pseudobulbar signs, and dementia.

Much remains unknown about its precise natural clinical history: the disease is elusive in its early stages unless the patient has overt symptoms that are easily recognized from the current neurological lexicon for stroke or dementia [Figure 3]. Proposed pathophysiological mechanisms underlying SVD are outside the scope of this review but are described in detail elsewhere.[2,11,12] We describe acute and chronic clinical and neuroimaging manifestations at various SVD stages.

Modes of presentation

"Silent" small vessel disease

"Silent" or "covert" SVD refers to disease incidentally detected on neuroimaging without the patient apparently having overt symptoms. While some lesions are truly clinically silent, for instance if small or located in less eloquent regions,[13] careful questioning about historical stroke or transient ischemic attack (TIA) symptoms is recommended, as a positive history may render such individuals eligible for secondary stroke prevention.[14] Furthermore, a comprehensive history and examination, including collateral history from an informant, may yield more subtle, associated features such as apathy, abrupt or insidious cognitive decline, fatigue or gait disturbances that do not necessarily meet diagnostic criteria for stroke or dementia but have been linked temporally with acute lesions on Diffusion-Weighted Imaging (DWI) MRI ($n = 6/649$ community sample, $n = 10/30$ vascular dementia population).[7,15] How patients report, and clinicians interpret, these symptoms is poorly understood and inter-individual factors influencing accurate reporting are complex. For instance, a "threshold effect" of sufficient SVD burden might accumulate before triggering symptoms[16] and this might vary between individuals and at different ages [Figure 4]. Similarly, physical reserve is likely to play a role: the fitter an individual, the more compensatory mechanisms can be employed despite accumulating deficits. Whether initially silent infarcts due to SVD are clinically "unmasked" later by increasing SVD burden and/or increasing physical frailty, revealing delayed typical or atypical symptoms, is a target for future research.

Subtle neurological symptoms

To uncover whether "non-stroke" symptoms may be associated with acute infarcts on brain imaging, some studies have focused on transient neurological attacks (TNAs). Almost one-quarter of TNA patients ($n = 13/56$) have corresponding DWI hyperintense lesions.[8] Moreover, both TNAs and Transient Focal Neurological Episodes, a subset of TNAs typified by spreading, recurrent, stereotyped episodes and associated with cerebral amyloid angiopathy (CAA),[17] herald a higher risk of future ischemic and hemorrhagic stroke, while TNAs also associate with chronic SVD features and

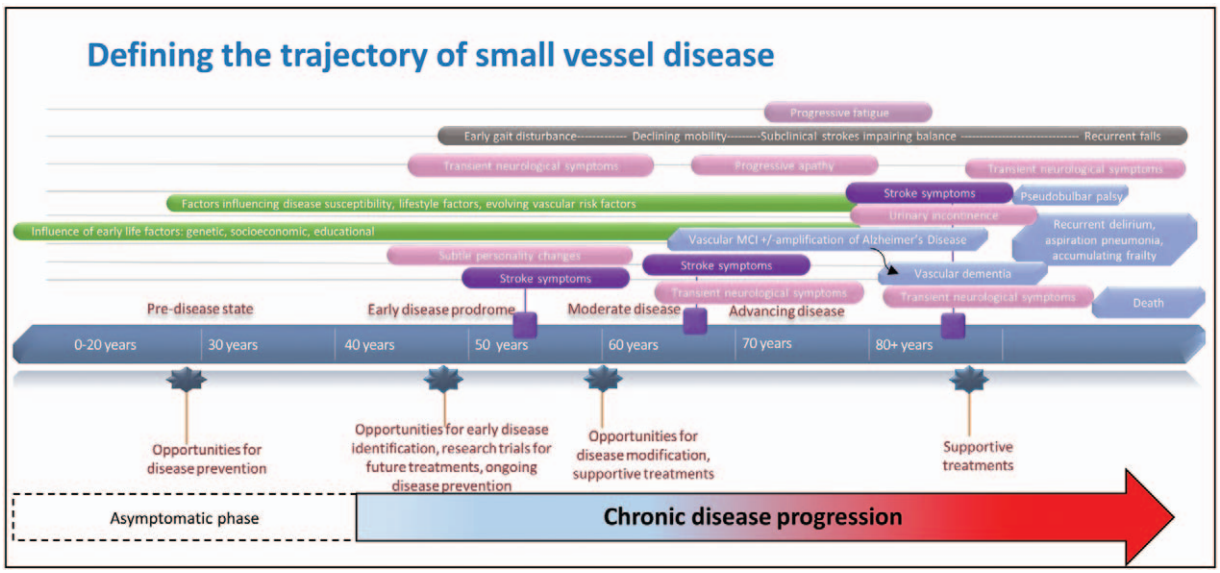

Figure 3: Defining the trajectory of small vessel disease. MCI: *Mild* cognitive impairment.

