2Clinical neuroimaging in intracerebral haemorrhage related to cerebral small vessel disease: contemporary practice and emerging concepts

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Abstract

Introduction: About 80% of all non-traumatic intracerebral haemorrhage (ICH) are caused by the sporadic cerebral small vessel diseases deep perforator arteriopathy (DPA, also termed hypertensive arteriopathy or arteriolosclerosis) and cerebral amyloid angiopathy (CAA), though these frequently co-exist in older people. Contemporary neuroimaging (MRI and CT) detects an increasing spectrum of haemorrhagic and non-haemorrhagic imaging biomarkers of small vessel disease which may identify the underlying arteriopathies.

Areas covered: We discuss biomarkers for cerebral small vessel disease subtypes in ICH, and explore their implications for clinical practice and research.

Expert opinion: ICH is not a single disease, but results from a defined range of vascular pathologies with important implications for prognosis and treatment. The terms "primary" and "hypertensive" ICH are poorly defined and should be avoided, as they encourage incomplete investigation and classification. Imaging-based criteria for CAA will show improved diagnostic accuracy, but specific imaging biomarkers of DPA are needed. Ultra-high-field 7T-MRI using structural and quantitative MRI may provide further insights into mechanisms and pathophysiology of small vessel disease. We expect neuroimaging biomarkers and classifications to allow personalized treatments (e.g. antithrombotic drugs) in clinical practice and to improve patient selection and monitoring in trials of targeted therapies directed at the underlying arteriopathies.

Key words: Intracerebral hemorrhage, small vessel diseases, cerebral amyloid angiopathy, deep perforator arteriopathy, hereditary small vessel disease, amyloid-related inflammation, neuroimaging, MRI, CT, emerging strategies

Article highlights

- As a first step in intracerebral haemorrhage (ICH) investigation, treatable causes, such as macrovascular bleeding sources should be sought. Age, lobar or posterior fossa haemorrhage location (versus deep ICH), absence of small vessel disease and abnormal vessels on CT angiography independently predict a higher probability of an underlying macrovascular cause[1].
- The majority of ICH is due to sporadic small vessel diseases (SVD), namely deep perforator arteriolopathy (DPA) and cerebral amyloid angiopathy (CAA). DPA mainly affects mainly small arteries and arterioles in the basal ganglia, thalami, brainstem, deep cerebellar nuclei and white matter (medullary) perforators[2], while CAA affects leptomeningeal and superficial cortical vessels[3].
- MRI is the gold-standard for the non-invasive diagnosis of SVD. Presence, distribution and severity of SVD markers (cerebral microbleeds, cortical superficial siderosis, white matter hyperintensities, lacunes, enlarged perivascular spaces) are associated with the underlying type and severity of the SVD and can help to predict ICH recurrence.
- Non-invasive diagnostic criteria for CAA allow the diagnosis of probable CAA even in the absence of supporting pathology. The Boston criteria include the presence of multiple lobar hemorrhagic manifestations (macro- and microbleeds, cSS) on MRI or CT and no concurrent cause for ICH[4], while the Edinburgh CT criteria require lobar haemorrhage with subarachnoid extension and/or finger-like projections in patients with at least one *APOE* ε4 allele[5]. No comparable criteria exist for DPA. Non-haemorrhagic MRI markers (e.g. enlarged perivascular spaces) also show promise as biomarkers of the type of underlying arteriopathy.
- CSF biomarkers including Aβ-40, Aβ-42 and others might be a promising marker to incorporate in future diagnostic studies and criteria for CAA. The differences in biomarker patterns for Aβ-40 and Aβ-42 in comparison to Alzheimer's disease presumably reflect specific differences in the pathophysiology of these amyloidopathies.
- Advanced and ultra high-field MRI might improves the detection, precise localisation and characterisation of previously underestimated SVD markers and contribute towards a profounder understanding of SVD.

1. Introduction

The term intracerebral haemorrhage (ICH) describes cerebral injury due to bleeding into the brain parenchyma resulting from rupture of a cerebral blood vessel. ICH is a devastating disease with high morbidity and mortality[6]. As for ischaemic stroke, ICH is not a single disease and occurs due to a distinct range of vascular pathologies. It is essential to investigate the cause of ICH since this influences optimal treatment strategies and the prognosis for recurrence and functional outcome[7, 8]. The great majority (> 75%) of non-traumatic ICHs are caused by cerebral small vessel diseases (figure 1)[9]. This has been termed "primary" ICH, but this term is strongly discouraged because it is non-specific, not well defined, and is likely to encourage inadequate investigation, diagnosis and classification.. Two major types of sporadic small vessel disease cause the vast majority of ICHs: cerebral amyloid angiopathy (CAA) and deep perforator arteriolosclerosis (DPA, a term preferred over "hypertensive" small vessel disease since hypertension is neither sufficient nor necessary to cause this arteriopathy or consequent ICH[10])[11]. While DPA is the most frequent ICH aetiology, 15-20% of ICHs are due to a variety of causes, the most common group being "macrovascular" lesions including arteriovenous malformations and aneurysms[12, 13]. Geographical variation is known for ICH with highest prevalences in Asian countries[14]. While we are not aware of studies investigating the prevalence of DPA in a general population, a Japanese study estimated the prevalence of CAA to 4.64/100'000 patients[15]. One study found that the proportion CAA-related ICH is lower in an Eastern compared to a Western hospital ICH population; this might be explained by a higher incidence of ICH related to hypertensive arteriopathy in East Asian populations[16]. CAA and DPA are both increasingly common with ageing, so many older people have concomitant CAA and DPA on neuroimaging[17] and post-mortem studies[5]. In addition, there are some monogenic cerebral small vessel diseases that may cause ICH, e.g. COL4A1/2 mutations, CADASIL or Fabry disease, but these are rare[18] .

