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Neuroimaging standards for research into small vessel disease – advances since 2013

STandards for **R**eport**I**ng **V**ascular Changes on N**E**uroimaging 2 (STRIVE-2)

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Appendix: Supplemental methods, text, tables, references, panels, and figures

Abstract

Cerebral small vessel disease (SVD) is common during ageing and may present as stroke, cognitive decline, neurobehavioural symptoms, or functional impairment. SVD frequently coexists with neurodegenerative disease, where it may exacerbate cognitive and other symptoms and affect activities of daily living. STRIVE-1 categorised and standardised the diverse features of SVD visible on structural MRI. Since then, new information on these established SVD markers and novel MRI sequences or imaging features have emerged. As the impact of combined SVD imaging features becomes clearer, a key role for quantitative imaging biomarkers to determine sub-visible tissue damage, subtle abnormalities visible at high-field strength MRI, and lesion-symptom patterns, is also apparent. Together with rapidly emerging machine learning methods, these metrics may more comprehensively capture the impact of SVD on the brain, serve as intermediary outcomes in clinical trials and future routine practice. Using a similar approach to that adopted in STRIVE-1, we updated the guidance on neuroimaging of vascular changes in studies of ageing and neurodegeneration to create STRIVE-2.

Introduction

Cerebral small vessel disease (SVD) causes 25% of ischaemic strokes, most intracerebral haemorrhages (ICH) in older people, most vascular dementia, and is associated with mobility, gait, neurobehavioural and mood disorders.[1]

The S**T**andards for **R**eport**I**ng **V**ascular changes on N**E**uroimaging (STRIVE-1),[2] published in 2013, aimed to clarify definitions of SVD features on neuroimaging; encourage consistent, unbiased use of agreed terminology; promote better understanding of the causes, symptomatology and prognosis of SVD ; and foster better prevention and treatment options. STRIVE-1 focused on recent small subcortical infarcts (RSSI), lacunes of presumed vascular origin, white matter hyperintensities of presumed vascular origin (WMH), perivascular spaces (PVS), cerebral microbleeds (CMB), and brain atrophy.

Since 2013, there have been significant advances in the understanding of SVD imaging features, including changes in the appearance of SVD imaging features over time, their inter-relatedness, novel SVD imaging features, and improved MRI biomarkers of brain structural and vascular functional impairments.

The STRIVE investigators reconvened to update the 2013 Standards and Recommendations for neuroimaging features of SVD, reflect upon and update the original terminology where necessary, and focusing on new information accruing since 2013. STRIVE-2 kept the focus on neuroimaging features and research use, not primarily on clinical features or clinical management of SVD. We thus also include emerging imaging features and key quantitative imaging methods that require standardisation in order to enable wider application in research.

Adoption of STRIVE-1 terminology

STRIVE-1[2] proposed terminology for key SVD features that described imaging characteristics and avoided assumptions about pathology, pathophysiology, and clinical associations. Optimal terms are specific, short, and related to prior usage if the prior usage was accurate, without assumptions.

Our systematic literature search (**appendix**, page 5) showed that STRIVE-recommended terms for WMH, PVS, and CMB have replaced more variable terms (**supplemental figure 1**). However, the preferred terms for RSSI, lacunes and brain atrophy were less well used. We reassessed these terms to determine if a better or more intuitive term might be available, adopting the same review process as in STRIVE-1, to improve standards.

Methods

See **Appendix** (page 2ff) for details. We convened 50 experts, some from STRIVE-1 plus new contributors, reflecting wide-ranging expertise, geographical location, and activity in SVD research. These divided into 10 working groups with a work-group lead, provided evidence-based text and proposals, which were discussed and agreed by the whole group. We invited new external advisors.

We systematically searched the literature to assess harmonisation of STRIVE-1 terminologies, and new findings. We surveyed the STRIVE group on their current clinical and research acquisition protocols.[2] As in STRIVE-1, *terms and definitions should reflect the imaging characteristics and avoid presumptions about mechanisms or pathological changes, especially when these are incompletely understood, so as not to prejudice future studies of SVD* – i.e., 'describe what you see and not what you think you see'.

We used the Delphi principle, including wide-ranging transparent discussion within workgroups, the whole group at two workshops and an anonymous online survey on contentious topics, before finalising the consensus document.[2] STRIVE-2 will update the STRIVE-1 entry on EQUATOR (Reporting guidelines | The EQUATOR Network, equator-network.org). To assist application and interpretation of STRIVE-2, we provide further details on unusual appearances, caveats, temporal evolution, and boundaries between features (**appendix**).

STRIVE-2 builds upon and extends STRIVE-1, focussing on new knowledge of SVD while avoiding repetition of previous information. STRIVE2 should thus be read and used in conjunction with STRIVE-1.

Search strategy and selection criteria

Data were derived from a structured literature search; for methodology, search strategy and selection criteria, see **appendix** (page 5ff).

Update on imaging features defined in STRIVE-1

Recent small subcortical infarct (RSSI)

A recent small subcortical infarct (RSSI) describes 'neuroimaging evidence of a recent infarction in the territory of one perforating artery, with imaging features and clinical symptoms consistent with a lesion occurring within the previous few weeks'. Among all terms proposed by STRIVE-1, RSSI is the least well applied, often called to 'acute lacunar infarcts' amongst other names, although authors are less likely to use the term 'lacune' to describe recent (and non cavitated) lesions. STRIVE-2 sought a more intuitive name, but after discussion and voting on six options, 'recent small subcortical infarct' remained the preferred term by a large margin. 'Recent' (meaning 'within the previous few weeks', as discussed and agreed in STRIVE-1) was preferred to 'acute' for the same reasons as in STRIVE-1; 'infarct' is used cautiously since the true pathology is not fully known. The territory of a single perforating artery was operationalised in STRIVE-1 by a size criterion, a maximal axial lesion diameter of 20 mm. RSSI are associated with other SVD features, supporting an intrinsic small vessel abnormality, although not all RSSI are due to intrinsic perforating arterial disease (**figure 1A**). An RSSI is clearly linked to corresponding clinical symptoms, i.e., a focal neurological deficit. This deviates from the STRIVE principle to only use imaging characteristics, but substantially improves the clarity of this feature's definition. The term does not apply to so-called 'covert' lesions, which are either asymptomatic, or associated with 'atypical neurobehavioural symptoms/signs', or more subtle/gradual neurological deterioration over longer time (**figure 1B**).[3] The nature of these covert lesions is currently less understood, and these lesions are thus currently not regarded as a core feature, but an emerging feature of SVD (see emerging features section). Non-intrinsic causes, large artery disease associations with RSSI, and acute imaging diagnosis are covered in more detail in the **appendix** (page 9f, **supplemental figure 2**).

Large variability in residual appearances of RSSI have emerged since STRIVE-1, including disappearance, <3 mm diameter lacune (see below), cavitation, a haemosiderin (T2*-hypointense) rim around the lacune,[4] or small haemosiderin (T2*-hypointense) 'smudge' with no other residual sequelae (**figure 2, supplemental table 1, supplemental figures 3, 4, 5** for examples).[5,6] White matter tract degeneration around the RSSI may lead to new adjacent WMH (referred to as 'cap' if superior, or 'track' if inferior to the RSSI).[7] Sources of variance in end-appearances are unclear but include initial lesion size, tissue injury, inflammation, comorbidities, location, microcirculatory variations, or individual vulnerabilities.[2,6,8]

Lacune (of presumed vascular origin)

STRIVE-1 defined the 'lacune of presumed vascular origin' as a round or ovoid, subcortical, fluid-filled (CSF-like) cavity that can arise from several causes.[2] Lacunes may be larger in the centrum semiovale and basal ganglia than elsewhere.[9] The size limits were defined as 3–15 mm (axial plane); however it is now clear that lacunes <3 mm can be the end result of an RSSI (**figure 2, supplemental figure 3**),[10] while occasional PVS are >3 mm diameter. Lacunes resulting from an RSSI may lack a T2-hyperintense rim. Therefore, perfect differentiation of lacunes from PVS is not possible by size or rim alone and may consider shape, co-located PVS, surrounding tissue signal, etc. (**supplemental table 1**).[11]

Use of the term 'lacune' remains variable (**supplemental figure 1**); however, we have not identified a better term. We encourage adoption of 'lacune', restricting its use to cavitated lesions and adding 'of presumed vascular origin' when there is reasonable certainty that it followed a vascular insult. In general, 'lacune' should not be linked with 'infarct' unless certain that it results from a small subcortical infarct, since lacunes may also result from haemorrhages,[2] appear *de novo* in normal tissue, or within or at edges[12] of WMH.

A lacune at least doubles the future risk of stroke in persons without stroke,[13] and after stroke, lacunes increase the risk of poor long-term outcomes.[14,15]

Lacunes are assessed visually on T1-, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, including their number and location; cavity volume can be used, with automatic methods in development; incident lacune detection requires strict imaging criteria and validated methods.[16]

White matter hyperintensity (of presumed vascular origin) (WMH)

WMH, the most studied SVD feature, are hyperintense on T2-weighted (preferably FLAIR) MRI sequences, typically symmetrical between hemispheres.[2] The term 'WMH of presumed vascular origin' proposed in STRIVE-1, has been widely adopted, should be encouraged (avoiding terms such as 'ischaemic WMH', **supplemental panel 1**). The term 'subcortical hyperintensities' to describe lesions in the deep grey matter or brainstem remains useful.

WMH associate with future risk of stroke, stroke severity, cognitive decline, and death,[13,17] dependency, impaired gait, and neuropsychiatric symptoms,[18] and affect all main cognitive domains including memory.[19,20]

WMH generally increase with age and time but amounts reported in 'healthy populations' by age vary considerably for reasons that are, as yet, not fully understood, which therefore currently precludes the provision of reliable normative age-stratified WMH data.[13,21]

WMH indicate areas of tissue damage that extend into apparently-normal surrounding tissue,[22] detectable by quantitative imaging (see below). WMH may also decrease,[21] perhaps reflecting resolution of excess interstitial fluid before permanent damage has occurred.[23]

WMH are associated with impaired CVR,[24] increased BBB permeability,[1] increased vascular pulsatility,[25] venous collagenosis,[26] reduced resting cerebral blood flow in cross-sectional studies but the longitudinal relationship between WMH and CBF remains unclear.[27]

Although many semi-automated and automated methods are available to assess WMH, their reproducibility and comparability still lack in-depth characterisation (**supplemental table 1**).[28] Deep learning-based algorithms[29] are in development, but these still require validation (see below). Thus, well-validated visual scores, described in STRIVE-1 and HARNESS,[2,30] remain useful.

Perivascular space (PVS)

PVS are fluid-filled round/ovoid or linear spaces, following typical courses of small perforating vessels in white or deep grey matter.[2,31] STRIVE-1 proposed the term 'perivascular space' to refer to PVS visible on MRI (without the adjective 'enlarged') which has been widely adopted (**supplemental figure 1**). On brain MRI, PVS signal intensity is similar to CSF. Unless located within a WMH, there is typically no T2-hyperintense rim. PVS are usually <3 mm maximum axial diameter (see lacunes and **supplemental table 1**).[32] They are most prominent in the basal ganglia and centrum semiovale, but should not be confused with solitary developmental perivascular invaginations found in the inferior basal ganglia. T2-weighted and susceptibility-weighted sequences,[33] and 7T MRI[34] showed that MRI-visible PVS are predominantly periarteriolar.

PVS increase in number with age and vascular risk factors,[35] are highly heritable,[36] and associations vary with location (**supplemental table 1**), so underlying pathophysiologies may differ by anatomical distribution.[31,37] In the Boston 2.0 diagnostic criteria, a high burden of centrum semiovale PVS in combination with a single strictly lobar haemorrhagic feature (intracerebral haemorrhage, cerebral microbleed or cortical superficial siderosis) indicates probable cerebral amyloid angiopathy (CAA).[37] While a few PVS may be physiological, in a wide age range,[38] a large PVS burden is associated with common neurological diseases (stroke,[13,31,35] CAA[37], Alzheimer's disease[35]). PVS may occur on brain MRI earlier than lacunes, or CMB,[31] and precede WMH.[39] PVS may reflect impaired brain fluid and waste clearance,[31] potentially during sleep.[40]

PVS are quantified with visual rating scales (**supplemental table 1**)[41] which are practical. Computational methods to quantify several PVS parameters are now available[42] (**supplemental table 1**), which show increased sensitivity for associations with WMH, retinal vessel diameters (smaller arterioles, wider venules, a proxy for cerebral small perforating arterioles and venules), or genetic variants (reflecting relevant vascular dysfunction mechanisms).[42,43] High-resolution T2-weighted images are recommended for best (most sensitive) PVS detection, but T1-weighted images may also be used.

Cerebral microbleed (CMB)

CMB were defined in STRIVE-1 as small, generally 2–5 mm diameter, lesions of low signal on MRI T2* or susceptibility-weighted sequences. The original STRIVE[2] term 'cerebral microbleed' has been widely adopted. MRI-guided neuropathological examinations have confirmed that most CMB correspond to microbleeds.[44] CMB can be found in different anatomical locations, typically cortical grey matter and juxtacortical white matter in CAA, or deep brain structures in arteriolosclerosis (deep grey and white matter, brainstem), but regions/pathologies overlap and may share pathophysiological mechanisms: vessel wall thickening, remodelling, and BBB dysfunction may be triggered by amyloid accumulation, arteriolosclerotic vasculopathy, or both.[45] Strictly lobar CMB in older patients have good diagnostic accuracy for CAA,[37] but other pathologies occur.[45,46] Mixed deep-lobar CMB probably reflect arteriolosclerosis.[47]

The Microbleeds International Collaborative Network (MICON) scores may predict risks of ICH and ischaemic stroke during antithrombotic therapy for secondary stroke prevention,[48] but absolute risks of recurrent ischaemic stroke exceed that of ICH, suggesting that CMB should not influence use of antiplatelet or anticoagulant drugs in secondary prevention. Limited randomised trial data also suggest that CMB do not modify effects of antithrombotic therapy on CMB formation[49] or clinical outcomes,[50,51] but more trials are needed. In CAA, the independent contribution of CMB to predict future lobar haemorrhage is limited once cortical superficial siderosis is also taken into account.[52]

CMB are assessed using visual rating.[2] They are challenging to detect computationally (small size, sparse, numerous "mimics" including blood vessels, mineralisation, cysticerci in relevant countries). CT can help differentiate true CMB from calcified cysticercus[53] and other mimics. Computational methods in development require validation.[54]

Cortical superficial siderosis (cSS)

cSS as defined in STRIVE-1 describes neuroimaging evidence of chronic blood products in or overlying the superficial cortex.

cSS may follow convexity subarachnoid haemorrhage, superficial cortical bleeding from vascular malformations, haemorrhagic transformation of infarcts, or trauma. Most cSS in older patients results from convexity subarachnoid haemorrhage from advanced leptomeningeal vessel CAA,[55] sometimes with secondary cortical ischaemic injury.

