

The Focused Review on Clinical and Neuroimaging of Cerebral Small Vessel Disease

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Abstract

Cerebral small vessel disease (CSVD) is a frequently occurring condition that is associated with the ageing process. It can manifest as stroke, decline in cognition, neurobehavioural symptoms, or age-related functional disability. 20% to 30% of ischaemic strokes and approximately 80% of non-traumatic intracerebral haemorrhage (ICH) are caused by sporadic CSVD, which is deep perforator arteriopathy, also called sporadic non-amyloid microangiopathy and cerebral amyloid angiopathy, type 1 and 2 CSVD, respectively, are the most prevalent forms. In clinical practice, it is crucial to establish an accurate diagnosis regarding underlying aetiopathogenic mechanisms of CSVD, which point and guide to appropriate prevention and management. The emergence of additional magnetic resonance markers significantly provides clinically useful, noninvasive classification and diagnosis criteria for particular CSVD or ICH subtypes, specifically of the two main CSVDs, including their combination. Understanding this knowledge will help identify possible targets for intervention and improve the accuracy of risk prediction for those affected by CSVD. This article aimed to provide a brief and concise review of clinical and neuroimaging markers of CSVD, which have recently progressed and implemented this knowledge in clinical practice as a comprehensive care for individuals affected by this particular type of cerebrovascular disease.

Keywords: Cerebral small vessel disease, Cerebral amyloid angiopathy, Deep perforating arteriopathy, Neuroimaging markers (J Thai Stroke Soc. 2025;24(1): 15–25)

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Introduction

Cerebral small vessel disease (CSVD) is a term used to describe a group of pathological disorders that possess distinct causes and affect small blood vessels in the brain, including arteries, arterioles, venules, and capillaries.¹ This condition causes approximately 25% of ischaemic strokes,² 80% of all non-traumatic intracerebral haemorrhage (ICH), and is the most prevalent underlying pathology of vascular cognitive impairment (VCI).³ Additionally, this stroke subtype is strongly associated with non-motor outcomes of stroke, namely gait, mood, and neurobehavioural disorders.⁴

CSVD is defined by particular magnetic resonance imaging (MRI) characteristics, which include lacunes and white matter hyperintensities (WMH) of presumed vascular origin, cerebral microbleeds (CMB), perivascular spaces (PVS), and brain atrophy.^{5, 6} Individually, these lesions may not show any clinical symptoms; however, a growing number of different types of lesions and combinations of lesions have been related to depression, cognitive impairment, dementia, mobility issues, higher risk of stroke, and poorer recovery following a stroke.^{4, 5} In this review, I discuss CSVD, focusing on aetiologic classification, clinical symptoms, neuroimaging markers, and novel or emerging MRI markers for diagnosing CSVD patients. A detailed treatment of therapeutic aspects is beyond the scope of this review, but it is essential to heighten the optimisation of vascular risk factors control and avoid inappropriate use of antithrombotic in cerebral amyloid angiopathy (CAA), which is the mainstay treatment.

Classification

There are six types of CSVD based on aetiopathogenic classification, including arteriolosclerosis, CAA, genetic CSVD,

immune-mediated and inflammation, venous collagenosis, and other types of CSVD.¹ The prevalence of these types varies significantly, with type 1, arteriolosclerosis or deep perforator arteriopathy (DPA, also termed hypertensive arteriopathy or sporadic non-amyloid microangiopathy), and type 2, sporadic and hereditary CAA, being the most common forms.

Clinical syndromes of CSVD

1. Lacunar stroke: neuropathology to clinical syndromes

A clinical lacunar syndrome may result from either ischaemia or a small haemorrhage.⁷ Lacunar ischaemic stroke or small-vessel occlusion (lacune), according to TOAST classification, is characterised by the traditional clinical lacunar syndromes and should not have evidence of cortical dysfunction. A small infarct less than 1.5 cm in diameter in a relevant subcortical hemisphere or brainstem could be demonstrated on computed tomography (CT) or MRI of the brain. Notably, there should be no potential cardiac sources for embolism, and the evaluation of the large extracranial arteries should show no more than a 50% narrowing in an artery on the affected side.^{8, 9} Based on an original narrative review on lacunar strokes and infarcts by CM Fisher, more than twenty clinical syndromes were classified as lacunar syndromes. However, there are five most common lacunar syndromes in routine clinical practice: pure sensory strokes or transient ischaemic attacks (TIA), pure motor hemiparesis, sensorimotor stroke, ataxic hemiparesis, and dysarthria-clumsy hand syndrome.⁸