Although early mortality after acute ICH is high, more than 70% of patients with ICH survive 3 months or longer[19]. These patients face not only the risk of recurrent ICH but also ischemic stroke and other vaso-occlusive vascular events[8]. The relative and absolute rates of these outcomes may depend on the presence and severity of the underlying small vessel disease, as well as vascular risk factors or medical treatments (e.g. antithrombotic drugs). Therefore, identifying and classifying small vessel disease in survivors of ICH is clinically relevant to inform patients, families, caregivers and treating physicians about prognosis and in planning secondary prevention strategies.

Modern neuroimaging using MRI is essential for in-vivo diagnosis of small vessel diseases by detecting an increasing variety of imaging markers of small vessel vascular damage[11]. These small vessel disease markers have been further complemented by novel techniques (advanced and novel MRI sequences, high-field MRI, PET), which allow even more in-depth exploration of the underlying small vessel diseases and their influence on brain architecture and metabolism.

In this review, we provide an overview on the role of neuroimaging practices for characterization of small vessel diseases in ICH, as well as our perspectives on emerging strategies for diagnosis.

2. Aetiological work-up and diagnostic criteria

The clinical diagnosis of a stroke syndrome requires immediate brain imaging (CT or MRI) to differentiate between stroke due to ICH or ischaemia (figure 2). Acute brain imaging can also detect findings associated with haematoma expansion (a major determinant of functional outcome) such as the spot sign[20] on contrast-enhanced CT angiography and heterogeneous density, hypodensities, a fluid level, or swirl, black hole, blend, island, or satellite signs on non-contrast CT[21].

As first diagnostic step, structural (tumor, brain metastases) or macrovascular (arteriovenous malformations, aneurysms and dural arteriovenous fistulae) causes should be sought and excluded[22] as these conditions may require dedicated treatments. Early CT angiography and magnetic resonance angiography (MRA) have a high diagnostic accuracy to identify intracranial vascular malformations in selected populations in comparison with acute catheter intra-arterial digital subtraction angiography. It is therefore reasonable for all patients with ICH to undergo acute CTA or MRA where possible, but the decision of whether to do intra-arterial digital subtraction angiography is more challenging given the procedural risk (around 0.5-1.0%). The selection of most-appropriate candidates for intra-arterial digital subtraction angiography, still considered as a reference standard to detect macrovascular causes, can be rationally guided using clinical and neuroimaging factors; a combination of CTA, small vessel disease markers and pre-haemorrhage hypertension can predict the likelihood of finding a macrovascular cause for acute ICH[22]. A recently developed score (DIAGRAM)[1] has been externally validated[13] . The score is based on three independent predictors: age, lobar or posterior fossa (vs deep) location of the bleeding and absence of small vessel disease and, optionally, CT-angiography. The probability of finding a macrovascular cause was 1% in patients aged 51-70 years with deep haemorrhage location and small vessel disease features, while the probability of a macrovascular cause was over 50% in patients aged 18-50 years with lobar or posterior fossa ICH and without small vessel disease. Noninvasive imaging with MRI arterial spin labelling shows promise to noninvasively identify arterial-venous shunting associated with macrovascular causes of ICH but is not yet in widespread clinical use[23].

MRI is the optimal imaging modality to detect small vessel diseases that causes more than 75% of all ICHs[9, 24]. We suggest that MRI should therefore be performed in all patients with ICH in the absence of contraindications as soon as possible to allow rapid diagnosis of the underlying small vessel disease, and assessment of prognosis. The optimal sequences include FLAIR, T2, T1, SWI, DWI/ADC (scanning time approximately 20-30 minutes) to detect the neuroimaging markers needed for diagnosis. If not yet performed in the acute phase, angiography should also be included at this time point. This MRI should

ideally be performed after a few days (to visualize small vessel disease markers), but can be of value at any time point after diagnosis; typically we recommend this is performed up to about 3 months. An advantage of delayed imaging is that the acute blood has had time to be cleared, giving a better chance of seeing – in addition to the necessary small vessel disease biomarkers - an underlying structural cause of ICH, for example cavernomas or mass lesions.

Additional examinations, such as cerebrospinal fluid (CSF) analysis or broader laboratory testing are not routinely performed, but should be considered if a rarer ICH cause (such as an infectious[25] or autoimmune[26] aetiology) is suspected.

3. Cerebral small vessel disease subtypes

Although cerebral small vessel disease comprises a wide spectrum of sporadic, genetic and inflammatory disease, the common sporadic types (DPA and CAA) make up the vast majority (figure 1). DPA affects mainly small deep perforating arteries and arterioles in the basal ganglia, thalami, brainstem, deep cerebellar nuclei and white matter (medullary) perforators[2]. Histological findings include concentric hyaline thickening of the small vessel wall. It is often called "hypertensive" arteriopathy in reference to one of the main risk factors, but hypertension is probably neither sufficient nor necessary to cause this disease process, so this term is not recommended[10]. The frequently heard diagnostic label of "hypertensive bleed" in patients with a history of hypertension and a deep ICH is also unhelpful, especially since the presence of these factors is not a reliable guide to exclude a macrovascular cause. Patients with DPA are at risk of subcortical ischaemic stroke, deep intracerebral hemorrhage and vascular cognitive impairment[2]. Although there are currently no validated diagnostic criteria for DPA, recognized imaging biomarkers include white matter hyperintensities, lacunes, recent small subcortical infarcts, basal ganglia enlarged perivascular spaces and deep cerebral microbleeds[24, 27].

In sporadic CAA, reduced perivascular drainage leads to β-amyloid deposition in the leptomeningeal and superficial cortical arteriolar walls causing vessel fragility[3]. CAA is mainly characterized clinically by symptomatic lobar parenchymal and convexity subarachnoid haemorrhages[3, 28] and cognitive impairment. Although pathophysiology of Alzheimer's disease and CAA are closely related, and overlap, different cognitive deficit profiles are described for patients with Alzheimer's disease and CAA[29]. About 15% of patients with CAA can experience transient, focal neurological episodes (TFNE) consisting typically of positive and negative symptoms spreading from one body part to another (often the hand into the face), which are most often due to cortical spreading depression due to convexity subarachnoid bleeding in a cortical sulcus[30].