T2*-weighted gradient echo or other blood-sensitive sequences show cSS as a linear hypointensity over the cortex. cSS (also cerebellar[56]) is an accurate diagnostic biomarker of advanced CAA in the appropriate clinical setting and thus included in the Boston Criteria 2.0.[37]

Transient focal neurological episodes, observed in patients with CAA and acute convexity SAH or cSS (and occasionally a CMB), are most often unilateral, recurrent, stereotyped, spreading somatosensory disturbances, correlating anatomically between clinical presentation and convexity SAH, cSS (or occasionally a CMB) location.[57]

cSS is a strong predictor of future clinical events in CAA, e.g., risk of future ICH, functional decline, and post-ICH dementia.[52]

Intracerebral haemorrhage (ICH) and other haemorrhagic markers

ICH is due to SVD in 85% of cases. STRIVE-1 recommended the consensus term ‘spontaneous ICH presumed due to SVD’, replacing ‘primary ICH’, because ‘primary’ is poorly defined and to avoid discouraging determination of ICH causes.

ICH due to SVD includes perforating artery (arteriolosclerotic) vasculopathy and CAA. CAA is associated with lobar ICH, and scoring instruments that improve and standardise the classification of deep vs. lobar ICH, such as Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS, validated for CT and MRI), may thus support the identification of patients at higher risk of CAA.[58] The Edinburgh CAA criteria using two CT-based biomarkers (subarachnoid extension and “finger-like projections” of the ICH) and *APOE* genotype may help diagnose CAA-associated ICH in the acute stage when MRI may not be available, or locations where MRI availability is limited.[59] The Edinburgh CT and Boston MRI CAA criteria have reasonable correspondence in acute ICH due to sporadic or hereditary CAA.

Brain atrophy

STRIVE-1 defined ‘brain atrophy’ as ‘lower brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction’. Ideally, brain atrophy refers to reduction in brain volume between several assessments; cross-sectionally, its definition requires a reference (e.g., intracranial volume), validated scales, local or global computational norms. We prefer ‘brain atrophy’ to ‘brain volume’ when referring to cSVD-related brain volume loss.

Brain atrophy is not a specific marker of SVD, and concomitant neurodegenerative disease can be a major contributor. Still, brain atrophy clearly occurs in SVD and has shown value for prognosis and monitoring. Since STRIVE-1, interest in brain atrophy in SVD has increased, with three times more publications in 2014-2021 as in the seven years preceding STRIVE-1. Both subcortical (e.g., increased ventricular volume) and cortical (thinning, sulcal widening) atrophy can result from SVD.[60] Potential mechanisms include secondary tract and focal cortical loss,[61] and possibly accumulation of smaller lesions, e.g., cortical microinfarcts.[62] Regional atrophy in SVD, including hippocampal atrophy, overlaps with those of other degenerative processes, including Alzheimer’s disease, but spatial patterns of brain atrophy in SVD remain to be clarified.[63,64] Since brain atrophy is not specific to SVD, co-occurring pathologies should be considered.

Brain atrophy measurement varies considerably, with increasing use of automated methods;[63] visual scales remain useful. Focal macroscopic (including vascular) lesions may confound brain atrophy measurement, with no agreement on how to handle focal lesions.[63] Cortical thickness measurements require extensive post-processing, which is error-prone with extensive SVD features,[65] also due to SVD effects on grey/white matter contrast.[66] To improve consistency and avoid post-processing issues, quantitative measures of brain atrophy should be postponed until any acute lesion is MRI-stable. Processing large datasets of patients with severe SVD should be performed with specific quality control procedures (**tables 1, 2**).

Context, terminology, and definitions of imaging features since STRIVE-1

Summary SVD score

Context

A challenge set in STRIVE-1 was to develop an imaging scale summarising SVD burden. Major drivers were to predict outcomes, and improve participant selection/stratification for trials.

Several scores are now available using visual rating, mostly for MRI.[67] One of the first, most widely used, the 'total SVD score',[68] includes WMH, lacunes, PVS, and CMB, and has good construct validity.[69,70] Further scales include modifications of the 'total SVD score', some specific for CAA,[71] or adapted for CT.[15]

Our consensus was that these scales are still being developed, with more work required to attain full generalisability. A summary SVD score may aid statistics or help in clinics, but the true advantage of a combined score over individual features, and the most useful situations, remain unclear.

Terminology

We found 1755 abstracts: 748 examined multivariable SVD markers, 198 different combinations of individual SVD markers. The commonest terms were: "cerebral small vessel disease (CSVD)" (n=73), "CSVD markers" (n=34), "CSVD burden" (n=26), with 29 papers using the additional qualifier "total".[15,68,70] Forty-nine papers combined SVD markers with Alzheimer's disease-related measures including amyloid and tau burden, while 30 combined SVD measures with brain atrophy (e.g., "brain health index").[72]

We propose the term '*summary SVD score*', avoiding the words "total," as no truly complete score exists *per se*, avoiding "burden" or "load," to avoid emotive implications.

Definitions

We define a summary SVD score as 'any grouping of accepted SVD markers into a single index, score, or unitary construct'. We endorse the inclusion of markers previously defined in STRIVE-1. For between studies' comparisons, we encourage the use of validated scales and quantification tools (e.g.,[70]). However, we emphasise the importance of incorporating new imaging markers and methods as they arise. Including automated measures to estimate WMH volume, lacunes, PVS, CMB, or diffusion metrics, appear promising[19] but require validation.

We discussed including clinical and functional metrics into SVD scores, but agreed to focus on neuroimaging markers, due to large between-study variation in non-imaging variables.

For reporting, we recommend referencing a validated score, and importantly, noting any adaptations. Scores incorporating simple qualitative visual ratings are intuitive and clinically useful. Incorporating quantitative measures may provide more sensitivity but may not be tenable outside research. New scores require careful validation and testing in diverse populations, which needs to be tailored to the intended use of a new score, e.g., as a prognostic marker.

Cortical cerebral microinfarct (CMI)

Context

CMI were first described as ‘small ischemic lesions invisible to the naked eye on gross pathology’.[62] They are frequently observed on microscopic neuropathological examination, predominantly in cortex, and considered the most widespread form of infarction in the ageing human brain, found in 16–42% of individuals at autopsy.[62] CMI are not specific for SVD but also occur as a result of microembolism from cardiac or arterial sources. Since STRIVE-1, consensus rating criteria for microinfarcts during life have been proposed, aided by ultra-high field MRI and histopathology.[62] CMI are associated with cognitive decline.[62] Larger cortical CMI (0.5–4 mm) can be detected using conventional MRI, including 3D-T1-weighted and FLAIR sequences,[62] and as hyperintense lesions on diffusion-weighted imaging (DWI) when recent[73] (see below). Ultra-high field MRI increases the sensitivity of CMI detection to smaller lesions, but still detects only a fraction of lesions seen on neuropathology.

Terminology

We screened 64 abstracts, identifying ‘cortical cerebral microinfarct’, ‘cortical microinfarction’, ‘cerebral microinfarct’, and ‘chronic microinfarct’. We propose the consensus term ‘cortical cerebral microinfarct’ (cortical CMI).[62]

Definitions

CMI detection is limited to cortical grey matter since CMI cannot be discriminated from WMH and PVS.[62] Old CMI appear T1-hypointense, T2/FLAIR-hyperintense and T2*-isointense, and typically wedge-shaped. Based on sparse MRI-neuropathology comparisons,[71] CMI have been defined operationally as an upper size limit of

4 mm,[62] differing from neuropathologically-defined microinfarcts as smaller microscopic lesions are below the resolution of current MRI.

Future directions

Define upper size limits, develop robust criteria to detect subcortical and cerebellar CMI, and improve recognition of CMI on MRI when subacute.[73]

Emerging feature

Incidental DWI+ lesion

Context

Diffusion-weighted imaging-positive (DWI+) small subcortical and tiny cortical lesions, mostly covert (without accompanying focal neurological deficit), are increasingly recognised.[10] They overlap with RSSIs when subcortical (**figure 1, 2**), and with recent CMI when <5 mm in cortex. They may disappear, evolve into a WMH, lacune, or old CMI (**figure 2, supplemental figure 3**), thus partly accounting for SVD progression. They are commonest in severe SVD (e.g., CADASIL, ICH), supporting an underlying intrinsic small vessel abnormality. However, like RSSI, they may also result from cardiac or arterial embolism or altered hemodynamics such as blood pressure drops (**appendix,** page 8f).

Terminology

Commonly-used terms include acute incidental infarct, DWI or DWI-positive lesion, DWI hyperintensity, covert brain infarct, etc. Since their origin, nature, and clinical significance is unclear, following much discussion and voting, we propose the consensus term 'incidental diffusion-weighted imaging-positive (DWI+) lesion' for incidentally detected DWI-hyperintense lesions with an axial plane diameter ≤20 mm. Incidental detection typically refers to a lesion on an MRI scan performed in the absence of a new focal neurological deficit, or where the lesion location is unrelated to any recent symptoms.

Definitions

Incidental DWI+ lesions appear as small hyperintense lesions on DWI, with a corresponding hypointense or isointense signal on ADC maps. Note, these lesions can also be seen as hyperintense on FLAIR or T2-weighted MRI and/or hypointense on T1-weighted MRI. An incidental DWI+ lesion accompanied by a hyperintense T1 signal, suggests an acute bleeding element (haemorrhagic transformation of an infarct or primary haemorrhage). DWI must thus be used in context with other core sequences. Vice versa, other incidental lesions (e.g., lacunes or WMH) could have been DWI+ if scanned timeously. As such, increased use of DWI could highlight recent covert lesions and should be encouraged.

Assessment of incidental DWI+ lesions is currently visual, computational methods are under development.

Future Directions

Research on this feature was very active in recent years. The STRIVE-2 group consensus was that research is still needed to address the unknowns in regard to aetiology, pathology, clinical relevance of incidental DWI+ lesions, relation to symptoms and the overlap with RSSI before this feature can advance to an established SVD marker.

Quantitative imaging markers of brain structure and function

Structural quantitative imaging markers of SVD brain damage

Context

Several quantitative imaging methods may characterise imaging features of SVD (**table 1** proposes acquisition standards).

Diffusion Imaging

Diffusion imaging, an umbrella term, encompasses image acquisition and processing/modelling. Simple DWI is used to detect acute ischemic lesions, multi-directional DWI acquisition together with diffusion modelling helps characterise tissue microstructure. Diffusion tensor imaging (DTI) is one model capturing magnitude and spatial anisotropy of water diffusion.[74] Techniques like 'Peak width of Skeletonised Mean Diffusivity' (PSMD) may detect associations with clinical deficits in SVD better than conventional markers.[75] Free water fraction, calculated using a bi-tensor model, shows similar potential.[76,77] Diffusion metrics can be derived automatically and work in multi-site studies.[75] Tractography and structural connectomics have yet to demonstrate benefit over simpler diffusion metrics in SVD.[78]

Diffusion imaging depend on acquisition choices, field strength and scanner manufacturer. Such information should always be reported.

While sensitive to SVD brain damage, diffusion metrics lack specificity. At least in memory clinic patients the effect of SVD seems to far exceed the effect of Alzheimer's disease on diffusion imaging.[79] Analysis on the fibre-population level within voxels ("fixel-based analysis") might further improve specificity.[80] We endorse that diffusion alterations are reported objectively (see **supplemental panel 2** for recommended terms), avoiding assumptions about specific pathological processes.

Brain tissue susceptibility mapping

Altered tissue susceptibility can reflect iron deposition,[2] or other mineralization,[81] which is associated with multiple brain pathologies, including vascular and Alzheimer's disease.[82] Currently established measurement methods, such as T2*-weighted and susceptibility-weighted imaging, are semiquantitative. Quantitative techniques, such as R2* relaxometry and quantitative susceptibility mapping (QSM), are promising (**appendix**, page 9).[83]

Future directions

Research is needed to determine the added value of diffusion or quantitative measures beyond conventional MRI.

Markers of cerebrovascular function in SVD

Context

SVD features addressed hitherto primarily concern tissue changes consequent upon disease originating in the vasculature. Markers of brain vascular *function* provide complementary, reliable measures of alterations in SVD (**supplemental table 2**).

Perfusion and flow imaging

Tissue perfusion is the volume of blood delivered to a unit mass of tissue per minute (cerebral blood flow, CBF), while change in tissue perfusion to a stimulus is cerebrovascular reactivity, CVR. Dynamic susceptibility contrast (DSC) MRI for static perfusion imaging and dynamic contrast-enhanced (DCE) MRI for blood-brain barrier imaging use injection of exogenous contrast to measure CBF or blood-brain barrier (BBB) function;[84] while arterial spin-labelling MRI[85] uses magnetic labelling of blood for static perfusion imaging (**supplemental table 2**).

Cross-sectionally, lower CBF associates with more WMH, CBF is lower in WMH than normal-appearing white matter,[27] and CVR is reduced in WMH,[86] but longitudinal studies are sparse.[27]

Phase contrast MRI (and duplex ultrasound) can assess blood flow velocities and pulsatility in large cranial arteries and sinuses, estimate total cerebral blood supply, and whole brain CBF. Pulsatility reflects vascular ‘stiffness’ at the measurement point, but also cardiac output, upstream and downstream vascular and tissue compliance. While numerous studies show increased vascular pulsatility in SVD cross-sectionally, longitudinally, worsening SVD may predate pulsatility increase.[87]

Blood-brain barrier imaging

Evidence since 2013 indicates that subtle BBB dysfunction is an early pathophysiologic mechanism of SVD, although is not specific. Recent MRI techniques measure BBB dysfunction through leakage of a gadolinium-based contrast agent from vessels and modelling its distribution over time. Dedicated complex methods, necessary due to the low contrast agent leakage, have demonstrated subtle BBB leakage associated with WMH, cognitive impairment, regional hypoperfusion, and increased tissue diffusivity reflecting tissue degeneration.[88]

Standards for imaging and analysing SVD

Image acquisition

MRI acquisition approaches, preferred to CT in SVD, are summarised in **table 1**, including findings from our survey among STRIVE-2 members. Several consortia have proposed standardised image acquisition protocols.[89,90]

MRI acquisition at 3T has supplanted 1.5T imaging. Higher field strengths improve visualization of CMI[62] and perforating arteries,[91] especially at 7T,[92] but availability remains limited.

Three dimensional (3D) or volumetric MR acquisition are widely used in research, and increasingly in clinical practice. Isotropic 1-mm voxels are now common spatial resolution for structural imaging and important for quantitative analyses. Innovative multislice/multiband imaging methods have decreased acquisition times and improved resolution of many 2D methods.

The imaging acquisition core clinical protocol for SVD remains focused on T1-weighted, T2-weighted, FLAIR, diffusion, and susceptibility imaging.