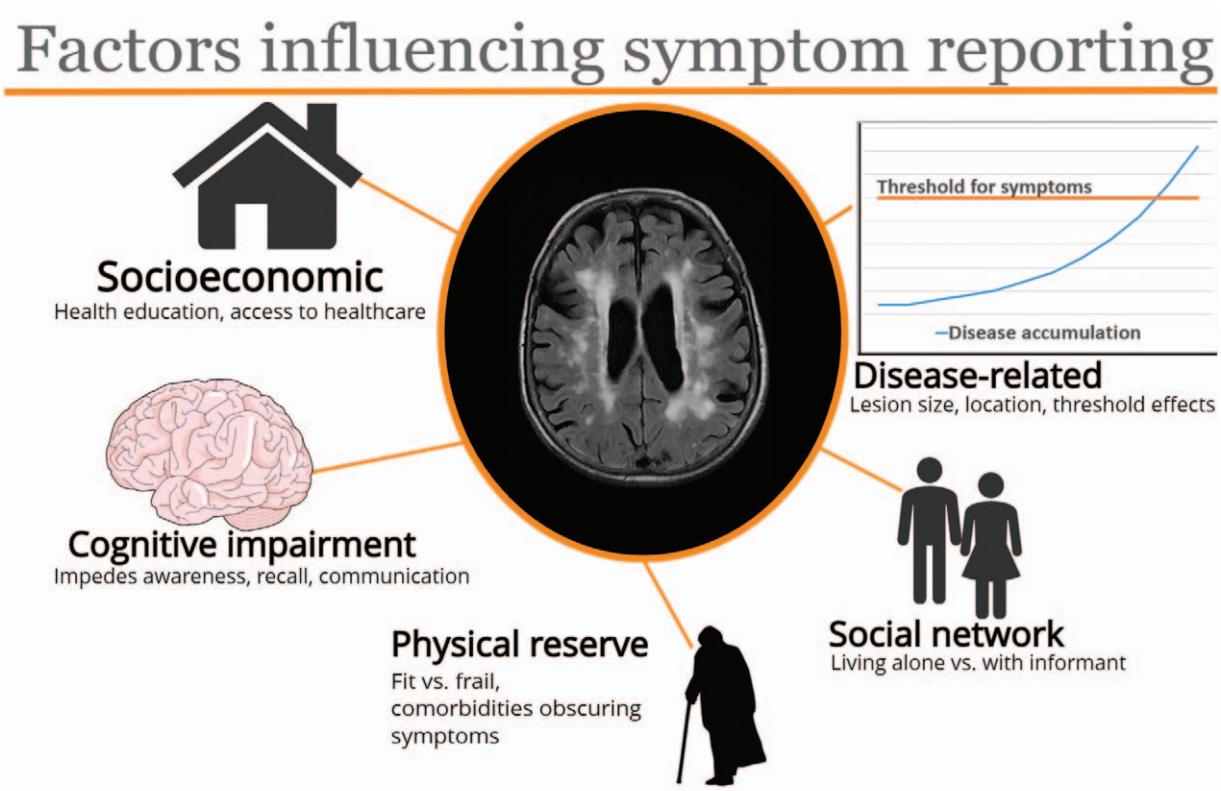

Figure 4: Factors influencing reporting of symptoms related to disease accumulation.

dementia.[4,18,19] Other neurological symptoms associated with SVD include dysphagia,[20] dysarthria,[21] pyramidal tract signs, and pseudobulbar palsy.[22]

Neuropsychiatric symptoms

Neuropsychiatric symptoms are common post-stroke and in individuals with vascular dementia, but whether there is a shared neuroanatomical substrate remain unclear and longitudinal studies are sparse. More severe WMH are associated with apathy, fatigue, and delirium but not subjective memory complaints or anxiety (submitted). There is inadequate evidence to determine whether other symptoms including delusions or emotional lability are associated with SVD due to insufficient data and mixed approaches to symptom assessments.

Future research should target whether emotional liability, delusions, and other neuropsychiatric symptoms relate to disease severity including progression.

Whether depression contributes to, or results from, SVD is unclear. Further pathological, clinical, and imaging relationships need investigation, focusing on interactions with shared vascular risk factors, medications, treatment resistance, neurotransmitter alterations, and associations with cognitive impairment.[23]

Lacunar stroke presentations

Lacunar stroke clinical syndrome (LACS) is a key SVD manifestation.[3] While specific syndromes including pure motor/hemisensory stroke and ataxic hemiparesis are more strongly associated with acute small subcortical infarcts,[24] LACS classification is imprecise[24,25] and one-third of minor strokes are not accompanied by a corresponding acute infarct radiologically, even on the most sensitive diffusion MRI (n = 264).[26] Non-lacunar pathology, for example, cortical infarcts, may manifest as LACS and conversely, small subcortical infarcts may present with other non-LACS syndromes[25,27] in around 15% to 20% ($n = 137$), or develop silently.[13] While some LACS may masquerade as cortical stroke syndromes when the responsible brain lesion is close to the cortex,[27] or in specific locations such as the thalamus. Other cases where LACS and partial anterior circulation stroke (PACS) are confused may simply reflect disappearance of, or failure to recognize, cortical symptoms, mistaking dysarthria for dysphasia, or overlooking visual field defects.[25] Furthermore, other comorbidities may alter or obscure stroke presentations [Figure 4], for example, a patient with arthritis and peripheral neuropathy may not notice an ataxic hemiparesis.