Post-mortem full brain histopathological analysis is the gold standard for diagnosis of CAA[31] but is seldom available in clinical practice. Biopsy is used as a surrogate, with the limitation of possible

sampling errors[32]. In clinical practice, only a minority of patients undergo haematoma evacuation offering the possibility of performing brain biopsy. Characteristic changes in CAA histopathology samples include congo red positive vessel walls and positive immunocytochemistry staining for amyloid[33]. In later stages, fibrinoid vessel wall necrosis and cracking vessels with a "vessel-within-a-vessel" aspect can be observed as well[33]. Typical findings in DPA are lipohyalinosis or fibrinoid necrosis of vessel walls as well as microaneurysms in the basal ganglia and thalamic vessels[33]. Several post-mortem neuropathological studies found that DPA and CAA were commonly observed simultaneously in patients with ICH[5, 34] One post-mortem study found that in patients with non-lobar intracerebral haemorrhage (generally considered exclusively due to DPA), 6/48 (12.5%) had severe CAA, while among patients with lobar haemorrhage, 48/62 (77%) had evidence of other small vessel disease in addition to CAA[7].

A rare subtype of CAA is CAA-related inflammation, which typically presents with a subacute encephalopathy, often with focal neurological signs or seizures. The brain imaging findings include asymmetric white matter oedema and CAA biomarkers including lobar CMBs and cortical superficial siderosis[35]. An inflammatory response to vascular amyloid deposition has been observed which responds well to immunosuppressants[36]. Inflammatory CAA covers a spectrum ranging from cerebral amyloid angiopathy-related inflammation (CAA-ri) characterized by perivascular, granulomatous inflammation[36] to amyloid-beta related angiopathy (ABRA) with granulomatous vasculitis and similarities to primary central nervous system angiitis[37]. Clinically, patients present with cognitive decline, epileptic seizures and headaches[38]. CAA-ri can often be diagnosed in patients aged 40 or older through clinicoradiological criteria (example in figure 3) to allow timely treatment of candidates in the absence of biopsy[35], but atypical features are reported and the diagnosis remains challenging.

Interestingly, a study investigating amyloid beta-antibodies for treatment of Alzheimer's disease had to be discontinued due to clinical and histopathological findings similar to CAA-ri [28, 39]. These amyloid-related imaging abnormalities (ARIA) can be classified into two categories: ARIA-E is characterized by sulcal effusions and vasogenic oedema in FLAIR sequences, while ARIA-H stands for haemosiderin depositions and microhaemorrhages on GRE-T2* sequences[40]. A systematic review and meta-analysis of phase III amyloid-antibody trials found an increased risk for ARIA in the active compared to the placebo group (relative risk 4.3) and calculated a number needed to harm of 4-8 patients[41].

Hereditary cerebral haemorrhage with amyloidosis-Dutch type (HCHWA-D) is a rare genetic disease due to a mutation in the amyloid-β E22Q gene that leads to a shift in β-40/ β-42 ratio. It clinically manifests as early-onset cerebral amyloid angiopathy and dementia[42]. MRI findings are similar to patients with sporadic CAA[43, 44]. Ischaemic manifestations of CAA may precede clinical symptoms (ICH, dementia), while hemorrhagic small vessel disease markers are more frequent in symptomatic

compared to pre-symptomatic patients[44]. Even in presymptomatic disease, patients show increased PiB retention in PiB-PET[45]. In comparison to controls or pre-symptomatic mutation carriers, HCHWA-D positive CAA patients show decreased structural connectivity in the periventricular frontal and occipital regions as well as the occipital lobe[46].

Monogenic cerebral small vessel diseases - including Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), COL4A1 or COL4A2 mutations - can also cause ICH. CADASIL is caused by various mutations in the NOTCH3 gene, a transmembrane receptor which is solely expressed in smooth muscle cells[47]. Although the mutation is known, pathophysiological mechanisms leading to lacunar ischaemia, dementia, migraine, neuropsychiatric disturbances and seizures are not fully understood yet[47, 48]. Intracerebral haemorrhage occurs in about 25% of CADASIL patients[49] and is seemingly associated with specific mutations (in particular R544C) and presence of deep cerebral microbleeds[50]. Clinical and neuroimaging characteristics associated with a high probability of NOTCH3-positive CADASIL include familial history of stroke, temporal pole hyperintensities, external capsule lacunes and severe white matter hyperintensities[51]. Given that only a minority of patients with suspected CADASIL test positive for NOTCH3 mutations[51], neuroimaging may be a useful screening method to identify patients with a high yield of genetic testing.
CARASIL is an autosomal recessive mutation in the HTRA1 gene, which is rarer than CADASIL[52]. Although it seems to predominantly affect Chinese and Japanese people, cases in Caucasians have been described as well[53]. Clinical presentation includes lacunar strokes, progressive dementia, alopecia and attacks of low back pain, ICH is rare[54]. Neuroimaging findings are comparable to those in CADASIL[52].

Autosomal-dominantly inherited mutations in the collagen 4 gene (COL4A1/COL4A2), coding for collagen type IV protein chains, which are present in basal membranes of small vessels, are associated with delayed development in childhood, early onset drug-resistant epilepsy, ICH and strokes early in life[55, 56]. MRI-findings in patients with COL4A1 or COL4A2 mutations include porencephaly, malformations of cortical development and white matter lesions such as periventricular leukoencephalopathy, ventricular dysmorphisms or white matter rarefication[56].

In an individual patient data meta-analysis in patients with ICH, lacunar strokes or white matter hyperintensity, presence of COL4A2 single nucleotide polymorphisms were associated with spontaneous (=non-hereditary) deep ICH and lacunar strokes, suggesting a role in the pathophysiology of sporadic small vessel disease as well[57, 58].