Most cases of ICH are caused by sporadic SVD, particularly DPA and CAA. DPA primarily impacts the small arteries and arterioles in the deep brain structures such as the basal ganglia, thalami, brainstem, deep cerebellar nuclei, and

white matter (medullary) perforators, whilst CAA affects the leptomeningeal and superficial cortical vessels.^{3, 10} DPA is an arteriosclerotic disease of perforating arterioles due to chronic hypertension causing deep macro- and microhaemorrhages. The deposition of β -amyloid ($A\beta$) in leptomeningeal arterioles causes vascular fragility and is prone to develop lobar ICH, lobar CMB, and convexity subarachnoid haemorrhage (cSAH), which chronically turn to cortical superficial siderosis (cSS), which is the significant hallmark for CAA and predicting risk of recurrent ICH in patients with CAA.^{10, 11}

2. Non-motor symptoms of CSVD

Various types and severity of non-motor symptoms or other manifestations associated with CSVD have been described. It can be categorised into four domains of symptoms, including cognitive performance, stance and balance consequences, psychiatric symptoms, and sphincteric functions.

2.1. Cognitive performance

CSVD has been demonstrated to be a major cause of decline in cognition and functional impairment in older individuals. Initially, subtle deficits in some particular cognitive domains, i.e., executive functions, attention, and set-shifting abilities, could be predominantly present and detected with specific neuropsychological tests.¹ The progression of cognitive deficit might reach an apparent deterioration and meet the criteria diagnosis of dementia or major neurocognitive disorders when daily living function is affected.¹² Lacunar infarcts and white matter lesions have been recognised as causing cognitive impairment. In recent years, silent lacunar infarcts and CMB were associated with cognition in patients with CSVD. Impairments in various cognitive domains, mainly executive functions, processing, attention, and visual memory, were associated with CMB

and its burden.¹³

2.2. Stance and balance consequences

In the initial stage, some CSVD patients have mild slowing gait or subjective postural instability before progression to apraxic gait—short-stepped, wide-based, shuffling gait (clinical picture of lower body parkinsonism).¹⁴ The so-called frontal gait disorder is closely correlated with SVD lesions, particularly lacunes, in basal ganglia and white matter lesions.¹⁵ Additionally, gait disturbance in CSVD and other higher-level gait disorders are further classified as follows: locomotion failure (LF), postural control failure (PCF), and gait ignition failure and freezing (GIF) (Table 1).¹⁶

2.3. Psychiatric symptoms

Depressive symptoms are the most prevalent psychiatric consequences following CSVD. A flattened mood or apathy might be the initial presentation.¹ WMH has been proposed to be a substrate for depression in CSVD patients due to the disruption of subcortical pathways, called frontal-subcortical-limbic network, which underlying mood regulation.¹⁷ Vascular depression was proposed in the 1990s for depressive disorder coupled with vascular risk factors or multiple localised cerebrovascular lesions.¹⁸

2.4. Sphincteric functions

Urinary complaints are common age-related disability among CSVD individuals, especially older people. The symptoms typically progress from urinary urgency to incontinence episodes and turn to complete urinary incontinence with a probability of faecal incontinence in some severe cases at the terminal stage.¹ Data from the Leukoaraiosis and Disability (LADIS) study demonstrated that severe age-related white matter change (ARWMC) was independently associated with urinary urgency.¹⁹ Frontal lobes function for bladder control, and WMH in such brain areas

is responsible for the presence and severity of urinary incontinence.

Neuroimaging markers for CSVD

According to the Standards for Reporting Vascular Changes on Neuroimaging 2 (STRIVE-2), MRI features of lesions related to CSVD findings in patients with CSVD can be grouped into haemorrhagic (CMB, cSS) and non-haemorrhagic (cortical cerebral microinfarct, lacune, PVS, RSSI, WMH) markers (**Figure 1**).^{3, 20}

1. Non-haemorrhagic lesions related to SVD^{5, 20}

1.1. Cortical cerebral microinfarct

Cortical microinfarct was described as a small ischaemic lesion varying between 0.5–4 mm. Although the lesions are small, the increased burden of these lesions produces quantifiable disruption to the structural connections in the brain and is responsible for cognitive decline.²¹ A large cortical microinfarct is usually seen on conventional MRI, whilst a smaller one requires a high-resolution structural or ultra-high field MRI to reveal and increase the sensitivity of the lesion detection. By definition, cortical cerebral microinfarct is a wedge-shaped lesion that is confined to the cortical grey matter. It typically appears as hypointensity on T1-weighted (T1-W) and hyperintensity on T2-weighted (T2-W) MRI.