Image analysis

There have been substantial advances in computational image analysis for all SVD lesion types, individually and in combination. International consortia such as HARNESS[30] and Mark VCID[90] have proposed frameworks for implementing image analysis tools that cover technical (scan-rescan repeatability, inter-scanner reproducibility) and clinical (proof-of-principle, proof-of-effectiveness) validation, with systematic validation efforts ongoing.[75,90]

Technical validation of imaging biomarker candidates

For almost all feature types, some (semi)automatic image analysis methods are available. Several (**table 2, supplemental table 1**) demonstrate good reliabiliy in limited settings but not yet in multiple sites or acquisition protocols. True technical validation requires test-retest (scan-rescan) repeatability, inter-site reproducibility across different scanners, and inter-rater reliability among analysts at participating sites.[75]

Some datasets with 'ground-truth' annotation are available for WMH,[93] lacunes, PVS, and CMB, to aid algorithm development and validation. Extensive testing is needed to determine the performance in large datasets with full spectra of SVD.

Application of machine learning / artificial intelligence (AI) methods

Machine learning tools should improve SVD quantification, but availability of appropriately annotated datasets, ability to handle real-life image acquisition/quality variability, and wide range of pathophysiological variations remain challenging. Linking AI quantification of SVD markers to functional and cognitive outcomes,[94] and enabling deeper insights into impacts of SVD on stroke,[95] are ongoing.

SVD measures in clinical trials

SVD features have been used as outcome measures in clinical trials[96] with some recent success (INFINITY[97] and SPRINT-MIND[98] substudies found slight reductions in WMH progression with intensive blood pressure reduction), although many trials using SVD features as outcomes were neutral.

Potential advantages of imaging outcomes include reduced sample size and biological relevance. Increased statistical power for longitudinal change compared with some clinical endpoints has been shown for WMH volume and diffusion metrics, such as PSMD[96] in observational studies, although some recent clinical measures (e.g., 7-level ordinal cognitive status score) are promising. Limitations of imaging outcomes include missing data, slow recruitment, increased trial costs, reduced generalisability, and (unless fully validated as surrogate endpoint) SVD features cannot replace clinical outcomes.[3] Optimal outcomes for clinical trials in SVD remain to be determined.

Since SVD burden is a strong outcome predictor, randomisation should be balanced on baseline SVD severity in clinical trials by stratifying on the SVD feature of interest plus other demographic/prognostic variables. This is particularly important if *change in an SVD feature* is a trial outcome.

Systematic frameworks have been proposed SVD imaging features for use in clinical trials, such as the HARNESS and FINESSE initiatives, to which the interested reader is referred for more information.[30,96]

Reporting standards for vascular findings on neuroimaging

We updated the reporting standards established in STRIVE-1, and available on the EQUATOR Network. These are summarised in **supplemental panel 3**. We encourage investigators to use the proposed terms and definitions in future studies. Adherence to the proposed reporting guidelines will increase comparability of future studies, thus facilitating meta-analyses and large-scale data analyses.

Future developments and challenges

Continually emerging SVD markers and methods may help differentiate between, or quantify, SVD and other pathologies in mixed disease, allowing faster or more consistent estimation of SVD severity, and change over time. Immediate future objectives (**supplemental panel 4**) are to differentiate RSSI due to intrinsic small vessel from non-intrinsic causes, determine the intrinsic small vessel pathology causing RSSI and DWI+ SVD features, identify the pathology that causes SVD (e.g., WMH) more gradually, determine risk factors for secondary brain damage from SVD features, and interventions to prevent, delay (or even reverse) SVD progression. Studies in low- and middle-income countries where SVD is common can facilitate our understanding of pathology and disease modifiers,[99] including genetic risk factors.[100]

Sophisticated imaging can facilitate pathophysiological and clinical insight, but has costs: it is not widely available; increases scan times; which may affect patient comfort, compliance or willingness to participate; has more missing data; and restricted generalisability. Studies that require imaging should balance pragmatism against perfectionism. New methods should demonstrate a clear benefit over existing markers for the intended use.

Conclusions

The steady evolution of knowledge in 10 years since STRIVE-1 has identified new SVD features, structural and functional biomarkers, accelerating understanding of SVD pathophysiology and vascular causes of neurodegeneration, bringing opportunities for prevention and treatment ever closer. We encourage use of these standards in studies of SVD and in neurodegenerative diseases, including where SVD may co-exist with several other common pathologies. They will help translate new findings into clinical practice. The challenge is to remain anchored in careful methods to ensure that truly relevant and informative findings are widely used in research and clinical practice.

These standards arose from consensus amongst many experts using rigorous methods. While the evidence base has advanced since 2013, some recommendations rely on sparse evidence in this rapidly advancing field. We did not include some very recently-described features or topics in STRIVE-2, since they are too recent, or the evidence-base for SVD is still very limited (e.g. amyloid or tau Positron Emission Tomography imaging). However, the field is moving ever-faster, and common pathologies frequently co-occur and likely interact emphasising the need for more research at these disease interfaces. More work is critical to strengthen the evidence, and bridge gaps in understanding of SVD pathophysiology. Promoting studies in less well-researched populations and regions will provide more representative and complete understanding of SVD.

Contributors

All authors contributed to the manuscript through attendance at the two virtual workshops, participation in specific workgroups, writing and editing the manuscript, and providing approval for final submission. JMW, MDi, ESS and MDu coordinated the overall process, organised the two workshops, coordinated the manuscript preparation, and finalised the paper for submission. YZ, RA, OHD, and HSM were external advisers who joined after the second workshop, read the manuscript draft in detail, provided in-depth critique, and approved the final paper for submission. Workgroup compositions are reported in the **appendix** (page 3f).

Declaration of interests

Actual or potential conflict of interest directly related to this work: HB: JLK (stocks). The other authors report no conflict of interest directly related to this work, but here declare interests and relationships outside the submitted work. MDu: MIAC AG (employment), Roche (consultant), Biogen (scientific advisory board), Hovid Berhad (adjudication board), Bayer Vital, Sanofi Genzyme (speaker honoraria), VasCog society (executive committee). GJB: Nestle HealthScience, Boehringer Ingelheim (consultant), European Stroke Organization, World Stroke Organization (scientific program committee). AB: Eisai, Roche (scientific advisory board), Biogen (scientific advisory board), Neurology, International Journal of Stroke (editorial board). CCh: "Moleac (consultant, research support), Cerecin, Actinogen, Eisai (scientific advisory board), World Stroke Organisation Future Leaders Programme (co-chair), Asian Society Against Dementia (chairman), Asian Oceanian Association of Neurology (secretary-treasurer). CCo: Biogen (scientific advisory board), BMS (speaker honoraria and international steering committee), Amgen (speaker honoraria), Stroke (associate editor). SD: European Stroke Organization (programme committee), World Stroke Organization (board of directors). EJ: European Stroke Organization (program committee, dementia committee, session chair, invited speaker), Abbvie Fondation Santé et Perspective (clinical research support). NSR: National Institutes of Health (U19NS115388, principal investigator), American Academy of Neurology (chair, science committee), AAN Institute Board member (ex officio); American Heart Association (ISC program committee), Stroke (associate editor), UptoDate (contributor). RAS: Recursion Pharmaceuticals, Bioxodes, PHRI McMaster University (consultant), European Stroke Organisation (workshop convenor, teaching course organiser). HB: Astrazeneca, AstraZeneca Korea Ltd, Bayer Korea, Boehringer Ingelheim Korea, Bristol Myers Squibb, Chong Gun Dang Pharmaceutical Corp., Daiichi Sankyo, Dong-A ST, GNT Pharma, Jeil Pharmaceutical Co. Ltd, Korean Drug Co. Ltd, SAMJIN Pharm., Shinpoong Pharm. Co. Ltd, Takeda Pharmaceuticals Korea Co. Lt., and Yuhan

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Figures, Tables and Panels

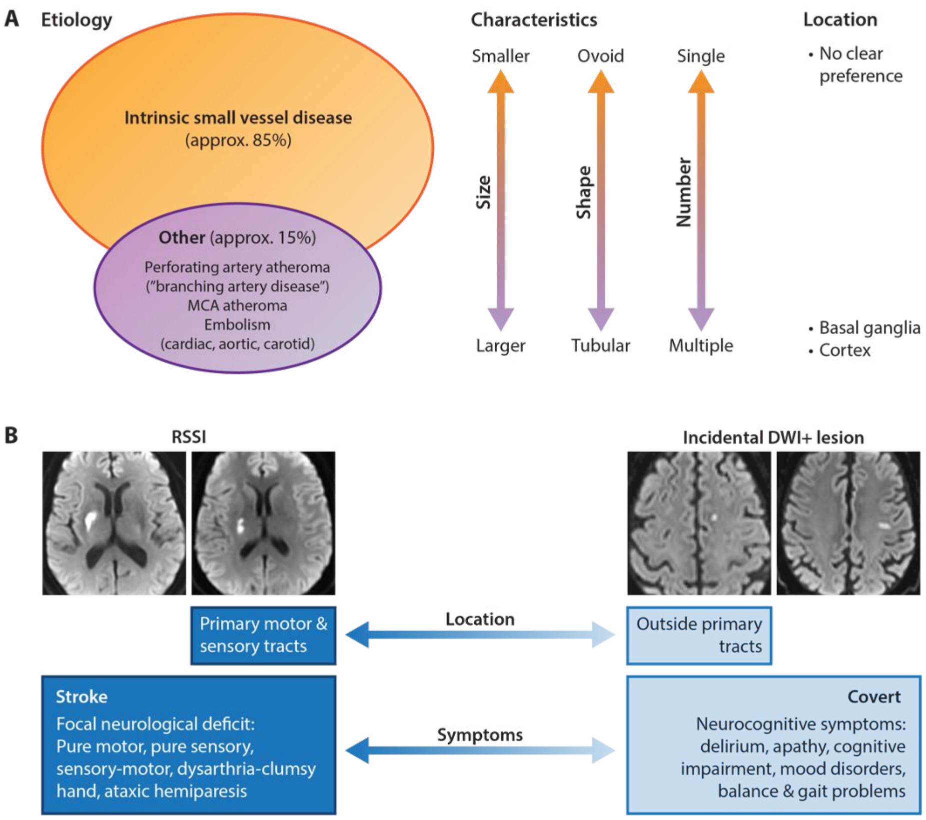


Figure 1: Neuroimaging features differentiating intrinsic SVD from other aetiologies and RSSIs from incidental DWI+ lesions. A. About 15% of RSSI or incidental DWI+ lesions are due to emboli from the heart or atheroma in the large head and neck arteries. These are more likely to be larger (although there is no size cut off), tubular (along the trajectory of the perforating artery) rather than round or ovoid, associated with concurrent acute lesions in other brain regions, and in the basal ganglia rather than the centrum semiovale. The presence of one or more acute or old infarcts in the cortex in addition to a small subcortical infarct particularly increases the likelihood of embolism and these should be carefully sought. B. Lesions which cause discrete stroke symptoms (RSSI) are usually in the primary motor and sensory pathways (depicted on the left). Covert lesions are usually outside those pathways or very small (depicted on the right along with the symptoms).

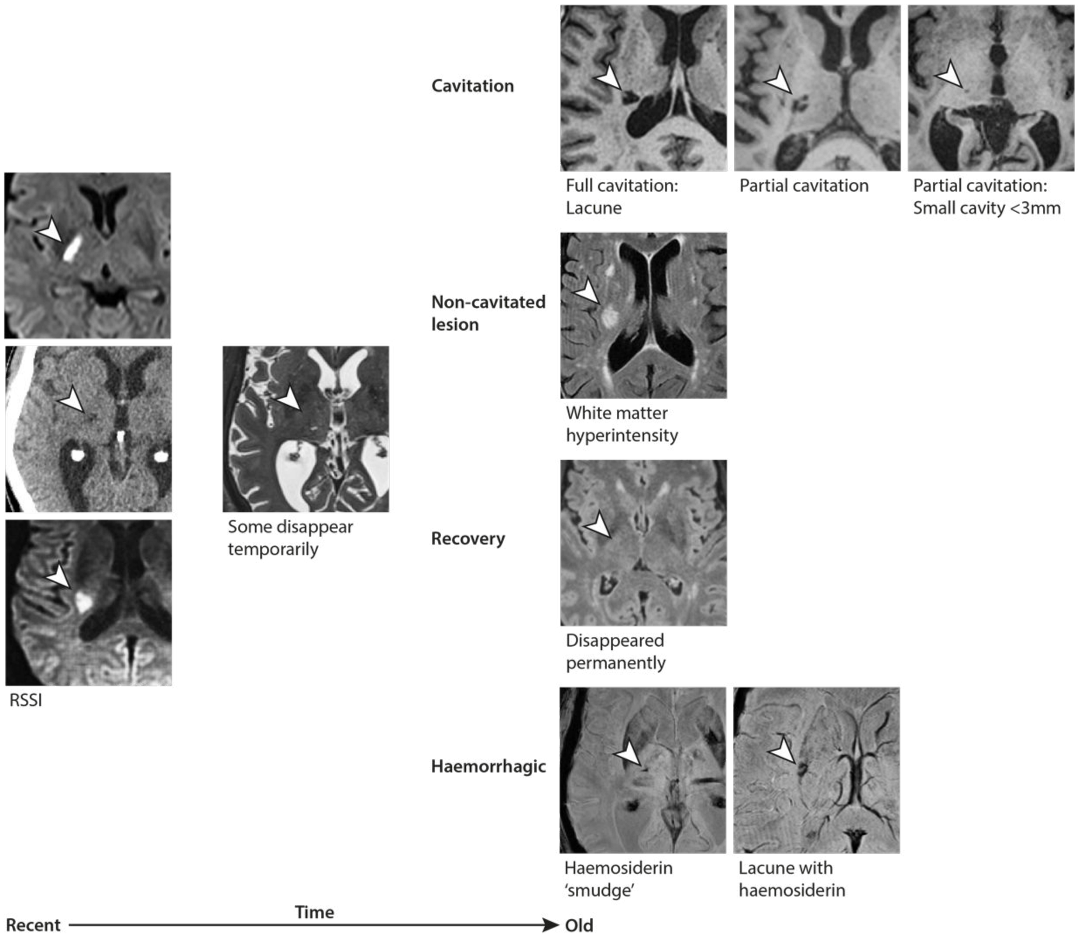
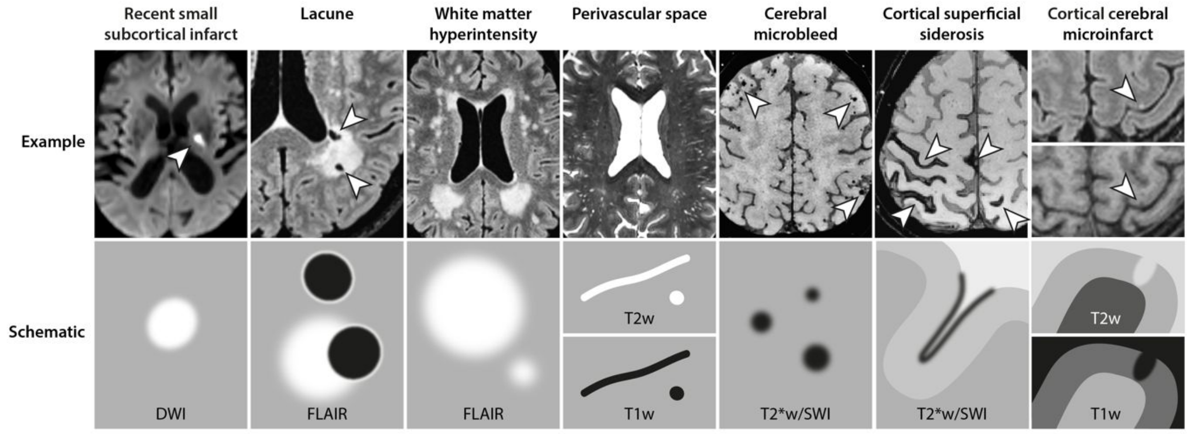


Figure 2: Range of recent (days to weeks) to long term (months to years) appearances of recent small subcortical infarcts and incidental DWI-positive lesions. Illustrates the range of acute SVD lesion appearances (L to R), from RSSI presenting as stroke and their long-term fates (right hand columns): some lesions may disappear temporarily while passing through a period of 'fogging' (second from L column, white arrow head) before reaching end-stage permanent appearance after some months or longer (right-hand columns), ranging from (top row) complete cavitation (left, lacune), partial cavitation (middle), tiny lacune <3mm diameter (right); no cavitation (WMH or grey matter FLAIR hyperintensity), disappear completely (recovery), or a residual haemosiderin small (T2* hypointense) 'smudge' (bottom row, L, white arrow head), or haemosidering rim (right, arrowhead) which could be mistaken for an old haemorrhage). More detailed images are presented in the appendix.