Associated short-term with infarct growth ($n = 61$)[28] and poor functional outcomes ($n = 4011$)[29] in stroke, SVD effects outlast the acute phase, contributing increased risk long-term of recurrent ischaemic stroke, disability, dementia, and death ($n = 71,298$).[30]

Mobility and movement

Gait and balance dysfunction, shortened stride length ($n = 431$),[6] unexplained dizziness ($n = 122$),[31] falls ($n = 187$),[32] and features of vascular parkinsonism such as bradykinesia, rigidity, and gait disturbances ($n = 503$ community-dwelling)[33] are all associated with SVD.

Urinary symptoms

Eight studies, mostly in older community dwelling-subjects, detected urinary symptom associations with WMH (total $n = 1944$),[34-41] while two did not ($n = 648$).[42,43] These findings need to be reproduced in large prospective blinded studies, adjusting for mobility, frailty and co-morbidities.

Vascular cognitive impairment: clinical features

Vascular cognitive impairment (VCI) is a broad term, encompassing mild cognitive impairment and dementia. We focus on the clinically sensitive DSM-V diagnostic criteria,[44] which require evidence of cognitive decline from a previous performance level in one or more domains including: (a) concern about decline from a patient, knowledgeable informant or clinician, and (b) objective impairment or decline on testing. To establish a vascular etiology, either a temporal association with stroke/s or prominent decline in complex attention/processing speed and frontal-executive functions is required, although it is increasingly apparent that SVD is not confined to specific domains,[45] in contrast to previous thinking that focused on domain-specific impairments. Further discrimination between mild cognitive impairment and dementia is based on whether cognition is sufficiently impaired to result in loss of functional independence.[44] This may be described by either patient or informant, e.g. non-specific reports of "not managing at home" or deficits in instrumental activities of daily living, e.g. inability to independently manage one's finances. Clinicians frequently rely on the informant account, which is invaluable, as many individuals with cognitive impairment lack insight or minimise their symptoms.

Distinguishing the subcortical subtype of vascular cognitive impairment

The small vessel contribution to dementia exceeds that of large vessel disease, with incident lacunes thought to herald the highest dementia risk at least in community-dwelling subjects.[46] Cognitive features include slow thought processing, poor memory retrieval, and executive dysfunction.[47] The subcortical vascular cognitive impairment (VCI) subtype is supported by symptoms such as impaired problem-solving, personality changes including apathy, mood disorders, pseudobulbar palsy, dysarthria, subtle sensory and motor deficits, urinary symptoms, and gait deterioration including postural instability.[47,48] Although these clinical symptoms are frequently cited as subcortical VCI features, many of these correlations are based on older, small, clinicopathological and CT-based studies. There is a scarcity of MRI studies confirming these associations in VCI populations, with recent studies' main clinical focus on cognitive tests and vascular risks. Abrupt cognitive impairment due to single strategic small subcortical infarcts has been described rarely,[47] is understudied, and requires further characterization.

The neurological examination provides clues to subtyping VCI: subtle abnormalities including dysarthria, dysphagia, and parkinsonian, rather than hemiplegic gait, are all more prevalent in subcortical vascular dementia ($n = 706$).[22] Subcortical may also be differentiated from cortical VCI and Alzheimer's disease by the absence of aphasia, apraxia, agnosia, amnesia, and hemianopia[48] although cortical and subcortical lesions, with or without Alzheimer's disease, frequently coexist so the specificity of these symptoms will be limited. Supportive findings on neuroimaging raise diagnostic certainty from possible to probable when there is no clear temporal relationship to stroke events,[44] although the extent of radiological SVD considered sufficient to contribute to a VCI diagnosis is debated.[49] Neuroimaging is particularly important for distinguishing SVD-related VCI, where stepwise cognitive

decline is often absent, instead characterized by insidious, fluctuating cognitive decline, punctuated by neurological deficits [Figure 3].[48]

Function

SVD substantially limits independence, contributing to functional impairment,[29] stroke recurrence, dementia, and mortality after stroke,[30] as well as functional decline and mortality in non-disabled adults.[50] SVD is associated with longer hospital lengths of stay in cognitively impaired,[51] and earlier institutionalization in stroke patients.[52]

Recommended approaches to patients presenting with the SVD syndrome

Many clinical features described in this review are non-specific when considered in isolation. However, clinical presentations are frequently multifactorial, particularly in older people in whom SVD is highly prevalent [Table 1]. When faced with these features in combination, supported by previous neuroimaging, and especially in individuals with a history of lacunar stroke or cognitive impairment, one should consider SVD presence and/or progression as a contributor.

Risk Factors for SVD and its Progression

Risk factors for progression in SVD include "traditional vascular risk factors" such as age and hypertension, and MRI biomarkers, which not only represent the cornerstone for SVD diagnosis but also identify risk of progression, provide a feasible strategy for monitoring patients, and a therapeutic target.