4. MRI- and CT-based diagnostic criteria for CAA

To overcome limitations of biopsy/histopathology-based diagnosis of small vessel disease, imaging-based diagnostic criteria have been developed to allow in-vivo diagnosis of CAA (figure 4). The modified Boston criteria allow the diagnosis of probable CAA in patients older than 55 years with appropriate clinical history and multiple lobar hemorrhagic manifestations (macro- and microbleedings, cSS) on CT or MRI and no concurrent cause for ICH even in the absence of supporting pathology. The modified Boston criteria have been validated using MRI against pathology with high sensitivity (94.7%; 95% CI 82.7–98.5) and specificity (81.2%; 95% CI 61.5–92.7)[4]. Currently, a consortium from the international CAA association is developing the Boston criteria 2.0, which aim to improve the sensitivity, while maintaining very good specificity, especially in non-ICH populations[59]. One of the most important clinical limitations of the Boston criteria is the requirement for absence of a concurrent cause for ICH or deep CMBs, given that a majority of elderly patients suffer from hypertension and often show signs of DPA at the same time[17].

As MRI has limited availability in many health care settings, alternative diagnostic criteria for CAA were developed. Recently the Edinburgh CT and apolipoprotein (*APOE*) genotype criteria were developed[5] in a subset of patients from a population-based, prospective cohort who subsequently underwent post-mortem autopsy after death. Among patients with lobar haemorrhage, the possession of at least one *APOE* ε4 allele, and the presence of two CT criteria - subarachnoid extension and finger-like projections - were all associated with CAA on autopsy. Subarachnoid hemorrhage and either *APOE* ε4 possession or finger-like projections showed 96% specificity (95% CI 78-100) for CAA and can be considered as 'rule in' criteria[5]. On the other hand, absence of subarachnoid haemorrhage and APOE ε4 allele allows to rule out CAA in patients with lobar ICH[5]. In the assessment of the diagnostic accuracy of a simpler model based on CT features alone, subarachnoid hemorrhage alone showed 89% sensitivity (95% CI 73-96), while the presence of both subarachnoid hemorrhage and finger-like projections showed 100% specificity (95% CI 84-100). The effective diagnosis of CAA based on acute CT features in patients with lobar ICH could rapidly provide important insights into the prognosis for the patient[60]. However, the Edinburgh criteria are not yet validated in survivors of ICH, and their diagnostic accuracy in such cohorts with less severe or smaller volume haemorrhages is not yet known.

External validation of the Edinburgh criteria in patients with Dutch-type hereditary CAA[61] showed a sensitivity of 76% for subarachnoid hemorrhage and 58% for finger-like projections. This study found also that in patients with large hematomas (>40 mL), the sensitivity of both subarachnoid hemorrhage and finger-like projections was over 81% (95% CI 70%-92%), meanwhile the sensitivity was lower (<50%) in small haemorrhages (<15 mL). Another study retrospectively applied the Edinburgh criteria to the first available brain CT scans of an unselected cohort of patients hospitalized for first-ever lobar ICH (*n*=178 with lobar ICH)[62] and found higher National Institutes of Health Stroke Scale (NIHSS) score and higher median haemorrhage volume compared to those with one or no features of the

Edinburgh CT criteria. Patients fulfilling the Edinburgh criteria also showed higher short-term fatality and higher modified Rankin scale scores at discharge.

5. Current practice in cerebral small vessel disease imaging

CT is the primary imaging modality to investigate acute stroke patients (including those with ICH) in most centers worldwide. Imaging features of small vessel disease that can be seen on CT scanning include leukoaraiosis, atrophy and lacunes[63]. Leukoaraiosis is described as areas of low attenuation in the periventricular and deep white matter on CT[64]. Lacunes are defined as round or ovoid subcortical fluid-filled cavities (between 3-15mm in diameter), with signal similar to cerebrospinal fluid[24]. Atrophy can also be assessed on CT, which can be related to small vessel disease, but is not specific[63]. However, MRI is the gold standard[11] as dedicated sequences allow identification and grading of a wide spectrum of haemorrhagic and non-haemorrhagic imaging features[24] (figure 5).

5.1 Haemorrhagic MRI markers

Haemorrhagic markers of small vessel diseases include cerebral microbleeds (CMB) and cortical superficial siderosis (cSS – figure 5, left panel). CMBs are defined as round or ovoid lesions of up to 10 (usually 2-5) mm diameter with signal void on susceptibility sequences[24]. Differential diagnosis of CMBs includes structures with paramagnetic (containing e.g. iron) or diamagnetic (containing e.g. calcium) characteristics, such as microaneurysms or –dissections and microcalcifications[65]. The MARS classification helps to determine CMB location according to a visual anatomical reference diagram in different relevant regions (lobar, deep and infratentorial)[66]. CMBs located in the thalamus, basal ganglia, brain stem and cerebellum are associated with hypertension and correspond to fibrohyalinosis in histopathology[67]. In patients with cardiovascular disease (lacunar ischaemic strokes, coronary heart disease etc.), presence of CMBs is associated with decreased cerebrovascular reactivity assessed with 7T-BOLD fMRI, possibly reflecting the increased vessel stiffness[68]. Cortical or subcortical microbleeds were only found in amyloid-positive brains[67] and their presence correlates with amyloid burden as assessed by C-Pittsburgh compound B (PiB)-PET scan[69]. However, sensitivity of premortal MRI for the presence of CMBs on autopsy was found to be as low as 51.9% (95% CI 37.6–66.0%)[70]. The role of cerebellar CMBs**,** which are prevalent in about 40% of patients with supratentorial haemorrhage[71], is not yet completely clear. However, emerging evidence suggests similar patterns compared to supratentorial CMB distributions. Currently, definitions of superficial versus deep cerebellar microbleeds vary and include dichotomization into cortex vs. dentate nucleus[72] or cortex or vermis vs. deep cerebellar gray nuclei and white matter[71]. While brainstem and deep cerebellar CMBs seem to be associated with supratentorial deep CMBs (indicating DPA), strictly superficial cerebellar CMBs are associated with MRI-signs of CAA according to the modified Boston criteria[72], amyloid-positive PET[73] as well as histopathological evidence of CAA[71]. Conversely, strictly superficial cerebellar haemorrhage is associated with supratentorial, strictly lobar CMBs[74].

