**Title**: Small vessel disease: mechanisms and clinical implications.

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**Glossary of terms:** see Panel

**Abstract**: Small vessel disease (SVD) is a disorder of cerebral microvessels that causes white matter hyperintensities and several other common abnormalities seen on brain imaging. Despite being a common cause of stroke and vascular dementia, the underlying pathogenesis is poorly understood. Recent research in patients has identified several manifestations of cerebral microvessel endothelial dysfunction including (in unknown order of importance) blood-brain barrier dysfunction, impaired vasodilation, vessel stiffening, dysfunctional blood flow and interstitial fluid drainage, white matter rarefaction, ischaemia, inflammation, myelin damage, and secondary neurodegeneration. The brain abnormalities are more dynamic and widespread than previously thought. Relationships between lesions and symptoms are highly variable but poorly understood. Major challenges are to determine which vascular dysfunction(s) are most important in pathogenesis, which abnormalities are reversible, and why lesion progression and symptomatology are so variable, so as to identify potential targets for intervention and improve risk prediction for individuals.

**Introduction**

The term ‘small vessel disease’ (SVD) describes a disorder of the brain’s small perforating arterioles, capillaries, and probably venules,1 that causes various lesions that are seen on pathology or brain imaging with magnetic resonance (MRI) or computed tomography (CT). The typical SVD lesions are white matter hyperintensities (WMH) of presumed vascular origin, lacunes, microbleeds, superficial siderosis, perivascular spaces (PVS) and microinfarcts.2,3 These may be clinically ‘silent’ individually, but increasing amounts of individual lesion types and combinations of lesions are associated with cognitive impairment, dementia, depression, mobility problems, increased risk of stroke,4 and worse outcome after stroke.5 Other typical SVD lesions are recent small subcortical (or lacunar) infarcts and intracerebral haemorrhage, which typically present with stroke.2 These varied clinical presentations have, until recently, typically been considered separately in research, and referred to separate stroke, cognition or mobility clinics. However, it is now clear that SVD causes about a quarter of ischemic strokes and most haemorrhagic strokes, is the commonest cause of vascular dementia, commonly occurs with Alzheimer’s disease and worsens the resulting cognitive impairment,6,7 thus contributing to approximately 50% of dementias worldwide, a massive health burden of stroke and dementia.4,7

The brain damage is not confined to the visible lesions, which increasingly are recognised to represent just the ‘tip of the iceberg’. Newer MRI methods show that there are pathological changes in the so-called ‘normal appearing’ white matter (NWM) and grey matter, that worsen as the SVD lesions increase,8,9 and white matter fibres passing through visible lesions can ‘die back’ leading to secondary degeneration in distant cortex or the brain stem , thus resulting in ‘global’ brain effects .8-10 Some MRI methods are exquisitely sensitive to small changes in fluid content and recent patient studies suggest that WMH, at least partly or in their early stages, represent areas of increased interstitial fluid,8,11 not just demyelination. The SVD spectrum is increasingly diverse, including rare familial and common sporadic (ie non-familial) forms, with apparently different subtypes even amongst sporadic forms. For example, cerebral amyloid angiopathy with microbleeds and superficial siderosis has different pathology to predominantly non-haemorrhagic SVDs.12

In this review, we focus on sporadic (ie non-familial) SVD as the commonest clinically-recognised form, focusing on causes and implications of white matter hyperintensities, lacunes, recent small subcortical infarcts and sub-visible findings. Microinfarcts, and haemorrhagic SVDs (cerebral amyloid angiopathy, microbleeds, superficial siderosis), were reviewed recently elsewhere.3,12,13 We discuss the evidence that sporadic SVD starts in the endothelium, , how this causes apparently focal lesions that are more dynamic than traditionally thought, and affects the whole brain. We consider potential explanations for the different clinical effects of SVDs, and potential therapeutic targets and interventions.

**SVD as a dynamic, whole brain disorder**

Pathology studies of SVD mechanisms describe abnormalities in arterioles such as ‘arteriolosclerosis’, lipohyalinosis, or ‘fibrinoid necrosis’,1,12,14 and risk factors, particularly hypertension (reviewed in1). In arteriolosclerosis and fibrinoid necrosis the arteriolar wall is thickened and the lumen may be narrowed, occluded, or dilated. Capillaries and venules can also be abnormal and arteriolar abnormalities and SVD lesions can occur in individuals without hypertension.12 This suggests that the pathogenesis of SVD is more complex than simply that arteriolar occlusion leads to infarcts. While undoubtedly the presence of arteriolosclerosis and fibrinoid necrosis are signs of vessel dysfunction that are likely to accelerate tissue damage, there is some debate on what *initiates* microvascular abnormalities and on how dysfunction of the arteriolar or capillary wall causes brain damage. The arteriolar endothelium continues into the capillary and the brain injury seen in SVD is not just periarteriolar.12,13 Hence, in order to understand more fully the pathogenesis of SVD at the earliest stages, it is important also to consider how capillary endothelial cells (ECs) and pericytes interact with astrocytes, oligodendrocytes and microglia, which together form the neuro-glio-vascular unit. Better understanding of SVD mechanisms is essential in order to find ways to prevent damage to the brain, to delay worsening of damage, or preferably reverse the damage or enhance repair, so as to prevent or delay the damaging clinical consequences of SVD.