Vascular risk factors

Several vascular risk factors are associated with SVD, but the two major ones are advancing age and hypertension.[50,53] Specifically, In community-based samples, WMH prevalence was low before 55 years of age but increased sharply with age thereafter, from 11% to 21% in the subjects 64 years of age on average to 94% in individuals 82 years of age on average.[14] Cerebral microbleeds (CMB), CAA, PVS and lacunes also increase with age.[17,50,54-56]

The most important modifiable vascular risk factor for SVD is arterial hypertension (defined as blood pressure greater than 140/90 mmHg).[57] Ambulatory blood pressure (BP) provides more accurate data on BP status than office-based BP measurements and may help BP control in patients with extensive SVD.[58] In addition, abnormal circadian BP variations during sleep, specifically non-dipping (<10% fall in nocturnal BP) and reverse-dipping patterns (rise in nocturnal BP) are associated with WMH.[59] Hypertension is also associated with CMBs in adults with and without established cerebrovascular disease.[60] SVD lesions can occur in individuals without hypertension,[61] plus recent data from large consortia genetic analyses indicate that some patients with more severe SVD may be particularly sensitive to any BP elevation (in press). Since it is currently difficult to identify individuals whose small vessels may be particularly sensitive to even minor BP elevations, it remains uncertain how intensively blood pressure should be lowered.[50]

Diabetes mellitus types 1 (relative ratio [RR] 7.2, 95% confidential interval [CI] 3.2–16.1) and 2 (RR 2.8, 95% CI 2.3–3.5) are associated with lacunar infarction[62] and other biomarkers of SVD on MRI, including atrophy[63] and CMBs.[60] Because the duration of diabetes is important in determining ischemic stroke risk, early onset of type 1 diabetes confers a cumulatively higher lacunar stroke risk in such patients. Furthermore, fasting glucose level (odds ratio [OR] 1.27, 95% CI 1.10–1.46) and high insulin resistance scores (OR 1.33, 95% CI 1.05–1.68) are also associated with increased incident lacunes.[54] People with type 2 diabetes have a 1.5 times increased risk of dementia, and high HbA_{1c}, concentration and glucose variability are negatively associated with cognitive function.[63] Interestingly, type 2 diabetes is associated with a greater increase in depressive symptoms, which SVD may contribute to.[23,64]

Additionally, metabolic syndrome is associated with silent brain infarction and incident lacunes.[53,54] The potential impact of dyslipidemia remains uncertain. In the atherosclerosis risk in communities (ARIC) study, high triglycerides increased the risk of incident lacunes (OR 1.24, 95% CI 1.04–1.47), while elevated high-density lipoproteins (HDL) reduced the risk (OR 0.77, 95% CI 0.59–0.99).[65] Moreover, the use of lipid-lowering medications was associated with fewer incident lacunes (OR 0.15, 95% CI 0.04–0.61) in an observational study,[55] but higher total (OR 1.67, 95% CI 1.20–2.31) and lobar (OR 1.52, 95% CI 1.02–2.27) CMB presence in a separate community-based study.[66] In contrast, lower HDL may predict WMH volume increase in people aged between 73 and 76 years[67] so the relationship between HDL and SVD needs further research.

Lifestyle risk factors

Regular exercise, healthy diet (Mediterranean diet, folic acid and vitamin B12),[68] and avoiding adverse lifestyle factors such as smoking, excess alcohol or high dietary sodium, are all associated with having fewer SVD features in observational studies.[69-71] Alcohol intake is associated with worse WMH in patients with minor stroke.[72] High dietary sodium (>5 g/d) increases stroke risk (crucially lacunar stroke) and worsens WMH and total SVD burden.[68,69] Disappointingly, a subsequent systematic review of lifestyle interventions including exercise did not slow cognitive decline.[73]

Sleep dysfunction is an important and so far largely overlooked risk factor for adverse brain health. Whether unusual sleep patterns increase the risk of SVD lesions is unclear although disordered night-time sleep is associated with brain atrophy and increased daytime sleep is associated with increased PVS on MRI.[74] Abnormal sleep, such as obstructive sleep apnea, may be associated with more WMH and silent lacunar infarction,[75] although inability to correct for co-associated factors like

smoking and hypertension may have overestimated the association.

Environmental, lifetime, and cultural risk factors

Genetic, environmental/lifestyle and cultural risk factors are likely related to SVD burden and to its associated outcomes such as cognitive impairment.[54] Data are currently unclear on male-female differences, and apparent differences may reflect age or recruitment bias, rather than a true difference in SVD burden, However, some hospital-based studies suggest that males have a higher burden of both sporadic[70] and monogenic SVDs,[71] but further research is needed to differentiate any true male-female difference in incidence or severity and the reasons behind any difference observed.

Regarding ethnic or geographical differences, it is difficult to disentangle effects of socioeconomic, dietary and medical histories, and use of different protocols, from true ethnic or geographical differences in the prevalence of SVD.[76]

Brain and cognitive reserves in later life are influenced by lifetime experiences, including those early in life.[77] Early life exposures could explain some of the variation between SVD and cognitive function[2] and include childhood cognitive ability, with lower cognitive ability in childhood being associated with increased total WMH scores ($r = -0.07$, 95% CI, −0.12 to −0.02, $I^2 = 0\%$) in later life. Similarly, adverse childhood socioeconomic status (SES) increases the risk of worse deep ($r = -0.181$) and periventricular ($r = -0.146$) WMH, and lower educational attainment is associated with more WMH in later life (OR 1.24; 95% CI, 1.05–1.47). The trends were similar for other SVD markers although sample sizes were not large enough to determine if similar associations are present for other SVD markers.[77] Consistent with this, in patients presenting with minor stroke, premorbid intelligence quotient (IQ) and educational attainment predict post-stroke cognitive impairment more than stroke severity or vascular risk factors.[72]