	Recent small subcortical infarct	Lacune	White matter hyperintensity	Perivascular space	Cerebral microbleed	Cortical superficial siderosis	Cortical cerebral microinfarct
Diameter	≤ 20 mm	3-15 mm	Variable	≤ 2 mm	≤ 10 mm	Variable	< 4 mm
DWI	↑	↔/(↓)	↔	↔	↔	↔	↔ / ↑ (acute)
FLAIR	↑	↓	↑	↓ / ↔	↔	↔	↑ / ↓
T2w	↑	↑	↑	↑	↔	↔	↑
T1w	↓	↓	↔/(↓)	↓	↔	↔	↓
T2*w/SWI	↔	↔	↑	↔	↓↓	↓↓	↔

↑ Hyperintense signal ↓ Hypointense signal ↔ Isointense signal

Figure 3: MRI features of small vessel disease. Shows examples (upper), schematic representation (middle), and summary of MRI characteristics of SVD features. See supplemental figures for examples of the emerging feature incidental DWI+ lesion. DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery. SWI=susceptibility-weighted imaging. T1w=T1-weighted. T2w=T2-weighted. T2*w=T2-weighted.

Panel 1: Glossary of proposed terms and definitions for neuroimaging features of small vessel disease

Recent small subcortical infarct:
Neuroimaging evidence of a recent infarction in the territory of one perforating arteriole, with imaging features and clinical symptoms consistent with a lesion occurring within the previous few weeks.

Lacune (of presumed vascular origin)
Round or ovoid, subcortical, fluid filled (similar signal to CSF) cavity up to 15 mm in diameter likely to be the end tissue damage from a recent small subcortical infarct, small subcortical haemorrhage, incidental DWI+ lesion, or end-stage cavitation in a WMH.

White matter hyperintensity (of presumed vascular origin)
Signal abnormality of variable size in the white matter showing the following characteristics: hyperintense on T2-weighted images like FLAIR without cavitation (signal different from CSF). Lesions in the subcortical grey matter or brain stem are not included into this category unless explicitly stated – where deep grey matter and brainstem hyperintensities are included as well, the collective name should be "subcortical hyperintensities".

Perivascular space
Fluid filled space, which follows the typical course of a vessel penetrating / traversing the brain through grey or white matter; has signal intensity similar to CSF on all sequences; has a round, ovoid, or linear shape (depending on the slice direction) with a diameter commonly not exceeding 2 mm when imaged perpendicular to the course of the vessel.

Cerebral microbleed
Small (usually 2 mm – 5 mm or sometimes 10 mm in size) areas of signal void with associated "blooming" on T2* or other MRI sequences sensitive to susceptibility effects.

Cortical superficial siderosis
Thin areas of hypointensity on T2*, or other MRI sequences sensitive to susceptibility effects, in or overlying the superficial cortex, which may be confined to one gyrus and adjacent sulci, or occasionally more widespread affecting several brain regions.

Brain atrophy
Brain volume loss, not related to a specific macroscopic focal injury such as trauma or infarction. Thus, the latter is not included in this measure unless explicitly stated.

Summary SVD score
A grouping of accepted SVD markers that serves to summarise SVD brain burden into a single index, score, or unitary construct.

(Old) cortical cerebral microinfarct
Small lesions appearing hypointense on T1-weighted, hyperintense on T2-weighted/FLAIR, and isointense on T2*-weighted MRI, operationally defined to be strictly cortical and with an upper size limit of 4 mm.

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Table 1: Proposed image acquisition standards for neuroimaging features of SVD.

	Purpose*	**Orientation**	**Target slice thickness, in-plane resolution**	**Comment**
Minimum essential sequences (*e.g.*, for clinical or large-scale epidemiological studies, generally available on most MR scanners)				
T1-weighted	To discriminate lacunes from PVS; for discriminating grey from white matter, for detecting CMI, and for measuring brain tissue volumes	3D	1-mm isotropic voxels	Allows post-acquisition reformatting for visualising full extent and orientation of many features
Diffusion imaging (typically with ≤6 encoded directions and one *b*-value shell)	To detect acute ischaemic lesions; positive for up to several weeks after cerebrovascular event	2D axial	3-5 mm, 1-2 mm x 1-2 mm	Reduced signal on apparent diffusion coefficient map helps identifying acute from subacute or old lesions. Optional acquisition of additional diffusion-encoding directions allows more detailed characterisation but with increased acquisition time (see research sequences)
T2-weighted	To characterise brain structure; to differentiate lacunes from WMH and PVS; to identify old infarcts	2D axial or 3D	2D: 1-2 mm, 1 mm x 1 mm 3D: 1-mm isotropic voxels	Allows post-acquisition reformatting for visualising full extent and orientation of many lesions
FLAIR	To identify WMH, established cortical or large subcortical infarcts, and CMI; to differentiate WMH from PVS and lacunes	2D axial or 3D	2D: 1-2 mm, 1 mm x 1 mm 3D: 1-mm isotropic voxels	Allows post-acquisition reformatting for visualising full extent and orientation of many lesions
Susceptibility imaging (*select at least one*)				
a) T2*-weighted GRE	To detect intracerebral haemorrhage, CMB, and cSS	2D axial	3-5 mm, 1 mm x 1 mm	Reliable routine sequence for detection of haemorrhagic markers
b) SWI or equivalent	To detect intracerebral haemorrhage, CMB, and cSS. Potentially more sensitive to haemosiderin. To measure intracranial volume (3D approaches)	2D axial or 3D	2D: 3-5 mm, 1 mm x 1 mm 3D: 1-mm isotropic voxels	Enhanced detection of CMB compared to T2*-weighted GRE imaging but more sensitive to artifacts including motion
MR angiography (MRA)	To detect stenosis in larger vessel in neck and brain (i.e., vertebral, basilar, internal carotid, middle cerebral, anterior cerebral, or posterior cerebral arteries)	3D post contrast or 3D TOF (intracranial)	1-mm isotropic voxels	Axial, coronal, sagittal reformats and projections examined, Only large vessels visible at 1.5 T or 3 T (*see mMRA below for imaging smaller arteries*)
Research sequences (*i.e.*, require research expertise)				
Advanced diffusion imaging (typically with many directions, higher *b*-values, and multiple shells)	To enable sophisticated (biophysical) modelling of microscopic tissue changes	2D axial	≤ 2-mm isotropic voxels	Allows for more advanced modelling of water diffusion in white matter that may provide superior quantitative measurements
Advanced susceptibility imaging (R2* mapping or QSM)	To provide quantitative measures of susceptibility changes in tissue	2D axial or 3D	2D: 3-5 mm, 2 mm x 2 mm 3D: 1-mm isotropic voxels	Uses an SWI-like GRE or emerging 3D EPI acquisition, but needs post-processing to produce estimates of changes to R2* or estimates of susceptibility

Perfusion imaging				
a) ASL	To measure blood perfusion in brain tissue; quantitative, with assumptions	2D axial or 3D (preferred)	2D: 3-5 mm, 2 mm x 2 mm 3D: ≤ 8 mm x 4 mm x 4 mm voxels	Acquisition and processing fairly standardised; Useful for GM perfusion visual or quantitative assessment; contrast injection not needed
b) DCE or DSC	To semi-quantitatively measure blood perfusion in brain tissue	2D axial	3-5 mm, 2 mm x 2 mm	Needs intravenous contrast injection and complex post-processing; optimum acquisition and processing not yet confirmed for T1- (DCE) or T2*-weighted (DSC) approaches
Permeability imaging	To estimate permeability-surface area product of the blood–brain barrier	2D axial or 3D; sequential pre- and post-contrast	3-5 mm, 2 mm x 2 mm 2-5mm, 1-2 x 1-2 mm	Needs intravenous contrast injection; complex post-processing; methods are improving
Brain activation imaging using task-based fMRI or resting-state fMRI	To measure brain function or vascular reactivity	2D axial	3-5 mm, 2 mm x 2 mm or approx. 3-mm isotropic voxels	Complex set up, acquisition and processing, plus need to provide appropriate stimuli in task-based fMRI
Magnetization transfer (MT) imaging	To detect demyelination and axonal loss	2D axial or 3D	2D: 3-5 mm, 1 mm x 1 mm 3D: 1-mm isotropic voxels	Requires experience in acquisition and interpretation; two measurements (with and without MT-pulse); MT ratio is confounded by T1 and $B1^+$
R1 Mapping	To estimate water content of tissue	2D axial or 3D	2D: 3-5 mm, 2 mm x 2 mm 3D: 1-mm isotropic voxels	Requires experience in acquisition and interpretation; also sensitive to myelin, paramagnetics, so not specific to water
Flow-based Imaging (e.g., PC)	To measure blood flow dynamics and pulsatility, typically in larger vessels in the neck and brain.	uncertain, emerging method	uncertain, emerging method	Promising experimental approach
mMRA (micro-atheroma/arteriolar Imaging)	To visualise perforating artery wall and lumen anatomy, and atheroma	uncertain, emerging method	uncertain, emerging method	Promising experimental approach that requires >3 T scanner
Double inversion recovery (DIR)	To enhance detection of CMI	uncertain, emerging method	uncertain, emerging method	Promising experimental approach that requires ≥3 T scanner

ASL=arterial spin labelling. CMB-cerebral microbleed. CMI-cortical microinfarct. cSS=cortical superficial siderosis. DCE=dynamic contrast-enhancement. DIR=double inversion recovery. DSC=dynamic susceptibility contrast. FLAIR=fluid-attenuated inversion recovery. fMRI=functional MRI. GRE=gradient-recalled echo. MRA=magnetic resonance angiography. MP-RAGE=magnetisation-prepared rapid acquisition with gradient echo. MT=magnetisation transfer. PC=phase contrast. PVS=perivascular space. QSM=quantitative susceptibility mapping. R1=1/T1. R2*=1/T2*. SWI=susceptibility-weighted imaging. TOF=Time of flight. WMH=white matter hyperintensity

*MRI at 3.0 T is preferred, minimum recommended field strength is 1.5 T. However, these standards are listed as minimum and essential to research-only applications. These categories are not absolute; purposes are variable, and will vary with investigators' interest, expertise, and available technology.

Table 2: Image Analysis approaches for small vessel disease

Endpoint	Measure of interest	Analysis standard	Suggested quality metrics	Automation status	Validation status	General comments
Point lesions (apparent size of a few voxels)	(old) cortical cerebral microinfarct	Visual count	Recall, false positive count, F1 Kappa and ICC are used but can be sensitive to outliers.	None, besides one semi-automatic single-cohort AI approach	None.	Depending on the apparent size of a lesion, it can be more appropriate to consider it as a point lesion or a volumetric lesion (or both). Quality metrics should be chosen accordingly.
	Cerebral microbleed	Validated visual rating scales (e.g., MARS, BOMBS)		Various semi-automatic and fully automatic approaches. False positive censoring needed.	Some studies on repeatability and reproducibility, mostly in single centres. Technical validation in biomedical challenges is pending.	
	Perivascular space	Visual rating, some validated rating scales		Some automatic approaches.	Technical validation in biomedical challenges is pending.	
Volumetric lesions (apparent size of many voxels)	Lacune	Visual count	Dice Similarity Coefficient, (modified) Hausdorff distance (or other surface distances), volumetric similarity.	A few automatic approaches.	Technical validation in biomedical challenges is pending.	
	Recent small subcortical infarct	Visual inspection/count, manual delineations		Very few automatic approaches.	None.	
	White matter hyperintensity	Validated visual rating scales (Fazekas, ARWMC), manual delineations		Many semi and fully automated approaches	Repeatability and reproducibility established in multiple centres and biomedical challenges.	

Non-lesion outcomes	Brain atrophy	Validated visual rating scales (e.g., GCA).	Intra/inter observer variation. For automatic methods: see volumetric lesions.	Many fully automated approaches. Some require manual corrections.	Repeatability and reproducibility established in multiple centres and biomedical challenges.	
	Perfusion	Visual inspection	Unknown	Unknown	Unknown	Various parameters can be derived with dedicated software packages, but objective quality metrics and technical validation is currently lacking or rare.
	Connectivity	Visual inspection	Unknown	Some software packages exist for individual steps of the analysis workflow.	Unknown	
	Microstructural integrity and diffusion imaging-based metrics	Unknown	ICC or Bland-Altman to evaluate repeatability.	Many semi-automated and some fully automated approaches.	Some studies on a subset of possible measures-of-interest show good (NODDI) to excellent (DTI, DKI) repeatability and reproducibility	Harmonisation of acquisition parameters is advised in prospective multi-centre studies.
	Lesion-symptom mapping; directly inferring clinical outcomes from (pre-processed) images.	Comparison to clinical outcomes	Cross-validation machine learning	Some software packages for (voxel-based) lesion-symptom mapping		

AI=artificial intelligence. ARWMC=age-related white matter changes. DKI=diffusion kurtosis imaging. DTI=diffusion tensor imaging. GCA= Global cortical atrophy. ICC=intra-class correlation coefficient. NODDI=neurite orientation dispersion and density imaging.