Starting at the cellular level, the vascularendothelium, together with a specialised basement membrane, pericytes/mural cells, and astrocyte end-feet, forms the blood-brain barrier (BBB), **Figure 1**, which controls what enters and leaves the brain parenchyma. The vascular endothelium also affects brain oxygenation, metabolite transport and interstitial fluid balance via effects on cerebral blood flow, active and passive transporters, and fluid clearance, most of which depend on interactions between ECs, pericytes, astrocytes, and oligodendroglial cells (**Figure 1**).15

Oligodendrocytes form myelin which accelerates axonal signal conduction, but are highly interconnected and also support axons by supplying energy. Oligodendrocytes arise from oligodendrocyte precursor cells (OPC), and when injured are replaced through maturation of other OPC. It was shown recently in a rodent model of sporadic SVD and on histopathology of human WMH, that dysfunctional ECs can block OPC maturation thus impairing myelination and myelin repair.16 In CARASAL (Cathepsin A-related arteriopathy with strokes and leukoencephalopathy), a rare familial SVD, endothelial dysfunction also blocked OPC maturation.17 Thus, there is evidence both from sporadic and monogenic SVD that dysfunctional ECs can hamper myelin formation and repair in addition to ‘direct’ damage to myelin from microvessel dysfunction.

Astrocytes connect neurons with capillaries, with astrocyte end-feet wrapping around the outside of the ECs at one end while their processes abut dendrites at the other end. Upon neuronal activity, astrocytes signal to the ECs to increase local blood flow and secure energy supply (**Figure 1**).15,18 Astrocyte end-feet have special molecules called aquaporin-4 (AQP4) that normally face the capillary. AQP4 molecules are thought to be important in regulating fluid flow through the interstitial space, thus helping to maintain the interstitial milieu required for proper neuronal function. In areas of damage, AQP4 molecules may relocate to the outer side of the astrocyte end-foot, as seen in human WMH.18

At the tissue level, we think that failure of the BBB may have several adverse effects: the leakage of fluids, proteins and other plasma constituents into the perivascular tissues may increase interstitial fluid (oedema) and may thicken and stiffen arteriole walls, thus impairing further vasodilatation, oxygen and nutrient transport (summarised below). Blood constituents may be harmful in multiple ways, e.g. after crossing the BBB, fibrinogen is cleaved to fibrin which activates microglia and recruits peripheral macrophages, promoting inflammation.19 Fibrinogen blocks OPC maturation (inhibiting myelin maintenance and repair). It further binds amyloid-β, blocking its clearance and promoting amyloid-β plaques and pericyte loss.19 Perivascular fibrin deposits are increased in patients with AD, providing a potential mechanistic link between SVD and AD pathology.19

Subtle, very mild BBB dysfunction occurs with normal human ageing,1 but may be accelerated by genetic predisposition. For example, genes such as *Foxf2* expressed in brain vascular ECs and pericytes, have been linked to sporadic small vessel stroke and WMH.20 *Notch3R169C* transgenic mice modelling CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) the commonest familial SVD, show changes in key BBB constituents (pericyte/mural cells, astrocytic end-feet, extracellular matrix (ECM).21 BBB leak is worse in vascular dementia and AD.22 Many clinical studies demonstrate BBB dysfunction in SVD in patients with stroke,23,24 cognitive25-27 or SVD features on imaging,26,28 using biochemical (CSF, blood),22 neuroimaging or neuropathology methods.12 BBB dysfunction increases with worsening WMH burden.8,27-29 BBB leakage is apparent in NWM of patients with SVD,8,25 and worsens with proximity to the WMH,28 a predilection site for future WMH expansion,30,31 and incident lacunes.32 In one study, BBB leak was worse in the perilesional NWM than in WMH,25 although others have found the opposite.28 BBB dysfunction was not found in some neuropathology studies33 which may reflect the fluctuating or focal nature of defects or difficulty identifying subtle changes. Consistent with BBB leak, interstitial fluid content increases in WMH and in NWM as WMH burden increases,11,28 and is highest in WMH, followed by perilesional NWM, then more distant tissue.8,11 Further indirect evidence for a causative role of BBB leak in human SVD comes from studies in patients presenting with acute lacunar stroke symptoms,28 or in CADASIL,34 in whom interstitial fluid and brain volume were higher at presentation with stroke symptoms then had declined several months later, changes that were paralleled by reductions in WMH,35 suggesting that the decrease in WMH and brain volume was not atrophy from cell loss but clearance of excess interstitial fluid. Finally, three studies found that long-term outcomes were associated with BBB disruption at initial assessment: BBB leak in NWM predicted poor functional outcome three years later;23 BBB leak in NWM predicted cognitive decline one year after lacunar stroke;28 and some areas with abnormal BBB permeability at baseline developed new WMH on follow-up scans.25