Use of brain imaging appearances to predict risk of SVD progression

The lesions seen on MRI adopted as biomarkers of SVD include recent small subcortical (or lacunar) infarct (RSSI), WMH, lacune, CMB, visible PVS, and cerebral atrophy.[78] All of these lesions have been associated with dysfunction of the cerebral small vessels when measured in patients using MRI, including blood-brain barrier leakage, impaired cerebral vasoreactivity and increased vascular pulsatility, reflecting impaired endothelial function and related effects on the glia and neurons.[2] These lesions are individually and collectively associated with increased risk of stroke, cognitive decline and dementia, and poor functional outcomes after stroke, and are highly heritable.[29,30,50,79]

The single strongest risk factor for SVD lesion progression identified so far is having a severe SVD lesion burden at presentation.[2] Potential advances in neuroimaging of SVD based on MRI, e.g. diffusion tensor imaging (DTI) metrics such as fractional anisotropy (FA) and mean diffusivity (MD), show promise in research for detecting early white matter damage and may in future become widely used clinical applications.[80]

Although SVD lesions were previously considered to be "focal" and "permanent", it is now clear that they represent more dynamic global disease. Thus, WMH progression is worse in those with increased baseline WMH volume,[81,82] and worsening WMH burden associates with brain atrophy including cortical thinning.[83] Since WMH may have some clinically meaningful reversible components,[81,82] the concept that prevention of worsening WMH-related brain damage may translate into long-term benefits for brain health is important.

Since the common SVD lesions are mostly visible on routine clinical brain MRI and computed tomography (CT) scanning (excluding CMB and PVS), greater use could be made of their potential for predicting prognosis. Several MRI scoring systems can be easily applied by clinicians to characterize SVD severity, many of which can predict clinical outcomes. The Fazekas scale is commonly used to evaluate WMH on MRI and can be used on CT.[78] Similarly, while less sensitive than MRI-based scores, equivalent CT-based scores for total SVD and "brain frailty"[29] predict poor functional outcome and cognitive impairment after stroke.[29,30] A simple and pragmatic score that may provide a more complete estimate of the full impact of SVD on the brain is the total SVD score (counting the presence of WMH, lacunes, CMB, and PVS on MRI as an ordinal score of 0 to 4), which could have potential for patient risk stratification.[70] Despite the increasing availability of MRI and limitations of CT, CT continues to be the most widely used neuroimaging tool in patients with neurological or neuropsychiatric symptoms, and can provide valuable information for SVD assessment.[29]

Therapeutic Approaches

Given the chronic nature and insidious progression of SVD, potential treatments will likely be required over the longer term as is done for the secondary prevention of vascular diseases. Due to the worldwide prevalence of SVD and association with increasing age, potential therapeutic agents will need to be affordable, easy to administer, safe, simple and have limited drug-drug interactions.[84,85] Currently, there is considerable variability in selection and definitions of end-points for SVD trials including of imaging endpoints and clinically relevant magnitudes of change, cognitive and functional outcomes, recurrent stroke, bleeding, and death. Hence, we report several outcomes depending on available data.

Lifestyle interventions

Lifestyle and behavioral interventions may have potential benefit in patients with SVD and are currently under investigation [Table 2]. Two trials have assessed aerobic exercise and found no difference in WMH volume[86,87] but did demonstrate improved cognitive scores at 6 months

Table 2: Therapeutic approaches for SVD.

Intervention	Study type	Population	Notes
Lifestyle interventions			
Aerobic exercise	RCT NCT01027858[86,88] AIBL[87]	70 patients with WMH and cognitive impairment 98 patients with subjective memory problems or mild cognitive impairment and at least 1 vascular risk factor	No difference in WMH volume in substudy ($n = 30$), but improved cognitive scores at 6 months No difference in WMH volume at 2 years
Resistance training	RCT NCT00426881[89]	54 patients with WMH but no cognitive impairment	Reduced WMH volume at 12 months
Smoking	Observational study Mild Stroke Study 2 (MSS-2)[70] Paris-Munich CADASIL[71] Lothian Birth Cohort[90]	264 patients with stroke 290 patients with CADASIL 504 community-dwelling older patients	Smoking increases: - SVD burden on imaging - risk of stroke and dementia - rate of cortical thinning
Dietary sodium	Observational study MSS-2[69]	264 patients with stroke	High dietary sodium increased risk of: lacunar > cortical stroke, WMH & total SVD burden on imaging.
Traditional stroke prevention			
Antiplatelet	Meta-analysis[93] RCT SPS3 [94] RCT subgroup RESTART[97]	42,234 patients with lacunar stroke 3020 patients with lacunar stroke 254 patients with spontaneous ICH taking antithrombotic therapy	Single antiplatelet therapy reduced recurrent stroke across 17 trials. Chronic aspirin + clopidogrel *vs.* aspirin stopped early due to excess bleeding and death in dual antiplatelet group Single antiplatelet therapy *vs.* avoiding antiplatelet therapy did not increase hazard of recurrent ICH in the presence of CMB
BP lowering	Meta-analysis[58] RCT SPS3[98,99] RCT subgroup SPRINT-MIND[100] RCT substudy PRESERVE[101,102]	1369 stroke patients 3020 patients with lacunar stroke 454 hypertensive patients with WMH 111 hypertensive patients with lacunar stroke and established SVD	Less WMH progression with intensive BP reduction. No difference in recurrent stroke or long-term cognition with intensive BP lowering Less progression of WMH but no difference in brain volume over 4 years with intensive *vs.* standard BP treatment No difference in white matter damage on DTI with intensive *vs.* standard BP lowering. CBF did not fall with BP reduction in a further subgroup (n = 62)
Lipid lowering	RCT Heart Protection Study[103] ROCAS[104] PROSPER[105] RCT Substudy VITATOPS[106]	20,536 patients with vascular risk factors 208 patients with TIA 5804 patients with vascular risk factors 81 patients with stroke and pre-stroke statin	Simvastatin did not influence cognitive outcomes Simvastatin did not influence WMH progression Pravastatin did not influence cognitive function (n = 5804) or WMH progression (n = 535) Less WMH progression with pre-stroke statin