STRIVE-2 Appendix

Table of Contents

Supplemental methods

Approach

We established a diverse group of 50 experts consisting of original contributors to STRIVE-1 and new contributors, from Europe, Asia, Australia, and North America, with expertise including neurology, neuroradiology, neuropathology, epidemiology, neuropsychology, medical physics, image analysis, stroke, gerontology, and dementia. We considered a high level of current research activity in SVD to be an essential criterion for participation in STRIVE-2. We allocated the 50 experts to 10 topic-focussed working groups each with a lead (**see below**). Each group included emerging and senior researchers, a mix of expertise and geographical location.

In May 2021, we convened in a one-day virtual meeting to discuss advances since 2013 in understanding of core SVD features described in STRIVE-1, including imaging features that were emerging at the time of publication that are now established, novel imaging features which have emerged since publication, structural and functional metrics, and image acquisition and analysis methods. We focused primarily on MRI methods but also considered CT. We did not include Positron Emission Tomography (PET) or other non-MRI/non-CT based methods due to space and a relative lack of data on SVD in the case of PET imaging. Prior to the meeting, each group prepared a short presentation of the main advances in their topic, which were each then discussed in detail by the group.

Following the meeting, each topic workgroup prepared text summarising the new knowledge since 2013. We performed systematic searches to identify relevant literature and to assess for harmonisation of terminologies since 2013 (**see below**). Using a questionnaire that adhered to the format of the STRIVE-1 acquisition recommendations,[3] we surveyed the STRIVE group on their current clinical and research acquisition protocols. Survey response rate was 41/50 (82%) with 22 respondents being primarily clinicians and 29 being primarily research; 11 were clinician-researchers.

We held a second meeting in October 2022 to present and discuss the findings, particularly to carefully consider if we should propose revised terminology for any features. Like STRIVE-1, new external advisors originating from Africa, South America, China, and Europe joined the group for additional review and comment.

Methods were based on the Delphi principle, where workgroups discussed and prepared a text proposal, followed by two workshops, and an anonymous online survey on open topics, before editing and finalising the consensus document.[3]

An important purpose of STRIVE-1 was to harmonise SVD terminology to improve scientific communication and thus accelerate understanding of SVD pathophysiology, epidemiology, and treatment. STRIVE-2 workgroups, therefore, considered if the STRIVE-1 terminology required revision and where new scientific knowledge was available. We provided a template to assist in preparation of text and, as in STRIVE-1, to focus on achieving a consensus on terminology, definitions, image acquisition, analysis and reporting standards, following principles endorsed by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Guideline Network, and to update the current STRIVE-1 entry on EQUATOR (Reporting guidelines | The EQUATOR Network, equator-network.org).

As in STRIVE-1, we agreed the important principle that terms and definitions should *reflect the imaging characteristics and avoid presumptions about mechanisms or pathological changes, especially when these are incompletely understood, so as not to prejudice future studies of SVD* – i.e., to *'describe what you see and not what you think you see'*. Finally, since judgement is required in the use of any classification system and understanding of the terminology and consistent use is needed to improve clinical practice, we provide further details in this **appendix** including features with unusual appearances, caveats in interpretation, temporal evolution of, and boundaries between features.

Composition of working groups

<u>Adoption of STRIVE-1 terminology</u>
Brown, Rosalind
Helmer, Karl
Jokinen, Hanna
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Literature search strategy

Based on a systematic literature search in PubMed, we aimed to evaluate the adoption of STRIVE-1 terminology, determine the success of STRIVE-1 in harmonising the SVD field and identify suboptimal terms. Specifically, we determined the number of manuscripts that reported on the main six SVD lesion types described in STRIVE-1 and assessed whether STRIVE terminology was adopted or whether non-preferred terminology was used in the title and/or abstract. Non-preferred variants were both retrieved from STRIVE-1 as well as determined by expert opinion. Specificity (i.e., relevance to the SVD field) was prioritised over sensitivity. Therefore, the following MeSH terms (all exploded) were added to the search code: "cerebral small vessel diseases", "dementia, vascular", "leukoaraiosis", "stroke", "magnetic resonance imaging" and "neuroimaging". Furthermore, results were restricted to human studies published in English. Additional MeSH terms were sometimes included to optimise the search results (i.e. MeSH terms "brain", "cerebral hemorrhage", and "tomography, x ray computed") as well as common abbreviations for several terms. The final combinations of terms for the main six SVD lesion types were reached after performing a series of searches in which different terms were added to or removed from the initial STRIVE-1 search code while evaluating whether key relevant papers were included based on expert opinion or recent systematic reviews. This was done for each lesion type separately. The exact search strategies for the main six SVD lesion types are given below. Searches were performed between 16 November and 2 December 2022. Except for "recent small subcortical infarcts" and "lacunes of presumed vascular origin", each member of the working group independently reviewed one SVD lesion type. Results are presented in **supplemental figure 1**.

Recent small subcortical infarct and lacune of presumed vascular origin

(("**recent small subcortical infarct***"[Title/Abstract] OR "**rssi***"[Title/Abstract]) AND ("cerebral small vessel diseases"[MeSH Terms] OR "dementia, vascular"[MeSH Terms] OR "stroke"[MeSH Terms] OR "leukoaraiosis"[MeSH Terms] OR "brain"[MeSH Terms]) AND ("magnetic resonance imaging"[MeSH Terms] OR "tomography, x ray computed"[MeSH Terms] OR "neuroimaging"[MeSH Terms]) AND 2014/01/01:2021/12/31[Date - Publication]) AND ((humans[Filter]) AND (english[Filter]))

((**Lacune of presumed vascular origin**[Title/Abstract]) OR (**Lacunes of presumed vascular origin**[Title/Abstract])) AND (("cerebral small vessel diseases"[MeSH Terms]) OR ("dementia, vascular"[MeSH Terms]) OR ("stroke"[MeSH Terms]) OR ("leukoaraiosis"[MeSH Terms]) OR ("brain"[MeSH Terms])) AND (("magnetic resonance imaging"[MeSH Terms]) OR ("tomography, x ray computed"[MeSH Terms]) OR ("neuroimaging"[MeSH Terms])) AND (("2014/01/01"[Date - Publication] : "2021/12/31"[Date - Publication])) AND ((humans[Filter]) AND (english[Filter]))

For the non-preferred terms, the searches were otherwise identical, but the keyword “recent small subcortical infarct*” was replaced with “lacunar infarct*”, “subcortical infarct*”, “lacune*”, “silent brain infarct*”, and “lacunar lesion*”.

Of note, the non-preferred term "subcortical infarct" overlaps with the full names for CADASIL and CARASIL. and the preferred term recent small subcortical infarct. Therefore, from the search results for the term "subcortical infarct", subsequently manuscripts were removed if they were part of the search results only due to mentioning the full names for CADASIL or CARASIL, or recent small subcortical infarct. In total, 169 manuscripts were removed. Similarly, due to overlap between proposed and non-preferred terms (i.e."*lacune* of presumed vascular origin" and "*lacune*"), manuscripts using the proposed terminology in the title or abstract were subsequently removed from the search results for "lacune".

White matter hyperintensity of presumed vascular origin

(("**white matter hyperintens***"[Title/Abstract]) OR ("**WMH**"[Title/Abstract])) AND (("cerebral small vessel diseases"[MeSH Terms]) OR ("dementia, vascular"[MeSH Terms]) OR ("stroke"[MeSH Terms]) OR ("leukoaraiosis"[MeSH Terms])) AND (("magnetic resonance imaging"[MeSH Terms]) OR ("tomography, x ray computed"[MeSH Terms]) OR ("neuroimaging"[MeSH Terms])) AND (("2014/01/01"[Date - Publication] : "2021/12/31"[Date - Publication])) AND ((humans[Filter]) AND (english[Filter]))

For the non-preferred terms, the searches were otherwise identical, but the keyword “white matter hyperintens* was replaced by “leukoaraiosis”, "white matter lesion*", "white matter chang*", “leukoencephalopath*", "white matter disease*", "white matter damage*" or “ischemic white matter disease*”. Citations with leukoencephalopathy only appearing in the full names of CADASIL/CARASIL and studies of non-SVD-related conditions were excluded. The search results for ischaemic and ischemic white matter disease were combined.

Notably, the longer version “white matter hyperintensities of presumed vascular origin” has been rarely included in the titles and abstracts of published articles. However, it may have been used in the main text, where our search did not extend.

Cerebral microbleed

("**cerebral microbleed***"[Title/Abstract] OR "**CMB**"[Title/Abstract]) AND ("cerebral small vessel diseases"[MeSH Terms] OR "cerebral hemorrhage"[MeSH Terms] OR "leukoaraiosis"[MeSH Terms] OR "dementia, vascular"[MeSH Terms] OR stroke[MeSH Terms]) AND ("magnetic resonance imaging"[MeSH Terms] OR "tomography, x-ray computed"[MeSH Terms] OR "neuroimaging"[MeSH Terms]) AND (("2014/01/01"[Date - Publication] : "2021/12/31"[Date - Publication])) AND ((humans[Filter]) AND (english[Filter]))

Searching for "microbleed" alone included articles that used the proposed term "cerebral microbleed", though "microbleed" was sometimes used in the title, while the proposed term "cerebral microbleed" was used in the abstract. To account for this, the search for the term "microbleed" was modified to (NOT "cerebral microbleed*"[Title/Abstract] OR "CMB"[Title/Abstract]) to determine the number of articles that used "microbleed" alone. Unlike "CMB", the abbreviation "MB" was not included in the search code as this would result in many irrelevant papers (e.g., on thro*mb*olysis). Non-preferred terms "microhemorrhage" and its variant spelling "microhaemorrhage", and "dot-like hemosiderin" and its variant" dot-like haemosiderin" were also searched (identical search as above after the initial "AND").

Perivascular space

("**Perivascular space***"[Title/Abstract] OR "**PVS**"[Title/Abstract]) AND (("cerebral small vessel diseases"[MeSH Terms]) OR ("dementia, vascular"[MeSH Terms]) OR ("stroke"[MeSH Terms]) OR ("leukoaraiosis"[MeSH Terms])) AND (("magnetic resonance imaging"[MeSH Terms]) OR ("neuroimaging"[MeSH Terms])) AND (("2014/01/01"[Date - Publication] : "2021/12/31"[Date - Publication])) AND ((humans[Filter]) AND (english[Filter]))

N = 9 manuscripts were deleted from the search results as PVS was used as a different abbreviation (e.g., pulmonary veins, prominent vessel sign, prominent veins). The non-preferred terms "Virchow Robin" or "Virchow-Robin", "type 3 lacune" and "état crible", were searched using the same filters.

Of note, most papers that featured Virchow Robin space referred primarily to PVS and stated Virchow Robin space as an alternative name. Of the 186 abstracts using the term "perivascular space", 103 referred to PVS as "enlarged"," or dilated". These terms were noted as unsuitable in STRIVE-1 as although it is larger PVS that become visible on neuroimaging, the lack of understanding of the clinical implications of PVS size and the dependence of PVS visibility on the imaging used between different studies was deemed problematical.

Brain atrophy

((“**brain atroph***”[Title/Abstract]) OR (“**cerebral atroph***” [Title/Abstract])) AND (("cerebral small vessel diseases"[MeSH Terms]) OR ("dementia, vascular"[MeSH Terms]) OR ("stroke"[MeSH Terms]) OR ("leukoaraiosis"[MeSH Terms])) AND (("magnetic resonance imaging"[MeSH Terms]) OR ("neuroimaging"[MeSH Terms])) AND (("2014/01/01"[Date - Publication] : "2021/12/31"[Date - Publication])) AND ((humans[Filter]) AND (english[Filter]))

The less preferred term “brain volume” was searched for using the same filters, operationalised as “brain volum*”[Title/Abstract] or “cerebral volum*”[Title/Abstract].

Summary SVD score

((“cerebral small vessel disease” OR (“small vessel disease” AND (“brain” OR “cerebral”))) AND ("score" OR "multivariable" OR "markers" OR "total brain burden" OR "rating" OR "qualitative" OR "lacune" OR "lacunar infarct" OR "subcortical infarct" OR "subcortical stroke" OR "fazekas" OR "microbleed" OR "MARS" OR

"BOMBS" OR "perivascular space" OR "EPVS score" OR "white matter hyperintensity") AND ((("2012/01/01"[Date - Publication] : "2020/12/31"[Date - Publication])))

Microinfarct

("microinfarct"[Title/Abstract] OR "microinfarction’"[Title/Abstract] OR "microischemia’"[Title/Abstract] OR "microvascular ischemia"[Title/Abstract] OR "microvascular infarct "[Title/Abstract])

Supplemental text, tables and references

Recent small subcortical infarcts on CT imaging

While MRI remains the most accurate technique to detect RSSI, urgent MRI is not always available, and CT-based techniques (non-contrast CT, with or without CT-angiography and CT-perfusion) are commonly used to assess patients presenting acutely with stroke. The sensitivity of CT for RSSI is low in the first hours after symptom-onset but might improve with CT-perfusion if it shows a focal small hypoperfusion in the relevant brain region (**supplemental figure 2**).[8]

Incidental DWI-positive lesions

These emerging features have similar imaging characteristics to recent small subcortical infarcts (RSSI) when subcortical, show similar long-term outcomes to those of RSSI, and similar associations with increasing amounts of other cerebral small vessel disease (SVD) features as are seen with RSSI. Thus their prevalence is low in cross-sectional (older) population-based studies (0-1.5%),[1-3] but higher in patient cohorts with increasing symptomatology and SVD severity: patients with white matter hyperintensities of presumed vascular origin (WMH) and a history of lacunar stroke (8%), CADASIL (10.5%), probable cerebral amyloid angiopathy (CAA) (18%), or (sub)acute spontaneous intracerebral haemorrhage (ICH) (20%).[4-6]

Unlike RSSI, these incidental diffusion-weighted imaging-positive (DWI+) lesions are commonly not associated with discrete neurological (i.e., stroke-like) symptoms. They more commonly associate with subtle clinical manifestations, indicating that they are likely to be clinically relevant, perhaps representing 'active' vascular disease.[1,7]

Considering that the incidental DWI+ lesions are only visible on MRI up to 2-4 weeks after onset, the detection of only a few incidental DWI+ lesions on opportunistic MRI suggests the occurrence of these lesions may be higher relative to covert DWI+ lesions over time.[5,8-10]

Incidental DWI+ lesions may disappear, or evolve into WMH, lacunes, or CMI, thus partly explaining progression of these markers, further supporting an intrinsic small vessel abnormality as their underlying cause, similar to RSSI. However, as with RSSIs (**figure 1**), incidental DWI+ lesions may also reflect embolism, e.g., from carotid atherosclerotic stenosis awaiting revascularisation, or the heart.[11,12] As such, our understanding of the pathophysiology of these incidental DWI+ lesions remains incomplete.