Compromise of cerebral blood flow (CBF) is another manifestation of endothelial function but the relationship between CBF and SVD lesion formation is complex. For example, in a meta-analysis, WMH were associated with lower resting CBF in cross-sectional studies, but this association disappears with proper age-matching and excluding patients with dementia,36 reflecting that impaired CBF occurs early in AD.37 Most larger longitudinal studies showed that high WMH burden predicts falling CBF, not vice versa,36,38 although CBF was reduced in normal-appearing tissue that became abnormal at follow-up in one study.30 Whole brain or tissue resting CBF is limited for determining lesion-relevant perfusion since resting CBF varies widely from minute to minute, between brain regions, and is lower in white than in grey matter.30 Furthermore, reduced resting CBF might reflect loss of viable tissue, rather than falling CBF causing tissue damage. A ‘mismatch’ between capillary flow and oxygen delivery, referred to as ‘capillary transit time heterogeneity’, has been observed in models and may occur in and around WMH.39 The mechanism for increased CBF heterogeneity may reflect a failure to direct blood flow to exactly where it is needed, or as suggested by the authors, to shunting, but remains to be determined.

Resting CBF is not a good indicator of oxygen extraction or of the ability to match tissue supply to demand.39 A better indication of the adequacy of tissue-level CBF in SVD may be cerebrovascular reactivity (CVR), which is the ability of arterioles and capillaries to dilate in response to increased neuronal activity or a metabolic or vasodilatory challenge such as breathing 6% carbon dioxide in inspired air.40 For example, patients with CADASIL had relatively normal resting CBF but impaired local increase in cortical CBF in response to neuronal activity.41 However, assessment of subcortical tissue-based CVR in patients is challenging and hence, so far, limited.42 Cross-sectional studies show that CVR declines with advancing age, hypertension, in lacunar versus non-lacunar stroke, and with increasing WMH burden. Longitudinally, reduced CVR may predict progression from NWM to WMH.43 CVR declined in deep grey and white matter with increased systolic blood pressure, pulse pressure and intracranial vascular pulsatility, but reduced CVR was not associated with resting CBF,44 similar to the dissociation of CVR from CBF seen in CADASIL.41 Patients with more WMH had lower CVR in white matter and higher intracranial vascular pulsatility,44 independent of age or BP, suggesting that impaired CVR and high intracranial vascular pulsatility may be more strongly linked to formation of WMH than reduced resting CBF. However, the relationship between the different components of endothelial dysfunction (BBB leak, CVR, intracranial pulsatility and CBF) and the order in which they occur, is unknown in humans. Studies measuring all these parameters simultaneously are ongoing (e.g. ISRCTN10514229) and should provide answers soon.

Fluid and compounds that enter the brain, and the waste generated, must be removed to maintain normal brain function. The main drainage conduits are the perivascular, or paravascular, spaces (PVS) which surround brain microvessels (**Figure 1**)45 and form part of the ‘glymphatic’ system.18 In rodents, glymphatic dynamic function demonstrated with optical imaging via cranial windows or MRI with intrathecal gadolinium showed that CSF from the basal cisterns and cerebral convexities enters the peri-arteriolar PVS to flush the interstitial space.18 In humans, PVS are visible on T2- and T1-weighted MRI as thin linear or round CSF-intensity structures that run parallel with perforating vessels2 recently shown to be arterioles on 7T MRI.46 There have been fewer studies of PVS than of the other SVD features to date, consequently PVS are not yet universally accepted as an SVD marker.4 However, in patients, PVS as seen on MRI are associated with several SVD-related factors: hypertension,47 circulating inflammatory markers, and cognitive decline (summarised in45) and (like several other SVD lesions) are highly heritable.48 Furthermore, PVS visibility increases with WMH, microbleeds and CAA, in lacunar versus non-lacunar stroke,45 mediated the association between plasma inflammatory markers and WMH,49 may predict progression of WMH,50 was associated with BBB leak1 and with increased intracranial and extracranial vascular pulsatility (stiffness).,44,47,51,52

In rodents, perivascular CSF flow depends on normal ‘elastic’ arteriolar pulsation and becomes slower and irregular if arteriolar pulsatility increases, such as with raised blood pressure, leading to fluid stagnation in PVS and impaired interstitial flushing.18,53 Therefore, the association between intracranial vascular pulsatility and PVS visibility in humans44 suggests that PVS visibility on MRI may be a marker of dysfunctional perivascular flow and consequently of impaired interstitial flushing. Dysfunctional perivascular flow may impair interstitial fluid drainage (in addition to any excess fluid from BBB leak) and impede clearance of metabolites (including β-amyloid and other proteins12) from tissues. Indeed, some investigators have described Alzheimer’s disease, CAA and several monogenic SVDs as ‘protein elimination failure angiopathies’.12 The increased interstitial fluid would also increase the distance over which oxygen and nutrients have to diffuse to reach neurons, thus propagating a worsening cycle of tissue injury.