On MRI, cSS can be identified in T2*-GRE or preferably on SWI sequences as curvilinear signal intensity in the subarachnoid space and/or superficial cortical layers[75]. cSS is described as focal (affecting ≤ 3 gyri) and disseminated (affecting > 3 gyri), based on the assumption that one bleeding focus usually affects at maximum 3 gyri[76]. Focal cSS should further be evaluated regarding multifocality with the recently proposed multifocality score[77]. Histopathologically, cSS corresponds to extracellular haemosiderin depositions in the superficial cortical layers I-III and the subarachnoid space and is associated with higher CAA severity in leptomeningeal vessels and reduced CAA severity in cortical vessels[78]. The same study found a correlation between high cSS severity and cortical microinfarcts[78]. Although the causal relationship is not confirmed, it seems pathophysiologically likely that cSS is the long-term sequelae resulting from acute convexity subarachnoid haemorrhage (cSAH). In a cohort study of CAA patients without previous haemorrhage, prevalence of disseminated cSS was found to be much higher in patients presenting with acute cSAH[79]. Furthermore, cortical subarachnoid haemorrhage associated with CAA can occur remote or even in the absence of CAA-related ICH and was found to be associated with a higher CAA-load in meningeal vessels in an autopsy study[80]. cSS and cSAH are both linked to transient focal neurological episodes (TFNE), sometimes also called "amyloid spells"[79, 81, 82].

Haemorrhagic SVD markers are prognostic markers,too. A retrospective MRI study found that presence of cSS was associated with more haematoma expansion, while the absence of CMBs was associated with larger hematoma volumes and hematoma expansion[83]. Furthermore, a meta-analysis demonstrated that CMBs are associated with a higher risk of recurrent ICH, correlating with higher CMB load (> 10 CMBs in non-CAA-related ICH OR 5.57, in CAA-related ICH OR 3.4)[84]. Similarly, patients with cSS have a higher risk of symptomatic lobar ICH (HR 2.53 for all cSS categories, HR 3.16 for disseminated cSS)[85].

5.2 Non-haemorrhagic MRI markers

The spectrum of non-haemorrhage MRI markers comprises subcortical white matter hyperintensities (WMH), enlarged perivascular spaces (ePVS), lacunes and recent, small subcortical infarctions (RSSI, figure 5 – right panel).

Subcortical WMH are punctate or extensive hyperintensities visible in T2-sequences and derivates (such as fluid attenuated inversion recovery) without central cavitation. Pathophysiology of WMH has not yet been completely understood. They seem to result from endothelial dysfunction[86] leading to an impaired blood-brain-barrier with leakage into the brain parenchyma[87], resulting in higher volumes of free extracellular fluid[88]. One major challenge in the interpretation of studies investigating small vessel disease-related subcortical hyperintensities is their high prevalence in the normal aging population[89].

The most widely used classification of WMH is the Fazekas scale[89], which grades the presence of WMH according to severity (0-3) and separately according to periventricular or deep location. Alternative classification (developed for CT) include the Van Swieten scale[90]. Recently different WMH distribution patterns have been defined[91] . While a multiple subcortical spots WMH pattern is associated with the presence of CAA markers independently of age, an association of a posterior-predominant white matter hyperintensity pattern with CAA has been found[91, 92]. In contrast, the peri–basal ganglia pattern seems to be associated with high DPA burden, but also with high total white matter hyperintensity burden and is therefore rather nonspecific[91].

Enlarged perivascular spaces are cerebrospinal fluid-filled spaces surrounding small brain vessels < 3mm wide with round or ovoid appearance in perpendicular and curvilinear appearance in transverse views. They appear isointense to the CSF (hyperintense in T2 and hypointense in T1 sequences)[24, 93]. Doubal et al. proposed a 5-grade grading system: Centrum semiovale perivascular spaces and basal ganglia perivascular spaces are assessed separately. For the grading, which is done by localization (centrum semiovale vs. basal ganglia), the hemisphere with the higher count is used[93]. Given their association with CAA-related haemorrhage[94] and pathology-proven CAA[95], centrum semiovale perivascular spaces are included as a supportive feature for CAA diagnosis in the Boston criteria 2.0[96, 97]. Perivascular spaces have recently been identified as a potential novel imaging marker for the risk of ICH among patients taking oral anticoagulants (multivariable HR 8.96, 95% CI 2.41–33.4), underlining their potential role as an imaging marker of severe small vessel disease[98].
Lacunes are residues of ischemic or hemorrhagic events related to small vessel occlusion or haemorrhage, and present as round or ovoid, cerebrospinal fluid-filled cavities of 3-15mm in diameter, corresponding to the territory of one arteriole[24]. In comparison to other small vessel disease markers, research on lacunes in ICH is sparse, although they are frequent in patients with DPA and CAA[99]. Lobar lacunes in ICH are independently associated with CAA, while this is the case for deep lacunes and DPA, and interrater agreements for the presence of lacunes seems to be good for both locations[99]. CAA-associated lacunes are often in close proximity to CMBs and white matter lesions, suggesting a potential pathophysiologic interrelationship[99, 100]. Whether lacunes are associated with decreased cerebrovascular reactivity, is debated and possibly related to the assessment method[68, 101].