Detection particularly of small incidental DWI+ lesions can be increased by using diffusion imaging with a high b-value (e.g., $b = 3000$ s/mm^2) compared to a standard diffusion-weighting of $b = 1000$ s/mm^2.[13]

Non-intrinsic vascular causes of recent small subcortical infarcts

Infrequent causes of RSSI include thromboembolism from cardiac or extracranial, intracranial large artery and arteriolar branch atheroma[14] (**figure 1**) which may be difficult to differentiate when multiple potential causes are present. Having more than one RSSI concurrently, especially when in multiple arterial territories, may indicate an embolic cause, however concurrent RSSI may occur in severe SVD without an identifiable embolic source.[15] A RSSI and concurrent acute cortical infarct, RSSI with axial diameter larger than 2 cm when acute, suggest a non-intrinsic cause.[14] Tubular long RSSI with inferior limit close to perforator origin may suggest parent artery or branch atheroma (see *Intracranial atherosclerosis* below).[16]

Perforating Arteries

Cerebral perforating arteries are small end-arteries which vascularise deep territories such as the basal ganglia, internal capsule, thalamus, and centrum semiovale white matter. Detection of these arteries and measurement of their blood flow velocity and pulsatility index have been shown to be feasible using ultra-high field MRI,[80] but techniques remain under development.[81]

Venules

Venules, described as hypointense vessels on gradient echo and susceptibility-weighted imaging, have been analysed with visual rating scales and computational measures at 3T and 7T.[36] Several assessment tools have been proposed but remain to be standardised, and longitudinal studies are unavailable. Venous collagenosis may be an underlying pathology that changes venule appearance on MRI,[29] but there is as yet no direct corroboration with venule imaging.

Intracranial atherosclerosis

Intracranial large artery disease has been associated with SVD and intracranial atherosclerosis and dolichoectasia (IAD),[17] the latter involving rarefaction of the tunica media elastic tissue and fragmentation of the internal elastic lamina.[18] IAD have been associated with RSSI, WMH, lacunes, cerebral microbleeds, atrophy and microinfarcts,[16,17,19] although it is unclear if these are direct associations and potentially causative, or co-associations due to shared risk factors, as seen with extracranial carotid stenosis.[20] One reason for questioning the directness of the relationship is that the RSSI often seems remote to the atheroma location,[21,22] with studies on this topic often not indicating if the RSSI was ipsilateral or contralateral to the IAD.

In addition to atheroma of parent arteries (usually middle cerebral artery [MCA] main stem or basilar artery) that might affect the basal perforating artery origins, atheroma may also occur in proximal perforating arteries, so called 'branch atheromatous disease' (BAD).[23] BAD is thought to be more likely in RSSI that are larger than 15 mm axial diameter and elongated or tubular in the infero-superior plane (e.g., 20 mm or more)[23] (**figure 1A**). However, the distinction in size between recent subcortical infarcts due to MCA atheroma or BAD and striatocapsular infarcts (due to MCA occlusion, either transient so too short to affect the superficial MCA territory, or where there are good collaterals that protect the superficial tissues) remains to be determined. Additionally, the proportion of tubular RSSI due to BAD versus intrinsic lipohyalinosis/fibrinoid necrosis is unknown. Advanced MRI sequences such as vessel wall imaging techniques with high-resolution MRI, ultrasmall superparamagnetic iron oxide (USPIO)-enhanced MRI to detect uptake into active atheroma, and 7T MRI are helping to visualise perforating artery structure, at least in the basal ganglia regions.[24,25]

Quantitative susceptibility mapping for measuring iron deposition

Quantitative susceptibility mapping (QSM) measures susceptibility change including due to cerebral iron deposition.[92] Altered iron deposition in basal ganglia, confirmed histologically, has been reported in CADASIL.[93] In sporadic SVD, iron deposition associates independently with cognitive impairments, suggesting that mineral deposition may be an indicator of small vessel pathology,[94] although not consistently.[95] Most R2* relaxometry methods use multiple gradient echo magnitude images. R2*, however, does not fully reflect local tissue magnetic properties,[92] making interpretation of R2* relaxometry difficult. Both methods also show increased tissue susceptibility in Alzheimer's

Supplemental table 1. Advances in understanding of specific features and implications of traditional SVD features and in their detection and characterisation

Feature	**Advance in understanding of morphology and implications**			**Notable features**		**Advances in detection or characterisation (image acquisition/analysis)**
	Size limits	***Aetiological hints***	***Long term change***	***Other characteristics***	***Miscellaneous***	
RSSI	A maximum axial diameter of 20mm is most often used for defining RSSI in clinical trials, sometimes up to 25 mm (on DWI) in the first hours after symptom onset,26 if within the territory of a single perforating artery. Of note, the longest axis of RSSI may lay on different planes in some locations (coronal for lenticulostriate and thalamo-perforating arteries).	Other SVD markers are more frequent in anterior-circulation RSSI,[27] especially in deep white matter (corona radiata, centrum semiovale [CSO]) compared with basal ganglia, thalamus, or brainstem.[27-30] Symptomatic RSSI are more likely to be located in/near main motor and sensory tracts than covert SVD lesions (lacunes, WMH).[30] RSSI in basal ganglia are more likely to have a potential embolic source than those in the CSO.[14] Larger RSSI are more frequent in basal ganglia and pons, associated with large artery atherosclerosis[27]. Branch atheromatous disease may cause RSSI, but small atherosclerotic plaques occluding perforating arteries are not visible on conventional MRI - new MRI vessel wall imaging techniques enhance their visibility.[16,25,31,32]	About a third of RSSI evolve to some cavitation (leading to a lacune), a third will convert into a WMH, and a third will disappear on follow-up imaging.[29,33-37] The detection of small cavities or residual WMH depends on MRI field strength, slice thickness, image quality and contrast, etc. Predictors of cavitation are still scarcely investigated, but include ADC decrease, free water-corrected mean diffusivity, size of DWI hyperintensity, associated SVD lesions, serum neurofilament light chain, and occurrence of BBB alterations.[33-36,38]	The shape of RSSI is classically described as round, ovoid, or tubular, but can be irregular, depending on the perforating artery distribution and level of occlusion. RSSI may disappear due to fogging (temporary loss of visibility of an infarct) and reappear (both on CT and MRI).[39,40]	Lacunar syndrome has a moderate predictive value for RSSI, but the latter may be improved by adding other clinical predictors (NIHSS <7).[41] Covert lesions may appear on DWI in the follow-up of patients with severe SVD.[6,8-10] New small DWI+ lesions may be cortical, subcortical or both. The nature of these lesions is unclear and not necessarily related to perforating artery occlusions (see corresponding sections in the main manuscript).	CT perfusion enhances acute lesion visibility in patients with acute lacunar syndromes eligible for intravenous thrombolysis (**supplemental figure 2**). Sensitivity and specificity vary with vendor, acquisition, and processing parameters, especially for small and infratentorial infarcts.[42-48] Automatic detection tools are not available. Confirmation on follow-up MRI is recommended. Two small studies using CT perfusion and MR perfusion-weighted imaging[49,50] suggest presence of collateral retrograde blood flow through the capillary bed in RSSI. A small blooming effect on gradient-echo derived sequences is seen in up to 20% of RSSI.[51,52] The nature of this sign is controversial (i.e., deoxygenated haemoglobin trapped in clots occluding small perforators, blood-brain barrier leakage, small haemorrhagic transformation).
Lacune	Upper size limit of 15 mm rarely exceeded; size limit may vary according to the predominant location of lesions in the vascular tree depending on the perforating arteries.[53] Lacunes are larger in the CSO and basal ganglia than in other locations.[54]	After an incident lacune in presence of an identified source of embolism, the association of old lacunes and white-matter lesions are useful for implicating an underlying SVD.[55] However, the presence of an identified embolic source of previous cortical strokes do not exclude coexisting different pathogenetic processes.[56]	Very few studies have explored longitudinal variations of lacunes; regression of lacunes over time was observed in <4% of older persons with SVD.[57]	Lacunes can develop at the edge of WMH suggesting undetermined factors of white matter vulnerability.[58] Lacunes typically align their long axis with the course of perforating vessels,[54] but their shape may also be prolonged by tissue alterations, e.g., along white matter tracts.	See above predictors in the development of a lacune after RSSI	Lacunes counting can be obtained easily in presence of few lesions, methods for their evaluation should be fully validated.[59] Various methods are under development for their automatic quantification and learning algorithms are currently evaluated for their diagnostic performances.[60]

Feature	Advance in understanding of morphology and implications			Notable features		Advances in detection or characterisation (image acquisition/analysis)
	Size limits	***Aetiological hints***	***Long term change***	***Other characteristics***	***Miscellaneous***	
WMH	No lower or upper size limits and WMH can be confluent or punctual.[61] Can also be characterised by concavity, fractal dimension, and eccentricity;[62] sphericity index;[63] compactness or curvedness.[64] Potential Growth Index based on signal around the WMH boundary.[65] Territories subdivided according to distance to ventricles (deep, periventricular); distance to cortex (sub-cortical and juxta-cortical);[66] basal ganglia, brainstem;[67] white matter tracts;[68-70] arterial territories (anterior, middle, and posterior);[71]; lobes[72] WMH covariation pattern approach identified 4 components including 3 components surrounding the ventricles (posterior, frontal and dorsal PVWMH) and one component included the deep WMH and was located laterally to the other 3 components). Findings suggest that WMH follow age and disease-dependent regional distribution patterns[73]	WMH in the anterior temporal poles, external capsules, and superior frontal regions are suggestive of CADASIL (sometimes CARASIL) and, compared to WMH in non-specific locations in CADASIL patients, their high-resolution imaging features suggest increased water content (edema).[74] The corpus callosum is often involved in CADASIL, in contrast to sporadic SVD, which can sometimes lead to misdiagnosis with multiple sclerosis.[75] Multiple subcortical WMH spots are more common in CAA compared to hypertensive arteriopathy; Peri-basal ganglia WMH are more common in hypertensive arteriopathy than in CAA.[76] WMH distribution predominates in posterior regions in CAA.[77,78]	WMH progression rates depend on the study population, with highest rates in SVD cohorts, intermediate rates in all stroke cohorts, and lower rates in the general population or patients with vascular risk factors. They are mostly influenced by age and baseline WMH volume.[79] Regression of WMH volume over time has also been reported in up to 20-25%.[80-82] Longitudinal studies identified different categories of growth dynamic, including stagnant, growing, new and lost WMH.[83,84] FLAIR signal within the core of WMH was also shown to decrease in some lesions, providing further evidence for plausible regression of WMH.[83] Antihypertensive treatment, especially with intensive BP lowering, is associated with a decreased progression of WMH.[85-91] Additional trials are underway (NCT02472028, NCT02913664).[92]	WMH texture can be assessed using indices derived from WMH voxel intensity distribution, including run-length matrix or grey-level co-occurrence matrices.[93,94] Studies using DTI and ASL have shown that WMH are surrounded by a region of more subtle injury,[95,96] referred to as WMH penumbra, at higher risk to convert into WMH over time,[58,83] suggesting that WM degeneration is a continuous process. Longitudinal studies using DCE and BOLD imaging showed that blood brain barrier and CVR at baseline were lower in NAWM regions converting into WMH over time.[97-99] Recent radiomics studies extracted high-dimensional data, describing NAWM by its size, shape, histogram, and relationship between voxels predictive of WMH burden, building a robust image-based signature of the subvisible manifestations of WMH.[100,101]	Measures of WMH volume have been reported to be associated with measures of cerebral blood flow (ASL, CT, DSC),[102] BBB (DCE),[103] diffusion imaging,[104,105] cerebrovascular reactivity (BOLD) in the healthy aging brain[106] and in SVD patients;[107] iron concentration and deposit (QSM, T2*/T1 mapping).[108,109] Histopathological correlates of WMH include myelin pallor, vacuolation, decreased cellularity and dilated PVS for deep WMH and subependymal gliosis, abnormalities in myelin, axons and astroglia, sometimes with increased subependymal gliosis, for periventricular WMH,[110] venous collagenosis of the deep medullary veins[111]	Although WMH volumetric assessment is now customary in research studies, a recent meta-analysis concluded that data on WMH volume in healthy adults appear to not be comparable across studies,[112] encouraging the development of automated WMH detection tools that provide reliable, reproducible and repeatable WMH measures.[113] Novel automated methods for WMH detection have been developed using supervised and unsupervised learning algorithms. Supervised algorithms include k-nearest neighbours, large margin classifiers, multi-atlas seg-mentation, neural networks, feature filters, regression models, random forest, support vector machine.[114,115] Unsupervised algorithm comprise Kolmogorov-Smirnov test, partial-volume tissue segmentation, autoencoder segmentation auto-encoder, Gumbel or Fréchet histogram distributions, Limited One-Time Sampling Irregularity Map, segmentation method Bayesian Model Selection.[114,115]
PVS	Maximum diameter usually 3 mm.[116] Lesions with a diameter >3 mm are sometimes considered. Regardless of size PVS are fluid filled spaces with a signal identical to CSF; round, ovoid, or linear shape depending on slice direction; no hyperintense rim on T2w or FLAIR sequences. Careful differentiation from lacunes required, especially for PVS $\geq$3mm[117], but also for PVS	Associations with age are strongest for PVS in basal ganglia.[119] High blood pressure is associated with PVS in basal ganglia but less strongly in white matter CSO).[119] Association of PVS with WMH are more prominent for PVS in the basal ganglia than in the CSO.[119] Significant genetic correlation was observed	There are some indications that WMH seem to form around PVS.[117,128,129]	7T MRI provides more detailed insight into the shape of PVS. PVS in basal ganglia frequently show calibre changes along their track. In the CSO, smoothly shaped PVS start a few millimetres below the cortex, converge and taper toward the ventricles.[130] Computational PVS measures open new avenues for studying	PVS are already detectable at a very young age and were for instance described to be present in a healthy adolescent cohort, with a higher burden in men than in women in this age group.[131] PVS burden appears to be highly heritable, especially in the white matter, suggesting that genetic studies could be useful tool to decipher underlying molecular mechanisms.[120]	New visual rating scales have been developed, mostly based on predefined MRI slices (e.g., for PVS in white matter, 1 cm above the lateral ventricles; for PVS in basal ganglia, the slice showing the anterior commissure).[132-134] Novel computational methods can now measure PVS count, volume, individual size, length, width, sphericity and orientation. Methods based primarily on image processing[135-141] have a limited

Feature	Advance in understanding of morphology and implications			Notable features		Advances in detection or characterisation (image acquisition/analysis)
	Size limits	***Aetiological hints***	***Long term change***	***Other characteristics***	***Miscellaneous***	
	<3mm. Indeed, RSSI up to 10 mm size can resolve to leave a lacune with <2 mm.[118]	between WMH and PVS in the basal ganglia only.[120] PVS in hippocampus and basal ganglia are associated with intracerebral haemorrhage (ICH),[121,122] and lacunar stroke.[123] Severe PVS in the CSO are frequent in patients with established CAA than controls,[124,125] and associated with recurrent ICH in CAA patients.[126] Juxtacortical PVS are associated with CAA severity.[127]		predictors and clinical significance of PVS shape.		interoperability. Methods based on deep learning[142-146] are very sensitive to the quality and amount of a priori knowledge available (and large and reliable learning sets require human operators to manually trace PVS on many subjects).