(*continued*)

Table 2
(continued).

Intervention	Study type	Population	Notes
Pharmacological agents under investigation			
Cilostazol	Meta-analysis[107] RCT LACI-1[108] LACI-2[109] (ongoing)	10,449 patients with ischaemic stroke 57 patients with lacunar stroke Patients with lacunar stroke (target 400)	Cilostazol reduced recurrent stroke (ischaemic and haemorrhagic) particularly in trials with larger populations of lacunar stroke patients. Cilostazol was associated with less WMH progression Effect of cilostazol on recurrent stroke, death and dependency, cognition and imaging SVD markers
NO donors	RCT ENOS[110,111] LACI-1[108] LACI-2[109] (ongoing)	4011 patients with stroke 57 patients with lacunar stroke Patients with lacunar stroke (target 400)	GTN given under 6 hours of onset (n = 273) was associated with improved clinical outcomes at 90 days Pilot trial of ISMN on cerebrovascular reactivity Effect of ISMN on recurrent stroke, death and dependency, cognition and imaging SVD markers
Vitamins	RCT Substudy VITATOPS[112]	359 patients with stroke	Vitamin B supplements for 2 years in patients with severe WMH had slower WMH progression
Allopurinol	RCT XILO-FIST (NCT02122718)	Patients with ischaemic stroke (target 464)	Effect of Allopurinol on recurrent stroke and WMH progression
RIC			
RIC	RCT Wang *et al*[113]	30 patients with SVD	RIC twice daily for 1 year reduced WMH and improved visuospatial and executive function

AIBL: Australian Imaging Biomarkers and Lifestyle study; BP: blood pressure; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBF: cerebral blood flow; CMB: cerebral microbleeds; DTI: diffuse tensor imaging; ENOS: Efficacy of Nitric Oxide in Stroke Trial; GTN: glyceryl trinitrate; ICH: intracerebral haemorrhage; ISMN: isosorbide mononitrate; LACI-1/2: LACunar Intervention Trial -1 or 2; MSS-2: Mild Stroke Study-2; NO: Nitric oxide; PRESERVE is the name of a trial, it is not an acronym; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; RCT: randomised controlled trial; RESTART: Restart or Stop Antithrombotics Randomised Trial; RIC: Remote ischaemic conditioning; ROCAS: Regression of Cerebral Artery Stenosis study; SPRINT-MIND: Systolic blood PRessure INtervention Trial-MIND; SPS3: Secondary Prevention of Small Subcortical Stroke Trial; SVD: small vessel disease; VITATOPS: VITAmins TO Prevent Stroke; WMH: white matter hyperintensities; XILO-FIST: Xanthine oxidase Inhibition for the Improvement of Long-term Outcomes Following Ischaemic Stroke and Transient ischaemic attack.

in those randomized to aerobic exercise as compared with those receiving usual care.[88] In a subgroup of a small trial ($n = 54$), resistance training was associated with reduced WMH volume at 12 months as compared with twice-weekly balance and tone exercises.[89] Several ongoing trials intend to build upon this data.

Smoking is strongly associated with an increased burden of SVD and cortical loss in observational studies,[70,71,90] and therefore, smoking cessation should be strongly encouraged.

High dietary sodium was associated with increased stroke, particularly lacunar events, WMH and SVD burden in patients with stroke[69] and with risk of stroke in population studies.[91] Trials assessing the effect of dietary sodium in SVD are lacking, as they are for other vascular disease, but reduction in dietary salt is good general health advice.