1.2. Lacune (of presumed vascular origin)

Lacune is an ovoid or round subcortical cavitory lesion, 3–15 mm. in diameter. This MRI feature is typically assessed and rated visually on T1-W, T2-W, and fluid-attenuated inversion recovery (FLAIR) MRI.²⁰ It has an MRI signal comparable to cerebrospinal fluid (CSF), and probably has a hypointense rim (**Figure 1D**). Lacunes presumed to be of vascular origin are considered to be caused by acute, small subcortical

infarcts or haemorrhages within the region of a single perforating artery.⁵

1.3. Perivascular space (PVS)

The PVS refers to the enlarged extracellular fluid space that surrounds the perforating vessels. The MRI reveals the presence of fluid-filled spaces that resemble the CSF. These spaces are aligned with the trajectory of the penetrating vessels and have either a linear or circular shape, depending on whether they are scanned parallel or perpendicular to the orientation of the vessels, respectively (**Figure 1E**).^{5, 20} The size of these features is usually less than 2 mm. According to the semiquantitative scale, these MRI markers can be counted and severity graded by visual assessment as 0–4: 0 = no PVS, 1 = <10 PVS, 2 = 11 to 20 PVS, 3 = 21 to 40 PVS, and 4 = >40 PVS. The numbers correspond to PVS on one hemisphere of the brain. In cases where there was a difference in size between the two hemispheres, the higher score was utilised. Additionally, PVS was counted in the brain slice with the greatest number of these lesions.²²

The distribution and pattern of PVS have been extensively studied and might guide the underlying aetiopathogenic classification of CSVD, especially DPA and CAA. In a study of spontaneous ICH patients, the prevalence of a centrum semiovale PVS (CSO-PVS)–predominant pattern was higher in cases of CAA-ICH compared to DPA-ICH.²³ In addition, the preponderance of CSO-PVS was significantly related to a higher burden of lobar CMB and cSS, which are the haemorrhagic markers of CAA according to the latest Boston criteria (version 2.0).²⁴

1.4. Recent small subcortical infarct (RSSI)

Diffusion-weighted imaging (DWI) can detect RSSI as a tiny hyperintensity, measuring less than 20 mm. on an axial slice within the

area of a single perforating arteriole. Subcortical microinfarcts, which are lesions smaller than 5 mm, can only be identified with high-resolution imaging techniques with field strengths of 3T and above.⁵ The term ‘recent’ used for RSSI describes neuroimaging evidence of infarction occurring within the previous 3 weeks. It is important to distinguish RSSI from incidental DWI-positive lesions by using the location of the lesions and stroke symptoms. RSSI typically occur in the primary motor and sensory tracts, which correspond with focal neurological deficits of the lacunar syndrome, namely pure motor, pure sensory, sensorimotor, dysarthria-clumsy hand, and ataxic hemiparesis.²⁰

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

On T2-weighted sequences, such as in FLAIR, bilateral hyperintensities, which are generally symmetrical, can be observed (**Figure 1G**). These structures vary in size and are primarily found in the deep and periventricular white matter regions.⁵ The Fazekas scale is widely utilised to visually assess the distribution and severity of WMH.²⁵ Periventricular WMH Fazekas 3 (extending into the deep white matter) and/or deep WMH Fazekas 2–3 (confluent or early confluent) are considered substantial features of CSVD (**Figure 1H–1I**).²⁶

Different subcortical WMH patterns have been described: large posterior subcortical patches WMH pattern, anterior subcortical patches WMH pattern, peri-basal ganglia WMH pattern, and multiple subcortical spots WMH pattern. Among these patterns, the multispot WMH pattern (**Figure 1F**) was significantly higher in patients with CAA, and the presence of this pattern was independently associated with lobar CMB and a high degree of CSO-PVS.²⁷ Consequently, WMH in a multispot pattern has been counted as

a white matter feature for probable and possible CAA based on the Boston criteria version 2.0.24. It is worthwhile to acknowledge that the multispot WMH pattern is characterised by the presence of over ten small circular or oval areas of increased intensity on T2-weighted FLAIR images located in the subcortical white matter of both hemispheres.²⁷