Recent small subcortical infarctions are small infarcts in the territory of one arteriole, which one can identify best on diffusion-weighted imaging (DWI) sequences[24]. They occur in about 20% of ICH patients[102]. DWI lesions adjacent to acute haematomas[103, 104] – resulting from local haematoma-related processes - have to be differentiated from remote lesions from the index haemorrhage, are frequent and may be due to aggressive blood pressure reduction in patients with reduced cerebral autoregulation or compression resulting from elevated intracranial pressure[104]. Considering the association of small vessel disease markers and DWI lesions[102, 103], a direct manifestation of the underlying small vessel disease

seems possible[105, 106]. A pro-ischaemic state after the index ICH as well as withdrawal of antithrombotic therapy leading to ischaemic events have been discussed as possible explanations for lesions occurring in the subacute phase, as well[104]. According to a meta-analysis, DWI lesions occur as frequently in DPA- than in CAA-associated haemorrhage[102], although several studies suggested a higher prevalence of DWI lesions in CAA[106, 107]. DWI lesion location differs amongst ICH subtypes with mostly frontal DWI lesions in CAA and parietal lesions in DPA[105].

In addition to determining the presence, location and severity of small vessel disease imaging markers to define the underlying small vessel disease type, we suggest to consider the ICH location with visual scales, such as the cerebral haemorrhage anatomic rating instrument (CHARTS)[108]. Table 1 gives an overview on relevant scales and scores for the workup of small vessel disease-related ICH.

6. Genetics and CSF

Knowledge about genetics in cerebral small vessel disease has emerged during the last years[52]. The role of *APOE* ε2 and ε4 alleles has been intensively studied[109-112] including its importance as risk factors for spontaneous lobar haemorrhage, haemorrhage volume mortality and poor functional outcome[110]. There is also emerging evidence for the association between cSS as key imaging marker of CAA and APOE genotype[113, 114]. The *APOE* ε2 and ε4 alleles are thought to be associated with different underlying mechanisms, where *APOE* ε4 has been suggested to promote vascular deposition of amyloid-β and *APOE* ε2 promotes vascular pathology, including vessel cracking and fibrinoid necrosis, which can contribute to vessel rupture[113].

Amyloid-β is produced by the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases[3]. A neuropathological indication of CAA is the progressive accumulation of amyloid-β in the walls of cortical and leptomeningeal small vessels. A recent meta-analysis investigated 4 core biomarkers of brain amyloid burden (amyloid-β 40 (Aβ40), amyloid-β 42 (Aβ42)), neurodegeneration (total tau (t-tau)) and tangle pathology (phosphorylated tau (p-tau)) in patients with symptomatic sporadic CAA compared to controls and patients with Alzheimer's disease[115]. The results suggested that analysis of core CSF biomarkers could differentiate patients with CAA from healthy age-matched controls or patients with Alzheimer's disease. Aβ40 was lower in patients with CAA compared to healthy controls or patients with Alzheimer's disease and Aβ42 was lower in patients with CAA compared to controls but of a similar level compared to patients with Alzheimer's disease. Moreover, CSF tau concentrations in patients with CAA were higher compared to controls, though lower compared to patients with Alzheimer's disease. Despite the neuropathological overlap between CAA and Alzheimer's disease, the findings from this meta-analysis suggest that distinct CSF patterns are able to distinguish between CAA and Alzheimer's disease in clinical practice[115]. Another similar study investigated the same core biomarkers in association with cSS in patients with probable or possible CAA according to modified Boston criteria and mild cognitive impairment[116]. Aβ42 levels were lower in

patients with cSS compared to those without cSS, and lower in patients with disseminated cSS compared to those with focal cSS. Meanwhile, this study found no difference in CSF levels of Aβ40, t-tau and p-tau in patients with and without cSS. These findings suggest that Aβ42 may be a potential biomarker of cSS severity, though further studies would be required to confirm this.

CSF biomarkers might represent a promising emerging strategy, particularly in the diagnosis of CAA. Significantly lower CSF levels of Aβ40 and Aβ42 in patients with possible or probable CAA likely indicates the entrapment of Aβ40 and Aβ42 in the cerebral vasculature[117]. Amyloid-β deposition within cerebral vessels can have many complex effects that can lead to brain injury. Key morphological changes include the loss of smooth muscle cells, thickening of vessel walls, lumen restriction, endothelial dysfunction and a reduction in vessel compliance, which can result in brittle, fragile vessels susceptible to rupture and leakage[3]. An increasing understanding of the molecular pathogenesis of Amyloid-β in the cerebral vasculature will help in the development of potential therapeutic interventions, such as anti-amyloid therapies[117]. Serum biomarkers might in future be a useful noninvasive way to detect and quantify relevant biomarkers for small vessel diseases.

7. Emerging imaging strategies

7.1 Advanced imaging using MRI

Quantitative susceptibility mapping (QSM) provides quantitative analysis of susceptibility artefacts and may be highly valuable to assess haemorrhagic lesions[118]. Quantitative MRI may be valuable to assess long-term progressive tissue structure changes in survivors of ICH with small vessel disease.

Diffusion-tensor imaging (DTI) detects fractional anisotropy, describing directionality of diffusion of water molecules, which can be used as a surrogate for the integrity of neural fibers[119]. A particular interest lies in visualization and quantification of organized fiber tracts, which can be interrupted or displaced by ICH[120]. Reduced fractional anisotropy in patients with subacute deep ICHs was associated with poor motor outcome[119, 121, 122], but has not yet established as a prognostic marker in clinical practice. Reasons for this may be the ongoing debate on the region of interest to assess fractional anisotropy and methodological and technical differences between studies, which impair comparability[122]. DTI in combination with white matter tract skeletonisation and mean diffusivity assessments was also used to quantify white matter lesion load in small vessel diseases: Peak width of skeletonized mean diffusivity was proposed as a sensitive marker for longitudinal monitoring in small vessel diseases[123], but is not currently used in clinical practice.