While the precise sequence of endothelial dysfunctions in humans is currently unknown, we suggest that BBB leakage may increase interstitial fluid, arteriolar wall and tissue damage. Arteriolar wall thickening and stiffening, including when secondary to vascular risk factors, increases pulsatility and restricts vasodilation, impairs normal perivascular fluid flushing and removal of waste. Together these effects reduce oxygen and nutrient supply (**Figure 1**). Although speculative, drawing these elements together provides a unifying explanation for the common microscopic and in vivo vascular and brain lesions found in humans, while retaining consistency with information emerging from relevant rodent models.18,53

The ‘snapshots’ used to visualise the human brain in vivo and post-mortem may obscure the brain’s dynamic rhythms from cardiovascular, respiratory,18 circadian and physical activity, and may have hampered understanding of SVD.10,54,55 Currently, SVD lesions are considered to be ‘permanent’, with WMH representing demyelination, axon loss, and gliosis, lacunes being cavities replacing destroyed tissue, and microbleeds being fixed haemorrhages. Many longitudinal studies document WMH progression,56 although some change included small WMH decreases.

Two recent studies demonstrate that SVD lesions can shrink or disappear as well as grow.35,57 The RUN DMC study assessed older community-dwelling subjects three times over nine years: WMH volume decreased in 9.4%, lacunes disappeared in 2.6% and microbleeds in 5.7% of participants between two assessments.57 In the Mild Stroke Study-2 (MSS-2), 20% of patients showed WMH volume decline over one year.35 Both studies also found WMH progression, which was associated with older age and high baseline WMH burden. MSS2 found that WMH decrease was associated with better blood pressure control between baseline and one year, while the RUN DMC study found no factors associated with lesion reduction. In MSS2, WMH reduction was also associated with slight reduction in brain volume and fluid content consistent with WMH being areas of increased tissue water, and with reduction in recurrent strokes.

SVD lesions progress partly by expansion into adjacent tissue. Longitudinal spatial mapping with MRI shows new WMH forming superficial to small subcortical infarcts (‘caps’),54 and new lacunes forming at the proximal margin of WMH (with regard to the perforating arterioles).32 In addition, quantitative MRI methods such as DTI, T1 mapping, or DCE-MRI, reveal increasingly abnormal tissue (increased MD, reduced FA, increased T1) in a perilesional zone of NWM around WMH8,28,31 and lacunes,58 and reduced CBF30 **(Figure 2**) thus identifying the perilesional zone as ‘vulnerable’ tissue with microstructural tissue changes liable to recruitment into lesions. This ‘perilesional zone’ extends outwards with a corresponding gradient of DTI, T1 (and BBB leak) that becomes more normal with distance from the WMH edge.8,28 Longitudinal DTI studies demonstrate progressive loss of tissue integrity in perilesional tissue over time and conversion of NWM to WMH: lower CBF, CVR,43 FA, and higher MD in perilesional tissue independently predicted conversion of NWM to WMH.30 Although, technical issues (partial volume effects, tissue misclassification) might account for some perilesional tissue findings on MRI, autopsy studies found molecular disorganization of axons adjacent to lacunes and micro-infarcts in the perilesional zone.13,58

The focus of SVD research on MRI visible lesions may have distracted attention from the ‘whole brain effects’ of SVD. These include the diffuse changes in NWM and grey matter detailed above,8,9 and secondary loss of connected overlying cortex and in long descending fibre tracts (**Figure 3**).10,54 Worse SVD lesions are associated with diffuse loss of white matter and cortex in connected and in unrelated brain areas.8,9,55,59 DTI and functional MRI also show loss of global network connectivity and reduced network efficiency with increasing WMH burden.59,60 Considering global visible and subvisible SVD effects together may better predict conversion to dementia,59 relationships with vascular risk,61 concurrent cognition,60 and mobility,62 although optimal combination and weighting of features remains unclear.63

**Clinical implications**

Many of the clinical manifestations of SVD, including stroke, cognitive decline,64 gait problems,65 apathy,66 depression,67 and extrapyramidal symptoms,68 relate to functions with structural and functional underpinnings in widely distributed neuronal networks, consistent with diffuse effects of SVD on the brain, and important when considering mechanisms and interventions. The presenting symptoms and clinical course of SVD are highly variable. We suggest that this relates to several factors, which we discuss below. These include: (i) variations in the vascular injury (location, type, and extent); (ii) variable degrees of secondary neurodegeneration; (iii) resilience factors such as brain reserve, and (iv) comorbid conditions (**Figure 4**).

Associations between typical acute lacunar motor and sensory syndromes and recent small subcortical infarcts in specific anatomical locations, and between sudden cognitive deficits and strategic infarcts in the thalamus, are well established.69 Lesion-symptom associations may reflect the total burden of lesions, preponderance in specific brain subregions, or sub-visible changes.11 The total lesion burden, whether of individual types of lesions such as WMH, or in aggregate as reflected by total SVD burden scores, is associated with declines in cognition,60,70-72 gait and balance,62 and mood.4,67 Voxel-based lesion-symptom mapping suggests that lesions in distinct subcortical grey and white matter structures are associated with cognitive deficits,73 or apathy.66 While it is unsurprising that lesion type (e.g. cavitating infarct vs WML vs hemorrhage) and extent (volume, number) affect symptoms, subvisible tissue changes may also account for clinical effects: the structural decline detected with DTI in normal-appearing white matter correlates with cognitive impairments.11 Similarly, subcortical microinfarcts, which are by definition invisible to the naked eye, correlate with arteriolar pathology13 and worsening cognition.3 However, more studies are needed to determine the effects of co-morbidities and whether this also applies to unselected patients attending typical cognition or mobility clinics.74