Encouragingly, exercise and a healthy Mediterranean diet with folic acid and vitamin B12, combined with guideline based vascular risk reduction (*ie*, multidomain intervention), slowed cognitive decline in older people at risk of dementia compared with vascular risk factor reduction alone.[92]

Traditional stroke prevention treatments

Antiplatelet medication

Single antiplatelet therapy reduced recurrent stroke as compared with no antiplatelet agent in a meta-analysis of 17 trials totaling 42,234 patients with previous lacunar

ischemic stroke.[93] The secondary prevention of small subcortical stroke (SPS3) trial randomized 3020 patients with a symptomatic lacunar stroke to chronic aspirin and clopidogrel versus aspirin alone and was stopped early due to excess bleeding and death in the dual antiplatelet group.[94] In observational studies, antiplatelet therapy has been associated with prevalent CMBs (OR 1.21; 95% CI 1.07–1.36)[95] while anticoagulants have been associated with prevalent and incident CMBs (OR 1.72, 95% CI 1.22–2.44; $I^2 = 19\%$).[96] Given the shared pathophysiology between CMB and ICH, the use of antiplatelet and anticoagulant therapy in the presence of CMB remains under study. A subgroup analysis from the randomized, controlled RESTART trial reported that individuals with a history of ICH taking antiplatelets in the presence of CMB did not experience increased hazard (hazard ratio [HR] 0.30, 95% CI 0.08–1.13 *vs.* 0.7, 95% CI 0.13–4.61).[97] Further randomized trials are needed to establish which treatments are beneficial or harmful to CMBs and ICH, both in stroke and non-stroke populations.

BP lowering

Intensive lowering of BP (<120 mmHg) in a subgroup ($n = 454$) of the large Systolic blood PRessure INtervention Trial (SPRINT) with WMH was associated with reduce WMH progression and decreased risk of mild cognitive impairment (HR 0.81; 95% CI 0.69–0.95) but no difference in brain volume neither risk of dementia over a 4 year period compared with standard BP management.[100] Similarly, a meta-analysis of trials including 1,369 patients with prior stroke found less WMH progression (standardized mean difference –0.19; 95% CI –0.32 to –0.06; $I^2 = 20\%$) with intensive BP lowering as compared with usual care.[58] The SPS3 trial also assessed intensive BP reduction but, in patients with prior lacunar ischemic stroke specifically, found reduced hemorrhagic stroke, however no difference in stroke recurrence[98] or long-term cognition[99] with intensive compared with standard BP lowering. In the PRESERVE trial, 111 hypertensive patients with lacunar ischemic stroke and established SVD were randomized to intensive BP lowering (<125 mmHg) *vs.* standard care and demonstrated no difference in white matter damage on diffusion tensor imaging,[101] while in a further subgroup cerebral blood flow was not compromised by intensive BP lowering.[102]

Lipid lowering

Unfortunately, there are no trial data pertaining to statins exclusively in lacunar stroke. The SPARCL trial revealed that atorvastatin reduced stroke recurrence in separate subgroups of patients with large artery atherosclerotic stroke and those with lacunar ischemic stroke.[114]

The effect of statins on other outcomes specific to SVD have had mixed results to date. Simvastatin did not influence cognitive outcome in the Heart Protection Study ($n = 20{,}536$),[103] nor WMH progression in the ROCAS study,[115] whilst pravastatin did not impact cognitive function ($n = 5804$) or WMH progression ($n = 535$) in the PROSPER study.[105] In contrast, patients with stroke and severe WMH had less progression of WMH if they were on a statin pre-stroke in the VITATOPS study.[106]

Pharmacological agents under investigation

Cilostazol

Cilostazol, a phosphodiesterase 3' inhibitor, is commonly used for stroke prevention in the Asia-Pacific region. As well as its weak antiplatelet effects, cilostazol may be beneficial in preventing SVD accumulation through endothelial stabilization,[116] myelin repair,[117] neuroprotective and anti-inflammatory mechanisms.[118] A meta-analysis including 10,449 patients with prior ischemic stroke, predominantly from the South Asian-Pacific region, found that cilostazol reduced recurrent ischemic stroke (OR 0.68, 95% CI 0.57 to 0.81), intracerebral hemorrhage (OR 0.43, 95% CI 0.29 to 0.64), and death (OR 0.64, 95% CI 0.49 to 0.83) as compared with either placebo, aspirin or clopidogrel.[107] When given longer term (>6 months), cilostazol reduced recurrent ischemic stroke to a greater degree than when given short-term without increasing bleeding, and particularly in trials with larger populations of lacunar stroke patients.[107]

Cilostazol's effects on cognition, death and dependency, and imaging are unclear. In 130 participants with acute lacunar stroke, the ECLIPSE trial found no difference in WMH volume change at 90 days between those randomized to cilostazol *vs.* placebo, but did demonstrate that cilostazol reduced cerebral arterial pulsatility measured using transcranial Doppler.[119] The small LACI-1 trial ($n = 57$) found that cilostazol was well tolerated over a 11 week period in patients with lacunar stroke and was associated with less progression of WMH as compared with patients randomised to no cilostazol.[108] The ongoing LACI-2 trial seeks to assess the effect of cilostazol on recurrent stroke, cognition, imaging markers of SVD and death and dependency in 400 participants with prior lacunar stroke.[109]

Nitric oxide donors

Nitric oxide (NO) and its donors, for example, organic nitrates (*eg,* glyceryl trinitrate [GTN] and isosorbide mononitrate [ISMN]), has multiple effects that might be beneficial in patients with SVD.[84] Transdermal GTN given within 6 h of stroke onset improved functional outcome and cognition at 90 days in a subgroup of a large randomized trial[111]; GTN administered between 6 and 48 hours did not improve outcome.[110] However, when administered within 4 h of stroke onset in the pre-hospital arena in a subsequent trial, GTN had a neutral effect on clinical outcomes.[120] Despite, ISMN being commonly used in the management of ischemic heart disease, data regarding its use in SVD and stroke are scanty. The previously mentioned LACI-1 trial randomized patients to ISMN, in addition to Cilostazol, in a factorial design. ISMN was well-tolerated and safe, but did not influence clinical or radiological outcomes in this small trial.[108] The ongoing LACI-2 trial is also assessing ISMN and its effects on safety and efficacy in clinical and radiological outcomes.[109]