7.2 Opportunities of ultrahigh field MRI – new imaging markers and novel techniques

Magnetic field strengths of 1.5 or 3 Tesla are frequently used in routine clinical practice[124]. In recent years, research on 7 Tesla MRI has emerged, which benefits from a better resolution and improved

signal-to-noise ratio[124]. 7T MRI allows an increase in sensitivity and better inter-rater-agreement for detection of small vessel disease lesions[124]. For CAA, several new markers preferentially visible on ultrahigh field MRI have been observed: in the occipital cortex of certain CAA patients, we can observe hypointense, linear stripes perpendicular to the cortex ("striped cortex"[125]), pathologically corresponding to calcified cortical penetrating vessels[126]. Intragyral haemorrhages are haemorrhages that only occur in the subcortical white matter of one gyrus[127] . Further, in comparison to lower field strengths, 7T MRI improves precision in assessment of traditional MRI small vessel disease markers such as CMBs (figure 6)[128]. 7T MRI improves the detection, precise localisation and characterisation of previously underestimated small vessel disease manifestations, such as microinfarcts[129] or iron deposits[130], which may help to improve our current understanding of small vessel disease pathophysiology.

To overcome limitations of conventional, qualitative MRI analysis, quantitative MRI provides measures of biophysical parameters including free water, water bound to micro- and macromolecules and the amount of paramagnetic substances (i.e. iron) which has a high sensitivity and specificity to focal and diffuse pathology that are not available through conventional MRI[118]. Quantitative T1 and T2-relaxometry mapping has been used in other chronic diseases of the central nervous system like multiple sclerosis to derive personalized pathology maps[131]. A new approach to quantitative magnetic resonance imaging that allows simultaneous measurement of multiple tissue properties in a single, time-efficient acquisition is Magnetic Resonance Fingerprinting (MRF)[132].

7.3 Amyloid positron emission tomography (PET) imaging

Detection of CAA at early stages with highly specific tests is currently impossible[133]. An early diagnosis of CAA based on amyloid imaging would have important clinical implications in terms of risk for ICH stratification and antithrombotic drug use. Amyloid PET imaging can measure the burden of cerebrovascular and parenchymal amyloid-β deposits.

A meta-analysis investigating amyloid-PET in the diagnosis of CAA found that the overall pooled sensitivity of amyloid-PET for CAA diagnosis was 79% (95% CI 62-89) with a pooled specificity of 78% (95% CI 67-86)[133]. In a subgroup analysis restricted to studies including patients with CAA with symptomatic lobar ICH, amyloid-PET showed 79% sensitivity (95% CI 61-90%) and 84% specificity (95% CI 65-93%). A further diagnostic accuracy meta-analysis of 2 studies using the amyloid tracer ^{18}F-florbetapir-PET, showed that the sensitivity for identifying probable lobar ICH with CAA compared to deep haemorrhage was 90% (95% CI 76-100%) and specificity was 88% (95% CI 74-100%). These findings suggest that amyloid-PET may have a moderate-to-good diagnostic accuracy in identifying patients with probable CAA. One drawback in the use of amyloid imaging is the likelihood of healthy older controls having incipient CAA pathology and/ or Alzheimer's disease, thus amyloid-PET may

have a limited specificity in the diagnosis of CAA[134]. Further studies using amyloid-PET in patients with ICH found higher mean global cortical florbetapir/PiB uptake in patients with CAA-related ICH[135-137] or lobar compared to mixed or deep CMB distribution[138]. Taken together, the role of Amyloid PET seems a promising tool to complement neuroimaging research in small vessel disease. However, the added value of PET to conventional MRI biomarkers in clinical practice remains to be seen.

8. Conclusion

The most frequent causes of ICH are cerebral SVD. Neuroimaging is a safe and non-invasive tool to detect, quantify and differentiate different subtypes including the most common ones, CAA and DPA. While a limited number of small vessel disease markers can be evaluated using CT, MRI is a reference standard for small vessel disease neuroimaging (with relevance for prognosis and potentially for treatment) and should be performed in every patient without evidence of a macrovascular bleeding source (unless there are contraindications), as it allows to determine the underlying small vessel disease. However, the available literature mainly focuses on CAA, leading to many unanswered questions in DPA. In particular, the diagnosis and presumably therapy of DPA might improve if diagnostic criteria for this disease were available. Current classifications do not account for the often observed concomitant pathology of DPA and CAA in the same patient, which may have important implications for long-term prognosis and risks. Given their easy assessment and the well documented correlation of suggestive MRI markers and histopathologic testing with the underlying small vessel disease, MRI markers could be useful in categorizing patients with ICH for future trials. Novel diagnostic criteria using CT allow rapid diagnosis of CAA and may prove significant clinical utility in the acute setting.

Novel developments including ultra-high-field MRI, genetics, Amyloid-PET and CSF may further enhance our understanding of small vessel disease. Current clinical practice focusses on acute phase imaging for small vessel disease, but the underlying cause of ICH is a chronic disease likely to progress over time. Our understanding of disease progression, its predictors, and implications for prognosis and clinical events including ICH remain largely unknown, and are key topics for future research.

9. Expert opinion: Current challenges and future developments

We expect that efforts to diagnose and classify the small vessel arteriopathies, which underly most cases of ICH, as ICH is a relevant contributor to disease burden[14]. The term “primary” ICH will become obsolete as it is nonspecific and discourages adequate investigation. Understanding the relative contributions of DPA and CAA using brain imaging should improve prognostication and, ultimately, allow personalized secondary prevention to maximise net benefit.

One of the major limitations in research on SVD is presumably the poor availability of histopathological correlation, which often inhibits the proof of concept in a larger cohort. Histopathological correlation

studies are of utmost importance to increase our understanding of pathomechanisms leading to SVD and ICH. Due to the invasive nature of this procedure, it is only performed in highly selected patients, introducing a bias to studies. As presented in this review, histopathological correlation with several MRI markers has been investigated thoroughly. We argue that state-of-the-art MRI techniques might provide similar information to the gold standard of brain autopsy and should be accepted as an appropriate surrogate for histopathology for larger clinical studies and trials. A deeper understanding of pathophysiological mechanisms of SVD, different subtypes and their prognosis should increase the likelihood of identifying effective treatments that ameliorate the effects of the underlying SVD processes on brain function.