Recent studies further emphasise a role ofsecondary neurodegeneration in determining clinical status. Discrete subcortical infarcts induce loss of connected cortex remote from the infarct via degeneration of white matter tracts.10 Increasing WMH burden associates with worse whole brain atrophy, cortex thinning overlying areas of high WMH density,59 and altered sulcal morphology,75 although the precise relationship between WMH progression and brain volume loss remains controversial.55 Importantly, brain atrophy is a strong independent predictor of clinical status and progression in SVD,76 and path analyses demonstrate that the effects of SVD-related vascular lesions on clinical status are in part mediated by changes in brain atrophy and cortex morphology.59,77 It may be that prevention of secondary atrophy may help delay the clinical effects of SVD.

Another factor contributing to the clinical expression of SVD is ‘resilience’, which refers to the capacity to cope with brain pathology. ‘Brain reserve’ refers to inter-individual differences in brain structure, whereas ‘cognitive reserve’ refers to differences in the way the brain processes specific tasks. Both reserves are influenced by experiences, including early in life,78 and are likely to be inter-related. While both concepts are still under development, both seem relevant to all clinical manifestations of SVD. High cognitive reserve, commonly operationalized as educational attainment and IQ, attenuates the effects of SVD burden on current cognition (e.g.79-81), influences motor functions,82 and age at stroke.80 ‘Brain resilience’ may depend on white matter structural integrity and network connectivity, since global white matter network efficiency mediated the effects of SVD lesions on cognition and progression to dementia.59 Premorbid cognitive ability (ie peak intelligence, a measure of ‘cognitive reserve’) can be estimated using tests such as the National Adult Reading Test, influences risk of SVD lesions in later life,78 and could explain some of the variation in SVD and cognitive function.80

Comorbid conditions are common in older patients, particularly in patients diagnosed with dementia. The most frequent finding in patients with dementia is mixed vascular and AD-type pathology, with individuals with multiple versus one pathology being more likely to have dementia.6 As such, comorbid neurodegenerative disease or other vascular lesions (e.g. large artery stroke) may also modify clinical expressions of SVD. The mechanisms and clinical effects of co-morbidities are subject to intensive research.

**Pharmacological and Lifestyle Interventions**

Evidence on prevention and treatment of SVD comes from completed trials of contemporary vascular risk modifying agents, drugs used in other fields with relevant modes of action,83 and lifestyle factors that can be modified (**Table 1**).

In the Secondary Prevention of Small Subcortical Stroke (SPS3) trial, long-term dual versus single antiplatelet therapy increased bleeding and death without reducing recurrent stroke.84 Guideline (systolic, 130-140mmHg) versus intensive (systolic, <120mmHg) BP reduction has mixed results: In SPS-3 (n=3020 lacunar stroke, mean age 63 years, duration 3.7 years) intensive BP reduction did not reduce recurrent stroke or cognitive decline85 but did reduce intracerebral hemorrhage; four BP lowering trials (n=1369, mean age 65, duration three years) found less WMH progression with BP reduction;86 PRESERVE (n=70, hypertension and SVD, mean age 69 years, duration three months) found no difference in CBF with BP reduction;87 full publication of SPRINT MIND (Systolic Blood Pressure Intervention Trial Memory and cognition IN Decreased hypertension, mean age 67.9) is awaited. While supporting rigorous BP control in patients with lacunar stroke or WMH who are in their 60s, WMH are commonest in patients aged over 80. Some believe that too rapid or large BP reductions in the over 80s, in whom brain perfusion may depend on elevated BP,88 or with severe SVD as in CADASIL,89 may lead to hypoperfusion. While the PRESERVE CBF substudy provides reassurance that intensive BP reduction did not affect CBF, the mean age was only 69. Hence, while rigorous BP control is important, data are lacking on optimal individual BP targets in older patients with severe WMH. Statins are now guideline therapy for secondary stroke/cardiovascular disease prevention, with no evidence of different effects in lacunar ischaemic stroke.83 Low dose rosuvastatin may delay WMH progression, particularly in patients with the APOE-4 allele,90 statins pre-stroke may reduce post-stroke WMH progression,91 and intensive lipid-lowering may reduce post-stroke cognitive impairment.92

Emerging targets include BBB integrity, vasoreactivity, vascular compliance, perivascular inflammation or myelin repair.16,83 Several drugs approved for other indications have relevant modes of action (**Table 1**). Cilostazol, a phosphodiesterase 3’ (PDE3) inhibitor is used for stroke prevention in Asia-Pacific countries, may reduce cognitive decline,93 reduce endothelial dysfunction, inflammation and enhance myelin repair,16 with supporting genetic data.20 Trials testing cilostazol for cognitive decline or recurrent stroke are ongoing. Nitric oxide donors (e.g. isosorbide mononitrate; glyceryl trinitrate, diet sources) may benefit SVD (improved BBB integrity, vasodilation, anti-inflammatory effects) with trials ongoing.