ADC=apparent diffusion coefficient. ASL=arterial spin labelling. BBB=blood-brain barrier. BOLD=blood oxygen level dependent imaging. CAA=cerebral amyloid angiopathy, CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CARASIL=cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. CSO=centrum semiovale. CT=computed tomography. CVR=cerebrovascular reactivity. DCE=dynamic contrast enhanced. DTI=diffusion tensor imaging. FLAIR=fluid-attenuated inversion recovery. ICH=intracranial haemorrhage. NAWM=normal appearing white matter. PVS=perivascular space. PVWMH=periventricular white matter hyperintensity. QSM=quantitative susceptibility mapping. RSSI=recent small subcortical infarct. SVD=small vessel disease. WM=white matter. WMH=white matter hyperintensity.

Supplemental table 2: MRI markers of cerebrovascular function

	Method	Biological phenomenon	SVD related changes	Caveats, point of attention	Considerations on reporting
MRI markers of tissue perfusion	Dynamic susceptibility contrast (DSC)-MRI	Cerebral blood flow (CBF) (tissue perfusion)	CBF lower in SVD, but longitudinal associations and whether reduced CBF is cause or effect remain unclear.	Requires gadolinium contrast administration and advanced signal processing. Not fully quantitative. DSC is considered the clinical standard for brain perfusion MRI.	Perfusion MRI reporting recommendations are currently being prepared by the Open-Science Initiative for Perfusion Imaging (https://osipi.org/OSIPI_CAPLEX/). Include details of contrast administration, MRI acquisition, image analysis and methods for generating ROIs.
	Dynamic Contrast Enhanced (DCE)-MRI			Requires gadolinium contrast administration and complex image processing.	
	Arterial spin labelling (ASL)			Low CNR in WM. Elevated arterial transit time may confound measurements.	
	BOLD or ASL MRI with hypercapnic challenge	Cerebrovascular reactivity: microvascular blood flow/volume change in response to CO_2 (regulated mostly at arteriolar level)	Low CVR associated with SVD severity and progression.	Require substantial ancillary equipment and patient cooperation. BOLD signal has complex dependence on biophysics properties. ASL signal has very low CNR in WM.	Harmonisation is at an early stage and reporting practice is varied.[147] We suggest to report CVR magnitude as the percent change in signal (BOLD) or CBF (ASL) per unit change in $EtCO_2$ [%/mmHg]. Include details of: MRI acquisition, image analysis and methods for generating ROIs.
MRI markers of flow at vessel level	Phase-contrast MRI carotid artery, primary arteries of circle of Willis; veins and venous sinuses; CSF.	Blood flow velocity. blood flow volume/time flow.[148] Flow pulsatility (possible indicator of arterial stiffness/ compliance) Flow response to CO_2 can also be assessed	Flow/CBF lower and pulsatility index higher in SVD,[149] however longitudinal associations and cause or effect remain unclear	Flow and pulsatility measured in a particular artery (e.g., MCA) may be determined at up- or downstream levels. Initially 2D, more complex 3D and 4D modelling of flow patterns emerging.	Report exact site of acquisition, preferably with images. Reports on pulsatility should include crude flow or velocity levels.
	Phase-contrast MRI perforating arteries basal ganglia, centrum semiovale	Blood flow velocity Flow velocity pulsatility (possible indicator of arterial stiffness/ compliance) Flow response to CO_2 can also be assessed	Indications that perforating artery flow is reduced and pulsatility index higher in SVD[150,151]	Flow, velocity and pulsatility measured in perforating arteries may be determined at up- or downstream levels. Requires high field (e.g., 7T MRI) Confounded by partial volume effects, low CNR.	Emerging technique, requires further evaluation in terms of reproducibility, standardisation of post-processing[152,153]
MRI markers of BBB function	DCE-MRI	BBB disruption, permeability	Increased BBB leakage to contrast medium, and association with white matter hyperintensities and cognitive deficits	Technique is relatively prone to noise and other factors, requires further developments and independent means of validation. Requires gadolinium contrast agent administration.	Report leakage rate (units: 1/min) and other quantities in specified brain regions. As the technique is prone to noise and novel developments are still emerging the reporting varies. Provide details of: contrast administration, MRI acquisition, T1 quantification, image analysis, pharmacokinetic modelling, and selection of ROIs, including vascular input function.[154]

	Method	Biological phenomenon	SVD related changes	Caveats, point of attention	Considerations on reporting
	ASL-based techniques (e.g., diffusion-prepared ASL, T2W-ASL)	Water exchange across blood-brain interface	Exchange decreased with ageing,[155] but not investigated yet in SVD.	Different techniques are currently under development. Water exchange is a natural transport phenomenon and experiences only a partial barrier at the blood-brain interface	Report exchange rate of water from blood to brain (units: 1/min) and, if possible, the permeability surface area product to water (units: mL blood or extracellular fluid/mL tissue/min) and other quantities in specified brain regions. Include details of: MRI acquisition, use of contrast agent, image processing and generation of ROIs.[156]
	Dynamic Glucose Enhanced (DGE) MRI	Glucose uptake through GLUT1 transporter protein	Reduced glucose uptake in Alzheimer's, but not yet investigated in SVD	Emerging technique, which requires advanced MRI hardware to generate high power off-resonance pulses to selectively saturate hydroxyl protons in D-glucose that exchange with water and sufficient spectral separation of the saturation offset frequency from the water resonance, for which ultra-high field (e.g., 7T) is beneficial	Method is at an early stage in development and has not been applied to SVD yet. Relative signal changes are reported.[157,158]

ASL=arterial spin labelling. BBB=blood-brain barrier. BOLD=blood oxygen level dependent. CBF=cerebral blood flow. CNR=contrast-to-noise ratio. CVR=cerebrovascular reactivity. DW-ASL=diffusion-weighted ASL. DCE=dynamic contrast enhanced. EtCO2=end-tidal CO_2 partial pressure. GLUT1=glucose transporter 1. MCA=middle cerebral artery. ROI=region of interest. SVD=small vessel disease. T2W=T2-weighted. WM=white matter.

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Supplemental panels

Supplemental panel 1: List of non-recommended terms

Recent small subcortical infarct
- Lacune
- Lacunar infarct
- Acute lacune

Lacune (of presumed vascular origin)
- Lacunar infarct
- Silent stroke
- Silent infarct
- Covert lacunar infarct

White matter hyperintensity (of presumed vascular origin)
- Ischaemic leukoaraiosis
- Ischaemic white matter hyperintensities
- White matter lesion

Perivascular space
- Enlarged perivascular space

Cerebral microbleed
- Microhaemorrhage

Cortical superficial siderosis
- Haemosiderosis

Brain atrophy
- Brain shrinkage

Summary SVD score
- Total SVD score
- SVD burden

Cortical cerebral microinfarct
- Cerebral microinfarcts
- Chronic microinfarcts

Supplemental panel 2: Terms for structural quantitative imaging markers of SVD brain damage

Preferred terms:

- Diffusion tensor imaging (DTI): quantification method and not a data acquisition scheme
- Mean diffusivity: marker of hindered / Gaussian diffusion
- Free water: (apparent) free water. In analogy to the apparent diffusion coefficient.
- Compartmental fractions derived from DWI models, free water: signal fraction and not volume fraction (unless corrected with a calibrated T2 value)
- R2*: data acquisition of iron content with a gradient echo
- QSM: quantification method of susceptibility

Terms to avoid:

- Mean diffusivity: cellular/parenchymal diffusion (due to sensitivity to other partial volume effects that might confound the biological interpretation)
- All DTI-derived metrics: axonal integrity, myelin integrity/demyelination, ultrastructural changes
- Free water: extracellular water, oedema, inflammation
- QSM: is not an acquisition technique

Supplemental panel 3: Proposed reporting standards for neuroimaging studies of small vessel disease

Details of the research participants and reference population

- Age, sex, and main inclusion/exclusion criteria for the study.
- Proportions of individuals with vascular risk factors and how these were measured.
- Proportions of individuals with stroke and its subtypes, as well as other clinically diagnosed vascular comorbidities.
- Proportions of individuals with cognitive impairment and its likely aetiology according to accepted consensus criteria.
- Time from disease presentation to imaging and clinical assessments (if relevant).
- Any clinical or imaging observational period with time intervals.
- For studies on cognition or specific physical functions: details of test versions used, who administered them, and their training.
- For cognitive studies: assessment of premorbid cognitive ability including education, and depression.

Image acquisition

- Scanner characteristics (type and manufacturer, field strength, software version, coils, and wherever relevant also consider reporting on use of high-order shim and shimming routines, quality assurance protocol for scanner and frequency of quality assurance assessment).
- Change of scanners or change to scanner system during study.
- MRI sequences, acquisition parameters (including as appropriate: repetition time, echo time, inversion time, echo train length), acquisition and reconstruction matrices, field-of-view, slice thickness including gaps and scanning plane, details of selected options (tailored excitation pulses, parallel imaging, flow compensation, preparation pulses, etc), and total acquisition time.
- Crucial sequence-specific details, e.g., for diffusion MRI: b-values, number of diffusion directions, use of multiband imaging.
- If a work-in-progress/in-development software package or MRI acquisition sequence is used, provide as much information as possible.

Image analysis and postprocessing

- Characteristics of analysis software application (manufacturer, software version, image data format used for processing, and computer platform).
- Expertise of those performing the analyses (or oversight of an expert); see below
- Use and qualification of a central analysis facility, or training procedure across several analysis centres.
- Disclose whether analyses were done blinded to initial presentation or to other data (should be specified) that might influence interpretation.
- Details of qualitative visual rating and quantitative computational methods, including the URL if available for download or an appendix describing the method in detail, including its validation.
- For visual ratings: whether images were rated centrally by one or more readers; the raters' background (e.g., neurology, psychiatry, neuroradiology, or radiology) and experience; rater reliability (intra-rater and inter-rater).
- For all studies, whether using visual assessments or computational image analysis programmes: training of the analysts, any expert supervision, and the background of the expert.
- Repeatability (scan-rescan) and reproducibility (inter-scanner) of the method.
- Statistical methods used in data analysis.
- Ideally, include power analysis information on sample size estimates.

Small vessel disease-specific aspects

- For **recent small subcortical infarcts**: specify whether infarcts are symptomatic or not; state the location, size, shape, and number; specify the delay from stroke to imaging; state the proportion with visible acute lesion on diffusion-weighted imaging and fluid-attenuated inversion recovery, plus T2-weighted imaging, or visible on CT if appropriate.
- For **lacunes (of presumed vascular origin)**: specify location, size, shape, and number; identify any haemorrhagic features; for volumetric methods, state whether lacunes are counted as part of CSF volume, as part of the white matter hyperintensity volume, or as separate lacune volume.
- For **white matter hyperintensities (of presumed vascular origin)**: specify the sequence used; specify whether deep grey matter and brainstem hyperintensities are included (and if so, refer to all hyperintensities collectively); state the rating scale or volume measurement software used, the reference or URL (if available) and observer reliability; specify whether the white matter hyperintensity volume was adjusted for intracranial or brain volume and how this was done; state whether lacunes were included in white matter hyperintensities or measured separately and whether acute lesions were masked.
- For **perivascular spaces**: separate perivascular spaces of the basal ganglia and white matter, and where available hippocampus and brainstem; describe how qualitative aspects (number, location, size, etc) are defined; state the observer reliability of the rating scale; for computational assessments, give full details of the software (URL where available), its validation, reproducibility, and the PVS parameters that are measured.
- For **cerebral microbleeds**: specify number and distribution divided into lobar, deep, and infratentorial (brainstem and cerebellum - the latter subdivided into deep and lobar); specify the sequence used; specify application of standardised rating scales. For computational assessments, give full details of the software (reference or URL where available), its validation, reproducibility, and the CMB parameters that are measured.
- For **cortical superficial siderosis**: state whether it is focal (involving ≤3 sulci) or disseminated (involving >3 sulci); state the scale used, its validation and repeatability, or similar details of any computational method used.
- For brain **atrophy**: specify the rating scale or method of volume measurement, whether corrected for intracranial volume, and method used to do this.
- For **summary SVD score**: we recommend reference to a validated score, noting any adaptation made, utilising reporting standards for each SVD included in the score. New scores will be developed and require careful validation and testing in diverse populations.
- For (old) cortical **cerebral microinfarcts**: the sequence used; the number, location, size; details of the assessment method, its reproducibility and whether validated externally; expertise of raters; details of computational assessment method.
- For **structural quantitative markers of SVD brain damage**: report processing pipeline and software used, avoid assumptions of underlying aetiology/pathology and report measures/values as derived from the acquisition method or post-processing.
- For **markers of cerebrovascular function**: report processing pipeline and software used, whether validated externally; its repeatability; tissues from which values were extracted and how these were delineated (ROI, voxel-based); methods used to reduce contamination of the tissue signal by vessels or other tissues.

Supplemental panel 4: Questions to be addressed in future imaging studies of small vessel disease

Recent small subcortical infarct

- Factors determining long term fate of the lesion itself and secondary features (secondary tract changes, cortical changes).
- Relationship of RSSI appearance to the likelihood of underlying intrinsic versus non-intrinsic aetiology (e.g., intra- or extracranial atheroma, or cardioembolic).
- Relationship of RSSI long term fate (of the lesion itself and secondary features) to functional, cognitive and neurobehavioural outcomes.

Lacune (of presumed vascular origin)

- Can lacunes truly disappear from imaging? If so, what are the associated factors?
- Can we improve the differentiation of lacunes from perivascular spaces?
- Does lacune aetiology differ by brain location?
- Is computational detection and assessment of lacunes feasible or reliable?

White matter hyperintensity (of presumed vascular origin)

- Is there a 'normal' WMH volume or score for age?
- Set minimum standards for WMH volume software accuracy with large practice datasets representative of a full range of feature and co-feature variation.
- Does WMH appearance vary with pathological stage (early, permanent)?
- Can reversible WMH be differentiated from permanent WMH?
- Identify factors influencing WMH regression vs progression.
- Does WMH aetiology differ by brain location and/or pattern (e.g., periventricular, multi-spot, peri-basal ganglia, posterior/confluent)?