2. Haemorrhagic lesions related to SVD^{5, 20}

2.1. Cerebral microbleed (CMB)

The CMB refers to the small accumulation of hemosiderin, which indicates the leakage of blood cells into brain tissue. On paramagnetic resonance sequences, e.g., T2*-weighted or susceptibility-weighted imaging (SWI), the CMB can be observed as small lesions with a diameter ranging from 2 to 10 mm (usually 2–5 mm), appearing as foci of hypointensity signal.^{5, 20} Deep CMBs (**Figure 1A**) underline the microangiopathy type of DPA, whilst lobar CMBs (**Figure 1B**) provide insight into the CAA as the dominant underlying mechanism.²⁸ According to a recent causal classification system for ICH subtypes, CLAS-ICH, mixed haemorrhages in both lobar and deep regions are well-defined subtypes of mixed CSVD.²⁹

2.2. Cortical superficial siderosis (cSS)

cSS refers to thin regions of hypointensity signal on T2* or other MRI sequences that are sensitive to susceptibility effects (gradient echo (GRE) or SWI).²⁰ This haemorrhagic marker is found in or above the superficial cortex and can be limited to one gyrus and adjoining sulci (focal cSS; 1–3 sulci) or, in other cases, more extensive, affecting many brain regions (disseminated cSS ≥4 sulci) (**Figure 1C**).³⁰ cSS is closely associated with symptomatic CAA as it causes cortical spreading depolarisation (CSD), which eventually develops transient focal neurological episodes

(TFNEs).³¹

The Boston criteria version 2.0 for CAA and a novel MRI-based classification of spontaneous ICH associated with CSVD

CAA is the primary contributor to lobar ICH and plays a significant role in age-related cognitive decline. As a result, obtaining a precise diagnosis of CAA is crucial, as this is essential for effective therapeutic treatment and for including individuals in research studies. Recently published Boston criteria v2.0 included emerging MRI markers of CAA that demonstrated appreciable sensitivity and specificity to diagnosing CAA in patients aged 50 years and older who presented with spontaneous ICH, cognitive impairment or dementia, or TFNEs (**Figure 2**).²⁴ Probable CAA could be diagnosed by demonstrating at least two strictly lobar haemorrhagic markers (ICH, CMBs, cSS, or cSAH) or one strictly lobar haemorrhagic lesion in combination with either severe CSO-PVSs or multispot WMH pattern. It is important to strictly follow the definitions in the original cohort of pathology-proven CAA that defined more than 20 PVSs in CSO of one cerebral hemisphere as severe CSO-PVSs.³² For possible CAA, the criteria require at least one strictly lobar haemorrhagic lesion or white matter feature of nonhaemorrhagic marker for CAA, as aforementioned. In all scenarios, the diagnosis of CAA cannot establish if there is evidence of any deep haemorrhagic lesions or the presence of other causes of ICH.²⁴

CADMUS, CAA, Arteriosclerosis/DPA, Mixed CAA-DPA SVD, Undetermined SVD, SVD classification was recently developed using ICH location and novel SVD MRI markers to practically classify ICH subtypes into four phenotypes: CAA, DPA, mixed CAA-DPA, and undetermined SVD (**Table 2** and **Figure 3**).³³ The

practicality and reliability of CADMUS represent a promising tool for enhancing the classification of ICH subtypes in both clinical practice and research.

Conclusions

Cerebral small vessel disease is a complex disorder affecting cerebral microvasculature, leading to the presence of white matter hyperintensities and various other abnormalities, e.g., lacunes, perivascular spaces, cerebral microbleeds, and cortical superficial siderosis that can be observed during brain imaging. It is a significant cause of pathogenic mechanisms for ischaemic stroke and other consequences, namely decline in cognitive performance and age-related disability. Progression of knowledge regarding underlying pathogenesis and neuroimaging markers provides more insight into the disease and highlights the significance of implementing appropriate prevention strategies and therapeutic approaches for this stroke subtype.

Originality and body of knowledge

The clinical spectrum of patients with cerebral small vessel disease is varied. Although lacunar strokes are prototypes of clinical manifestations, other symptoms or deficits could consequently develop, namely cognitive impairment, mood disorders, bladder control dysfunctions, and gait disability. The progression and advancement of neuroimaging and neuropathologic studies concerning CSVD, especially CAA, provide a tremendous body of knowledge of the clinical and pathophysiology of the disease. Locations and characteristics of haemorrhagic and nonhaemorrhagic features from MRI add value to these markers to distinguish the two main types of CSVD, DPA and CAA, and heighten the difference of underlying mechanisms, which

point toward suitable preventive approaches for each disease subtype.