Amongst lifestyle modifications, smoking cessation is a priority for patients with SVD; smoking accelerates lesion progression in CADASIL,76 predicts total SVD lesion burden in sporadic SVDs,61 and accelerates cortical thinning.94 Regular exercise, diet and guideline-based vascular risk reduction slowed cognitive decline in participants at risk of dementia.95 High dietary sodium increases stroke risk, worsens WMH and total SVD burden.96 A ‘Mediterranean’ diet and B12/folate may limit WMH.96 Common sense should include good sleep hygiene, since brain interstitial fluid and waste clearance via PVS may accelerate during sleep.18,45

**Conclusions and future directions**

Small vessel disease causes a quarter to a fifth of strokes, age-related cognitive, physical and mood decline and about half of all dementias. This burden of disease has only been appreciated recently, so a complete understanding of the pathophysiology has been lacking. Much recent understanding of pathophysiological mechanisms in humans derives from advanced neuroimaging methods, which demonstrate dysfunctions of the cerebrovascular endothelium including subtle but diffuse BBB dysfunction,28 impaired vasoreactivity,43 increased intracranial vascular pulsatility,44 early white matter oedema,34 lesion regression as well as progression,57 and diffuse structural effects throughout normal appearing white matter29 and secondary remote tissue atrophy.75 These are supported by other data pointing to common pathophysiological pathways offering targets for SVD prevention and therapy.16,20 Improved awareness of the dynamic, whole brain effects, balance of primary versus secondary injury, balance of risk factor exposure versus resilience and complex disease patterns should inform future clinical trials, observational human studies, experimental models, and clinical practice. Future studies should address the order of, and interactions between, BBB failure, impaired vasoreactivity, increased pulsatility, vessel wall damage, impaired interstitial fluid drainage and PVS function in sporadic SVDs. Trials of agents that maintain endothelial function, improve risk factors and of lifestyle improvements should be encouraged.83 An approach that integrates from cells to tissues to systems, and across clinical specialties, would facilitate progress in SVD and should be encouraged. Since humans are their own best model, better pathology-imaging correlations,12 and brain banking with data linkage, are needed.97

**Panel: Search strategy and selection criteria**

We searched PubMed, Google Scholar, clinicaltrials.gov, Cochrane library, from 01/12/2012–31/12/2018, using search terms ‘lacunar’, ‘stroke’, ‘dementia’, ‘small vessel disease’ and its terminologies (‘white matter hyperintensities’, ‘white matter lesions’, ‘leukoaraiosis’, ‘lacune’, ‘microbleed’, ‘perivascular space’, ‘Virchow-Robin space’), ‘meta-analysis’, ‘systematic review’, and ‘randomised clinical trial’, restricting to ‘human’ studies, published in English, German, Spanish, French, Mandarin. We checked reference lists of reviews. The final reference list included systematic reviews where available, high quality observational studies and clinical trials.

**Panel: Definitions of terminology used in Small Vessel Diseases**

*Small vessel diseases*

Refers to neuroimaging and neuropathological abnormalities in the cerebral white and deep grey matter that are thought to arise from abnormalities in the microscopic perforating cerebral arterioles, capillaries and venules. Many affected individuals do not have symptoms but the brain damage can lead to stroke (25% of ischaemic and most haemorrhagic strokes), cognitive decline or dementia (the commonest cause of vascular dementia and common in mixed dementias), gait and balance problems and mood disorders in older people. Most small vessel disease is ‘sporadic’, perhaps related to hypertension or other vascular risk factors, but a small proportion are due to rare genetic variants of which the commonest is CADASIL.

*White matter hyperintensities, lacunes, microbleeds, perivascular spaces, recent small subcortical infarcts*

Are the common types of small vessel lesions seen on neuroimaging or neuropathology where the brain is most damaged. Many lesions gradually worsen although some lesions may improve for unknown reasons. Normal appearing brain is often abnormal if assessed with sensitive imaging methods, especially as the number of lesions increases and in the tissue around the visible lesions.

*Endothelial dysfunction*

When the layer of cells that line the blood vessels in the brain are not functioning properly. This is manifest in several ways. The cells lining the capillaries should regulate transport of fluid, nutrients and waste in and out of the brain, but they become leaky leading to perivascular tissue and arteriolar wall damage. The arterioles lose the ability to contract and dilate so as to match blood supply to demand in the brain. The vessels stiffen so that the pulsatility of the pulse wave increases, and this in turn diminishes the flow of fluid in the perivascular spaces which is thought to affect interstitial fluid flushing.

*Neurogliovascular unit*

Refers to the way in which the common types of vascular and brain cells - endothelial cells, pericytes, astrocytes, oligodendrocytes and neurons - are organised and linked together into millions of functional units in the brain. In these groupings, the cells interact to regulate entry of fluid and nutrients into the interstitium, manage blood supply, maintain and repair myelin, clear fluid and waste, and maintain the interstitial milieu for proper cell function.