Perivascular space

- Do PVS predate development of other SVD lesions?
- Do PVS independently predict future cognitive decline?
- Is involvement of particular brain regions in increasing PVS an indicator of particular disease processes?
- Do PVS reflect impaired fluid flow?
- Are PVS clinically relevant?

Cerebral microbleed

- Development of (semi)-automated methods for detection and mapping of CMB.
- Building large prospective studies assessing CMB accrual and precise location, with functional and cognitive outcomes.
- RCT integrating CMB assessment: (1) on pre-randomisation MRI to assess possible modification of the treatment effect and (2) during follow-up to see if CMBs are a surrogate for later clinical outcomes.

Cortical superficial siderosis

- Development of (semi)-automated methods for detection and mapping of cSS.
- Building large prospective studies assessing cSS accrual and precise location, with the risk of future cerebrovascular events as well as with functional and cognitive outcomes.
- RCT integrating cSS assessment: (1) on pre-randomisation MRI to assess possible modification of the treatment effect and (2) during follow-up to see if cSS is a surrogate for later clinical outcomes.

Brain atrophy

- Set minimum standards for computational methods for determining brain atrophy to reduce variation between methods and streamline quality assurance.
- Are some regional or global patterns of brain atrophy specific to SVD including particular SVD feature types or severities?

Summary SVD score

- How can we create a validation matrix for future summary SVD scores that incorporate new imaging markers?
- How can we validate summary SVD scores that incorporate automated measures of SVD imaging features?
- How can we develop a summary SVD score for progression of SVD?
- How do we incorporate non-imaging SVD metrics, such as functional, cognitive, genetic, and blood biomarkers, into future multi-variable summary scores?

(Old) cortical cerebral microinfarct

- Development of (semi)-automated methods for detection and mapping of old/chronic/persistent cortical CMI.
- What is the maximum size that can be considered as a CMI in acute to long term stages?
- What is the aetiology of cortical CMI – are they due to intrinsic SVD or extracerebral (e.g., embolic) causes?
- What is the optimal method (sequence) to detect CMI outside the cortical grey matter?

Incident DWI-positive lesion

- Determine why some lesions are asymptomatic whereas others cause acute stroke-like symptoms.
- Determine the aetiology and pathology of DWI+ lesions.
- Determine the clinical relevance of DWI+ lesions.

Structural quantitative imaging markers of SVD brain damage

- What is the specificity of quantitative imaging markers in SVD?
- Is there a meaningful role for quantitative imaging markers as clinical biomarkers?
- Can we provide a "standardised operational procedure" for the (automated) analysis of quantitative imaging markers?
- Provide histopathological validation of quantitative imaging markers.

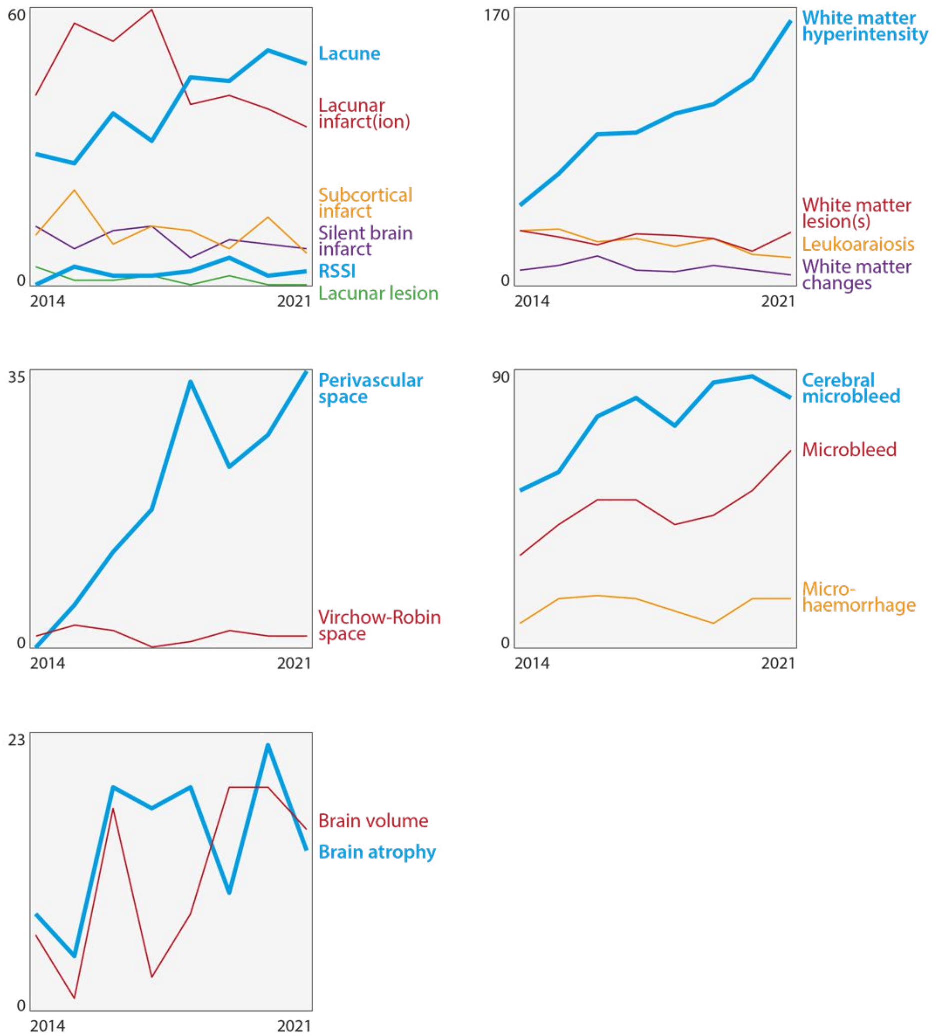
Markers of cerebrovascular function in SVD

- Establish which aspects of vascular function are abnormal in SVD.
- Establish to which extent abnormal vascular function precedes lesion formation.
- Establish risk factors and possible biological processes (e.g., to proteomics) for abnormal vascular function in SVD.

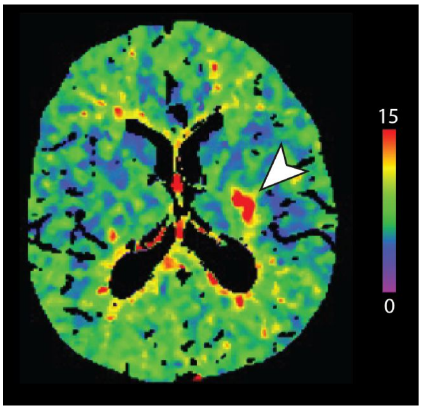
General

- Define best practices for image analysis when applied to large datasets to help overcome sequence and scanner variation.
- What is the added value of structural or functional imaging biomarkers over conventional visible SVD features in relation to clinical expression or prognosis?
- Identify the extent of overlap of SVD features with features of other common neurodegenerative pathologies such as Alzheimer's disease, including whether SVD features alter amyloid-PET or tau-PET tracer uptake, whether PET imaging helps differentiate the vascular from Alzheimer's disease contribution to cognitive impairment in vivo, or predict future decline.

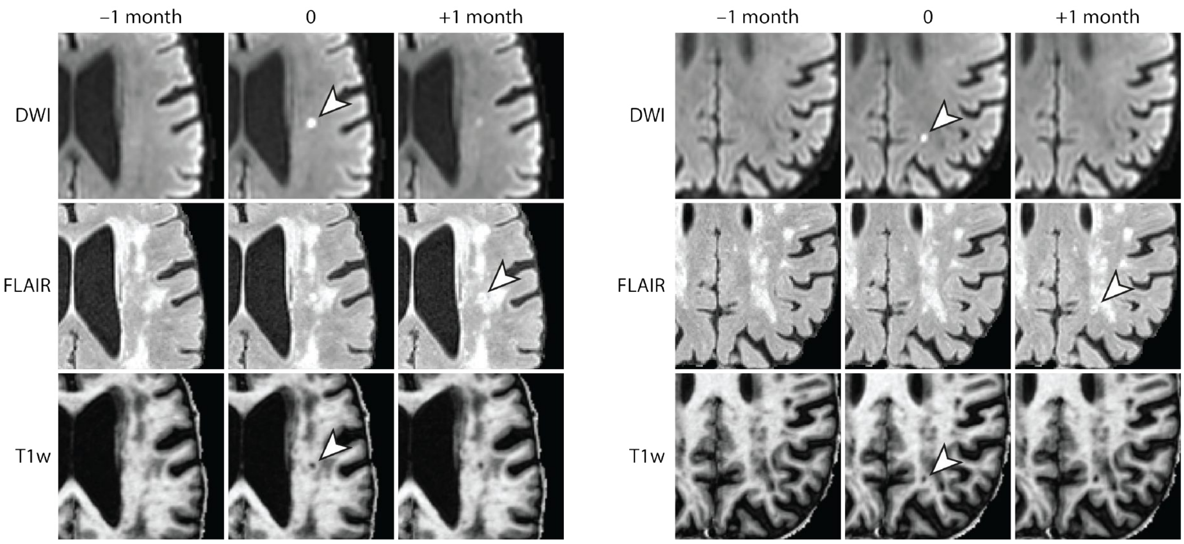
Supplemental figures



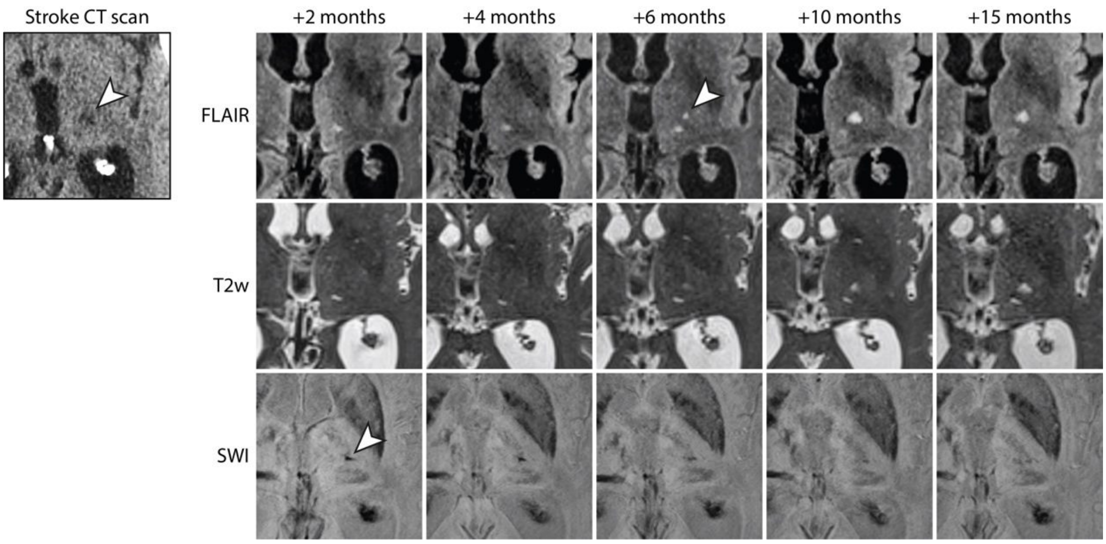
Supplemental figure 1: Adoption of STRIVE-1 terminology in the literature since 2014
Publication frequency of STRIVE-1 terms over time. The STRIVE-1 terminologies are plotted in blue and compared with the most frequent alternative terms. Search terms described in the literature search strategy that yielded very low numbers were omitted from the figure for improved readability. The numbers are absolute number of papers found per year, based on the literature search strategy (page 5). Note one paper might contribute more than one term (e.g., if a paper uses in the title "lacune" and as key word "silent brain infarct" it would be counted towards each of these terms).



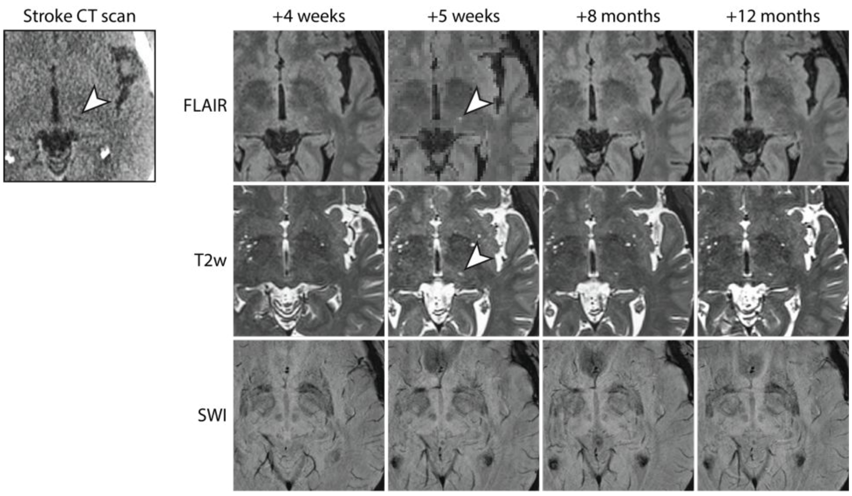
Supplemental figure 2: CT perfusion time to drain maps. Delayed perfusion in the left lenticular nucleus corresponding to a RSSI (Syngo.via CT neuroperfusion, Siemens Healthineers, Erlangen, Germany).



Supplemental figure 3: Time series illustrating the evolution of two incidental DWI+ lesions into small cavities. Two DWI+ lesions were identified in monthly MRI scanning (time point 0, arrow). While the DWI+ lesion fades, high-resolution (0.85 mm isotropic) 3D-FLAIR and 3D-T1-weighted (T1w) imaging show the development of small cavities (arrows), which are less than 3 mm in diameter and thus do not fulfil the criteria of a lacune (of presumed vascular origin). As expected, the cavities are barely visible on FLAIR and best seen on T1w images. All images were brain-extracted and registered with a longitudinal FLAIR template as reference. Data from the RUN DMC – InTENse high-frequency serial imaging study.[9]



Supplemental figure 4: Time series illustrating the evolution of a recent small subcortical infarct. The CT in the subacute phase of stroke shows a new left thalamic RSSI (arrow). By time of the first MRI (2 months after the CT scan) the RSSI has fogged on FLAIR and T2-weighted images (T2w) but is visible on susceptibility-weighted imaging (SWI) as a small triangular T2*hypointensity ('smudge') (arrow). The lesion then gradually reappears on FLAIR (arrow) and then T2w, while the SWI lesion gradually 'dissolves'.



Supplemental figure 5: Time series illustrating the evolution of a recent small subcortical infarct. The RSSI is just visible on subacute phase CT in the left thalamus (arrow). By time of the first MRI, the left thalamic RSSI has largely fogged. It then reappears as a lesion on FLAIR and T2-weighted (T2w) images (arrows).