Conflict of interest statement

The author declares no conflict of interest.

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Figure 1. MRI examples of haemorrhagic and non-haemorrhagic markers of cerebral small vessel disease. A) Deep cerebral microbleed (CMB) at right thalamus. B) Multiple lobar CMBs. C) Disseminated cortical superficial siderosis (cSS). D) Lacunes (white arrow) and large confluent areas of severe white matter hyperintensity (WMH) (Fazekas 3, black arrow). E) Severe centrum semiovale perivascular spaces (CSO-PVSs) (scale 4 on semiquantitative scale ≥ 40 PVSs). F) Multispot WMH pattern. G) WMH, Fazekas scale 1. H) WMH, Fazekas scale 2 (beginning confluence). I) WMH, Fazekas scale 3.

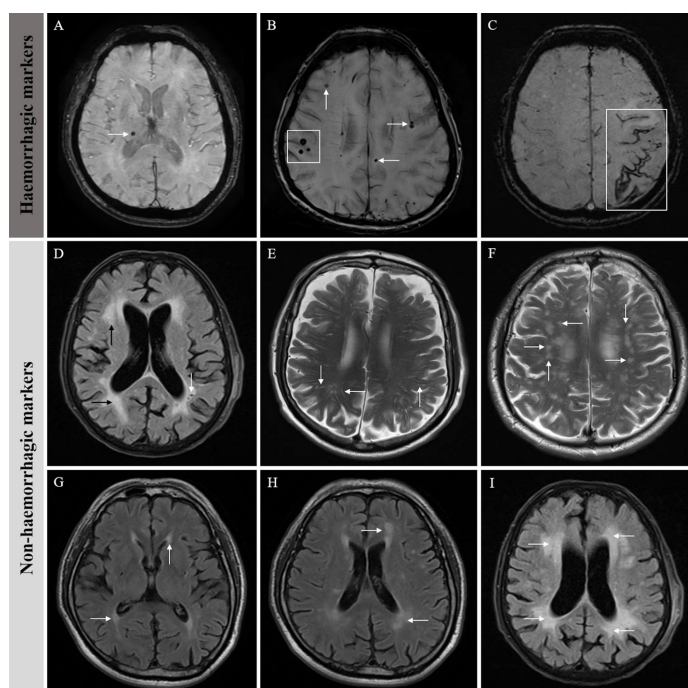


Figure 2. MRI examples of a 66-year-old man with right intracerebral haemorrhage (ICH) fulfilling Boston criteria v2.0 for diagnosis of sporadic cerebral amyloid angiopathy. A) Axial non-contrast CT brain revealed lobar ICH at the right temporoparietal lobe with finger-like projection (FLP). B) Axial SWI demonstrated disseminated cortical superficial siderosis (white box) and multiple lobar cerebral microbleeds (white arrow). C) and D) Axial T2-weighted MRI showed confluent areas of white matter hyperintensity (white arrow) and moderate perivascular spaces (PVSs) in centrum semiovale (black arrow).

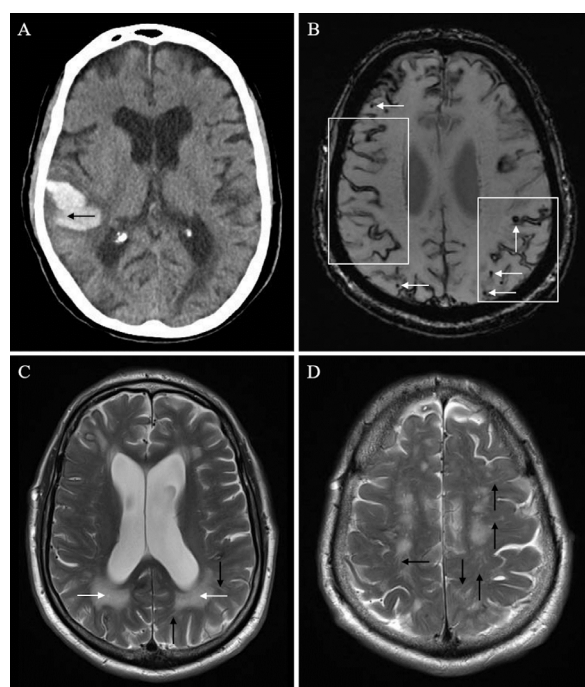


Figure 3. MRI examples of an 81-year-old hypertensive woman diagnosed with mixed cerebral small vessel disease (cerebral amyloid angiopathy–deep perforator arteriopathy). A) and B) Axial FLAIR showed confluent patchy T2/FLAIR hyperintense white matter lesions at the bilateral cerebral deep and periventricular white matter. C) and D) Axial SWI demonstrated multiple hypointense foci of cerebral microbleeds at deep (bilateral thalami and basal ganglia) (white arrow), subcortical, and lobar (black arrow) areas.