**Panel: Future Priorities**

Research is needed to determine the relative contribution(s) of different manifestations of endothelial dysfunctions to brain damage in patients with small vessel diseases and their timescales. Longitudinal studies with detailed risk factor assessment and lesion monitoring are needed to determine reasons for the wide variation in rates of progression of SVD lesions, why some lesions regress, and why some lesions lead to secondary damage in remote brain regions. This knowledge would help predict disease impact on clinical, physical and cognitive outcomes. Understanding the reasons for the variable symptomologies, and the role of ‘brain reserve’ and ‘cognitive reserve’, would improve detection, diagnosis and in future also help tailor the clinical management of individual patients. Understanding the role of genetic susceptibilities versus environment and risk factor exposures, from birth to later life, is also important to understand variation in SVD lesion development and clinical expression. Clinical trials should test the numerous licenced drugs that have relevant effects. New interventions are needed to target the molecular underpinnings of the endothelial dysfunction(s) seen in SVD.

**Declarations of interest**

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**Authors’ contributions**

JMW, MD and CS each drafted sections of text. JMW combined the text. All three authors edited the text, helped to prepare the figures, provided insight, context and balanced interpretation of evidence through discussion and approved the final version for submission.

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**Table 1. Summary of pharmacological and lifestyle interventions in small vessel disease.** Meta-analyses are cited where available, otherwise randomised controlled trials (RCT). A ‘ – ‘ in the N column or ‘analysing’ indicates that the trial is ongoing. Trial registration numbers or published protocols are cited for ongoing studies where more details of trial protocols may be found. References are cited for main trial results papers. The table is divided into sub sections for different groups of pharmacological and lifestyle interventions.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Intervention** | **Design** | **Population** | **N** | **Age yrs** | **Comments** |
| ***Classical pharmacology for stroke prevention***  |
| Antiplatelet | *Meta-analysis* 17 trials 84 | Patients with lacunar stroke | 42234 | 64.4 | Includes SPS3; follow-up 4 weeks to 3.5 years; single vs no antiplatelet reduced recurrent stroke; no difference between several antiplatelet drugs; long term dual antiplatelet in SPS3 increased ICH. |
| Anti-hyper-tensive | *RCT*SPS3; 85 *Meta-analysis*ACCORD-MIND, PRoFESS, PROGRESS, SCOPE86*RCT substudy*PRESERVE | Patients with lacunar strokeAny strokeHT, lacunar stroke, severe WMH  | **3020****1369** **62** | 63±1162±566±861±1277±4 69  | Different BP lowering agents at the discretion of the treating clinician. No reduction in stroke, cognitive decline with intensive vs usual BP reduction;Follow-up 28-47months; less WMH progression with intensive vs usual BP reduction.CBF did not fall with BP reduction |
| Statins | *RCT Substudy*VITATOPS91 *RCT substudy* in Shandong, China | Patients with stroke and pre-stroke statin, rosuvastatin |  81668 | >60 | Less WMH progression with pre-stroke statin Follow-up 61.8 (SD: 2.2) months; less WMH progression with statin than non statin and in non APO-e4 v APOE-4 carriers |
| ***Novel pharmacology: endothelial and other effects – ongoing unless otherwise stated*** |
| Nitric Oxide | *RCT*ENOSRIGHT-2(ISRCTN26986053)LACI trials (LACI-1 (EudraCT 2015‐001953‐33); LACI-2, EudraCT 2016-002277-35) | Patients with stroke including lacunar stroke98Patients with stroke including lacunar strokePatients with lacunar strokePatients with lacunar stroke | 40111050 57 - | 70±12Analysing66±11 | Effect of short term GTN on neurological, functional, cognitive outcomes; analysing 1397 with lacunar stroke of whom 41% had WMHEffect of short term GTN on neurological, functional, cognitive outcomes Effect of isosorbide mononitrate on recurrent stroke, cognitive decline, SVD lesion burden. |
| PDE3’ inhibitor (Cilostazol)  | *Meta-analysis*Trials of stroke prevention*RCT*LACI trials (LACI-1 (EudraCT 2015‐001953‐33); LACI-2, EudraCT 2016-002277-35)*Observational*National Registry Taiwan93 | Patients with ischaemic strokePatients with lacunar strokePatients with lacunar strokePatients in central hospital registry | 600057 -9148 |  67 66±11 - >40 | Reduced recurrent strokeEffect of cilostazol on recurrent stroke, cognitive decline, SVD lesion burden.Effect of cilostazol on recurrent stroke, cognitive decline, SVD lesion burdenCilostazol use was associated with a reduction in incident dementia,  |
| xanthine oxidase inhibitor (Allopurinol) | *RCT*XYLO-FIST (NCT02122718)  | Ischaemic stroke  |  - |  - | Effect of Allopurinol on WMH progression and recurrent stroke,  |
| PDE5’ inhibitors | *RCT*PASTIS (EudraCT 2015-001235-20)  | Patients with WMH |  - |  - | Effect of Tadalafil single dose on resting CBF,  |
| B12/Folate | *Substudies in RCT* VITATOPS96 | Patients with stroke | 359 |  64 | Vitamin supplements for 2 years reduced WMH progression in patients with the worst WMH at baseline;  |
| ***Lifestyle*** |
| Smoking  | *Observational*MSS261Paris-Munich CADASIL76Lothian Birth Cohort94 | Patients with stroke; Patients with CADASILOlder subjects in community |   264 290 504 |  6750.6±11.4  73 | Smoking increases: - SVD score- risk of stroke and dementia-accelerates rate of cortical thinning |
| Exercise | *RCT* FINGER trial95 | Older subjects at risk of dementia | 1260 |  69.5 | Dietary, exercise encouragement and medical risk factor reduction versus usual health messages and guideline vascular risk factor reduction, reduced cognitive decline, and WMH progression in substudy |
| Diet: sodium chloride | *Observational*MSS-296 | Patients with stroke  | 264 |  67 | High dietary sodium increased risk of: stroke, lacunar versus cortical stroke, WMH & total SVD burden.  |