Vitamins

The vitamins of interest in SVD include vitamins B6, B12 and folate. Low levels of B12 have been associated with more severe WMH.[121] A substudy from the VITATOPS trial suggested that patients with severe WMH who received B vitamins for 2 years had slower WMH progression.[112]

Xanthine oxidase inhibitors

Allopurinol, a xanthine oxidase inhibitor, has multiple effects that may be beneficial in SVD.[84] A trial of 80 patients with ischemic stroke (1/2 lacunar etiology) demonstrated reduced BP, augmentation index and carotid intima-media thickness progression following one year of receiving allopurinol.[122] Larger trials assessing allopurinol, including Xilo-FIST (ClinicalTrials.gov: NCT02122718), are ongoing.

Remote ischemic conditioning

Remote ischemic conditioning (RIC)—transient ischemia induced to a limb using a BP cuff—has been shown to be neuroprotective in pre-clinical models.[123] In a small study of 30 patients with SVD, RIC delivered twice daily for 1 year improved visuospatial and executive function and reduced WMH compared with sham.[113] The effects of RIC in lacunar stroke are unclear; the planned RECAST-3 [ISRCTN63231313] and Remote Ischemic Conditioning in Patients With Acute Stroke [RESIST, NCT03481777] trials will shed more light on this area.

Discussion and Conclusions

We recommend a holistic, multidisciplinary assessment of individual needs in patients with suspected SVD. This includes rigorous management of modifiable risk factors including smoking cessation, dietary improvements, and appropriate evidence-based medications while balancing risks of side effects. In advancing disease, onwards referral to relevant services should be considered to maximize independence including cognitive clinics, physiotherapists, occupational therapists, and social care. We suggest highlighting awareness of practical issues including driving, accessible home environments, appointing power of attorney, and advance care planning. We support close liaison with patients, family members and general practitioners to monitor for clinical deterioration. We note wide variability in choice and definitions of end-points used in trials in SVD that would benefit from some standardization. Finally, we advocate for more clinical trials to identify effective lifestyle and pharmaceutical interventions.

Future targets for clinical practice and research

We need better recognition of symptoms that best predict disease progression in longitudinal clinical-imaging-pathological studies across healthy, cognitively impaired, and stroke populations, establishing the natural history of SVD. Serial imaging studies assessing neuropsychiatric symptoms are especially lacking. Further work on interactions between SVD, depression, and their confounders will help to clarify the vascular depression hypothesis. Urinary symptom relationships with SVD require appropriate adjustment for confounders. Research should give greater prominence to informants, paralleling clinical practice.

We need to determine whether widely-accepted clinical features of subcortical VCI described in early pathological and CT studies still hold true on longitudinal MRI studies in VCI populations. How lesion volume, location, background SVD burden and rate of lesion change interact with symptoms, cognition, function, and physical and cognitive reserves needs to be determined. The natural history of VCI including subcortical subtypes needs to be better defined, for example, prevalence of stepwise *vs.* progressive cognitive decline.

Further work is needed to understand the pathophysiology of SVD, using advanced preclinical, neuroimaging, and pathological research methods. We need more trials of medications and simple lifestyle modifications, or combinations thereof. Further, detailed, observational research on modifiable and non-modifiable factors is required, integrating these into clinical trial design, determining whether using different treatment strategies for individuals with non-modifiable risk factors produces any additional benefit.

Integrating approaches to research and clinical care of patients with SVD

We should empower patients and informants to self-monitor symptoms, signs, vascular risk factors, and cognitive test performance, e.g. using mobile phone applications, virtual clinics, and evolving smart technology that recognizes alterations in gait or speech patterns. We should use healthcare encounters to opportunistically seek features of SVD progression, for example, screening during vascular risk factor reviews. We should devise electronic record-based alerts based on notification of relevant healthcare referrals [Table 1], combined with existing imaging data. We should devise composite prediction scores of SVD progression for use as screening tools in everyday clinical settings, incorporating available symptom, risk factor, cognitive, demographic, and imaging reports, similar to those used for estimating cardiovascular or fracture risks.

Efforts to refine an SVD phenotype including, but extending beyond, stroke and cognitive impairment, are necessary. Apart from initial identification, we need to recognize those at the highest risk of SVD progression, tracking which clinical and imaging features herald progression. This will allow us to research targeted interventions earlier in the SVD course, preventing progression before its most disabling manifestations develop.

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Conflicts of interest

Conflicts of interest: The authors declare academic grants for research as listed above; JMW chairs the ESOC 2021 Planning Group, and participates in two ESO Guidelines; CA, JPA and UC have no conflicts to disclose. PMB has received honoraria as Chief Investigator or Steering Committee Chair of trials (DiaMedica, Phagenesis) and attending Advisory Boards (Moleac, Nestle, Sanofi).

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