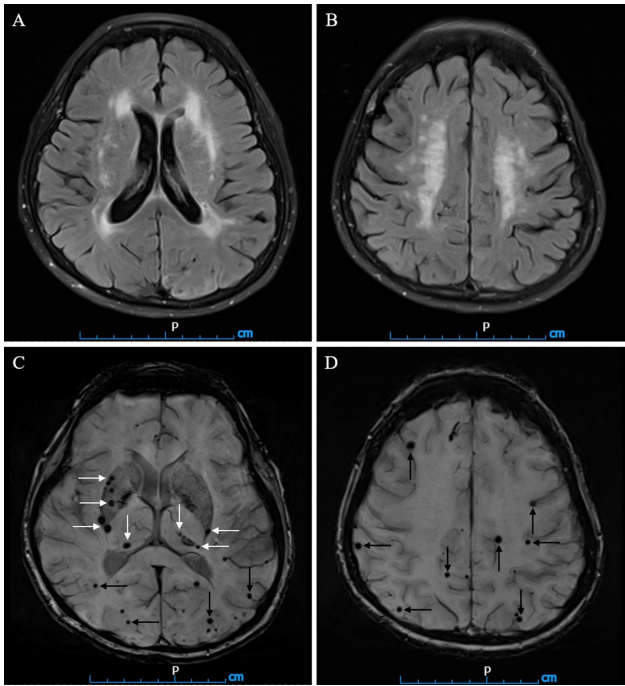


Table 1 Grading of gait disturbance in CSVD. Adapted from the reference.¹⁶

Gait disturbance	Grade 1: mild	Grade 2: moderate	Grade 3: severe
LF	Mild unsteadiness, walks slowly, small steps, broadened base, regular rhythm	Severe unsteadiness, breakdown of gait rhythm with irregular step length and timing	Unable to walk
PCF	Difficulties with turns and on stairs without handrail, occasional falls	Stands with minor support, falls if unsupported when turning or raising from chair	Unable to stand unsupported
GIF	Mild start hesitation, occasional freezing	Severe start hesitation, frequent freezing	Unable to initiate walking

Abbreviations: CSVD, cerebral small vessel disease; GIF, gait ignition failure and freezing; LF, locomotion failure; PCF, postural control failure.

Table 2. SVD CADMUS phenotype criteria. Adapted from the reference.³³

	Main classification
CAA	Boston criteria v2.0 Supratentorial lobar ICH or non-aneurysmatic, cSAH <u>AND</u> ≥1 of the following: <ul style="list-style-type: none"> • ≥1 additional, supratentorial lobar, cortical or subcortical haemorrhagic lesion (ICH, CMB, cSS/cSAH distant to the index ICH) • >20 CSO-PVSs per hemisphere† • Multispot WMH pattern‡
DPA	Deep supratentorial or brainstem ICH <u>AND</u> ≥1 of the following: <ul style="list-style-type: none"> • ≥1 additional, deep supratentorial or brainstem haemorrhagic lesion (ICH, CMB) • ≥1 deep supratentorial or brainstem lacune • Periventricular white matter lesions Fazekas grade ≥2 Additional SVD features can be
Mixed CAA–DPA*	Concomitant presence of characteristic features for CAA and DPA
Undetermined SVD*	Signs of SVD on MRI but not fulfilling criteria for CAA, DPA, or mixed

† and ‡ used the same definitions with the Boston criteria v2.0

* Details of the main classification for mixed CAA–DPA and undetermined SVD are fully illustrated in the reference.³³

Abbreviations: CAA, cerebral amyloid angiopathy; CADMUS, CAA, Arteriosclerosis/DPA, Mixed CAA–DPA SVD, Undetermined SVD; CMB, cerebral microbleed; cSAH, convexity subarachnoid haemorrhage; CSO-PVSs, centrum semiovale perivascular spaces; cSS, cortical superficial siderosis; DPA, deep perforator arteriopathy, ICH, intracerebral haemorrhage; SVD, small vessel disease, WMH, white matter hyperintensity.