SPS3: Secondary prevention of small subcortical stroke trial. ACCORD-MIND: Action to Control Cardiovascular Risk in Diabetes: Memory in Diabetes (MIND) substudy. PRoFESS: Prevention Regimen for Effectively Avoiding Second Strokes. PROGRESS: Peridopril protection against recurrent stroke study. SCOPE: Study on Cognition and Prognosis in the Elderly. VITATOPS: VITAmins TO Prevent Stroke trial. ENOS Efficacy of Nitric Oxide in Stroke. RIGHT-2: Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial. LACI: Lacunar Intervention Trial. XYLO-FIST: Xanthine Oxidase Inhibition for Improvement of Long-term Outcomes Following Ischaemic Stroke and Transient Ischaemic Attack. PASTIS: Perfusion by Arterial Spin Labelling Following Single Dose Tadalafil in Small Vessel Disease (PASTIS) Trial. MSS2 Mild Stroke Study. CADASIL Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability.

**Figure legends**

**Figure 1. Key constituents of the vascular-glio-neuronal unit and possible entry points for disease mechanisms in cerebral SVD.** Arterioles penetrate the brain and ultimately branch into capillaries. They are each surrounded by a perivascular space (PVS) that is connected to the cerebrospinal fluid (CSF). Capillary endothelial cells (EC) including their connecting tight junctions (TJ), a specialized basement membrane (BM), pericytes/mural cells (PC), and astrocyte endfeet collectively form the blood-brain barrier (BBB). The latter is essential for maintaining the interstitial milieu. Astrocytes maintain the interstitial fluid balance, provide energy to neurons and relay signals between neurons and other cells to the vasculature to adapt blood flow to energy demand. Oligodendrocytes form and repair myelin around axons to which they also provide metabolic and trophic support. At cellular level, EC dysfunction and BBB leak increase interstitial fluid and proteins, disrupt astrocyte end feet impairing interstitial fluid exchange, block oligodendrocyte precursor cell (OPC) maturation impairing myelination and repair and energy support to axons, and impedes normal astrocyte function decreasing neuronal energy supply. The order of these events is not yet determined. Several of the cellular and functional constituents of the vasculo-glio-neuronal unit represent possible entry points for disease mechanisms in cerebral small vessel disease (SVD). For further explanations see text. Graphics provided by Antonia Weingart.

**Figure 2. Cerebral SVD lesions, their long-term fate and the perilesional zone**. White matter hyperintensities (WMH, detectable on FLAIR or T2 weighted MR sequences at conventional field strengths), represented by the grey circles, may (from top down) regress (arrow), expand (arrow), remain stable, develop incident lacunes at the edge of the WMH (arrow), or cavitate (i.e. turn into a lacune, arrow). Examples of initial and follow-up MRI are shown on the right hand of the image, initial MRI in the left-hand and follow-up MRI in the right-hand columns. WMH and other SVD lesions are typically surrounded by a zone of increasingly abnormal tissue (indicated in orange) that appears normal on conventional FLAIR or T2-weighed MRI or pathology (normal appearing white matter, NWM) but shows altered signal characteristics on several MRI modalities including diffusion tensor imaging (DTI) and at pathology.

**Figure 3. Cerebral SVD affects the whole brain**. Shown left to right is a progression of SVD lesions detectable on MRI. Note that incident lesions such as infarcts and microbleeds may occur at variable time points during disease progression, or be absent. Acute infarcts and white matter hyperintensities (WMH; visible on FLAIR and T2 weighted MR sequences) cause secondary loss of grey and white matter in connected brain regions, and regions with less obvious direct connections, resulting in cortical thinning, brain atrophy and neurodegeneration. Left: interstitial fluid increases produce subtle changes in normal white matter (WM) leading to WMH formation. Middle: WMH progress leading to secondary cortical thinning, acute small subcortical infarcts may appear. Right: WMH, lacunes, microbleeds worsen, secondary cortical thinning and long tract degeneration worsens. Figure graphics provided by Antonia Weingart.

**Figure 4. Factors influencing the clinical expression of cerebral SVD**. The clinical presentation and course of cerebral SVD is highly variable. Shown are factors that contribute to this variability, including by affected brain location,69,73 lesion type and extent.59 Age, environmental and genetic factors all have a determining role e.g. by influencing vascular risk (exposure) or premorbid risk.78,79

For explanations please see text.