As current validated neuroimaging diagnostic criteria for the SVD types underlying ICH are only available for CAA[4] and CAA-related inflammation[35], there is an urgent need for new, non-invasive diagnostic criteria with a high sensitivity and specificity for all sporadic SVD subtypes, including DPA and mixed phaenotypes. In particular, new classifications should differentiate between risk factors and underlying diseases and be easily applicable in daily clinical practice. Several groups have proposed[139, 140] and are developing new classifications for SVD-related ICH and SVD subtypes[59] using clinical and neuroimaging information. This should further increase diagnostic accuracy, such as this was demonstrated with the Edinburgh CT criteria combining CT imaging and genetic testing[5]. Future clinical trials of ICH should incorporate subgroup analysis including SVD subtypes to investigate how interventions might interact with ICH associated with different arteriopathies.

Research into SVD should strive towards developing personalized medicine approaches, aiming at identification of effective treatment targets in an individual patient with as little side effects as possible. We are confident that in five years, ICH will be considered as a complication of several underlying diseases that require different workup and management. We expect to see new biomarkers reflecting the pathophysiology of certain SVD subtypes. For example, recent evidence described an inflammatory component[141] in the pathogenesis of CAA[142] and DPA[143], suggesting a potential role for blood-brain barrier disruption or anti-Aβ autoantibodies[144]. Currently, lack of reference data, validation studies and availability preclude a routine use of such biomarkers in clinical practice. Advanced imaging methods such as quantitative or ultra-high field MRI, diffusion-tensor imaging or amyloid-PET may provide novel quantitative in-vivo information, which mirrors the current state of the disease better than conventional rating scales for SVD markers. Advanced MRI might be particularly helpful to detect SVD at early subclinical disease stages (when primary preventive interventions might be most effective) and to monitor disease activity or longitudinal changes.[118] Although not yet available, the ultimate goal should be to apply MR microscopy to diagnose and monitor SVD in-vivo. Large-scale genome-wide genetic studies of ICH should allow the identification of new components of the pathophysiology with implications for new treatment targets[145]. Increased knowledge on genotypes might also contribute towards precise selection for treatments and to guide dosing.

In addition to clinical research investigating disease manifestations and progression in humans, there is a strong need for stringent basic and translational research on biochemical pathomechanisms, such as protein folding and aggregation as well as the pathways leading to these processes[146]. We expect resulting findings to challenge our current understanding of disease concepts.

We believe, research into ICH and SVD will be an appealing field for the next decades: As seen in ischaemic stroke research, more specific questions will arise as soon as the basic ones are resolved. Advanced techniques to investigate biochemical mechanisms, such as metabolomics, proteomics and genomics, are becoming increasingly popular. They will eventually lead to the discovery of new mechanisms involved in evolution and progression of SVD. New therapeutic strategies, i.e. nanoparticles or gene-modifying therapies are currently tested for other diseases and might eventually contribute to lower the burden of ICH.

While we encourage all effort to improve diagnosis of SVD subtypes and investigate their prognosis, it still remains a high priority to identify and elaborate primary preventive and therapeutic strategies to reduce the burden of SVD on a longer term. We are convinced that this aim can only be achieved through large-scale interprofessional collaborations including basic, translational and clinical researchers. Taken together, we are optimistic that conjoint efforts will ultimately lead to a comprehensive understanding of SVD pathophysiology allowing to diagnose and monitor the disease non-invasively and propose safe, effective and well-tolerable treatments.

Disclosure statement

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10. Figure legends

Figure 1: Cerebral small vessel disease and ICH. The interplay of vascular risk factors (i.e. hypertension, diabetes), genetics (APOE genotype) and age causes cerebral small vessel disease, which may cause ICH. While cerebral amyloid angiopathy affects leptomeningeal arterioles, arteriosclerotic deep perforator arteriolopathy affects penetrating arteries in deep and lobar brain regions and is also a major cause of small subcortical infarcts and lacunes associated with lacunar ischaemic stroke syndromes.

Figure 2: Sequential imaging in patients with ICH. First, diagnosis of ICH should be confirmed using acute neuroimaging (CT or MRI according to local standard). If there is a suspicion of macrocular bleeding source (e.g. young age, lobar/infratentorial bleeding location and/or positiv CT/MRI-angiogram – use DIAGRAM score), a intra-arterial digitral substraction angiography should be performed within the next days. Detection, grading and phenotyping of cererbal small vessel diseases warrents MRI with sufficient imaging quality, usually performed days/weeks after the index event when patients comply with advanced imaging protocols.

Figure 3: MRI examples of CAA-related inflammation (CAA-ri). An 84-year-old female patient presenting with sudden-onset headache and focal seizures. MRI revealed focal, asymmetric subcortical white-matter-hyperintensities with cortical and subcortical lobar cerebral microbleeds. After treatment with steroids (3 days of 1g i.v. followed by 8 weeks of oral treatment 1mg/kg bodyweight), she fully recovered and focal white-matter changes improved significantly. After discontinuing steroid therapy, she remained without relapse for 24 months (last clinical and imaging follow-up 07/2021).

Figure 4: CT- and MRI-based criteria for the diagnosis of cerebral amyloid angiopathy (CAA). The modified Boston criteria use MRI and presence of a spectrum of haemorrhagic imaging marker (lobar haemorrhage, microbleeds, cortical superficial siderosis/cSS) and may be supplemented by evidence from histopathology grading the diagnosis of CAA into different certainty (possible – probable – probable with supporting pathology). The Edinburgh criteria are CT based using two morphological features of the haemorrhage: finger-like projections (FLP) and subarachnoid extension (SAH). Their absence has 100% sensitivity to rule-out CAA while their presence has 96% specificity to rule-in CAA.

Figure 5: MRI examples of haemorrhagic (left) and non-haemorrhagic (right) imaging markers of small vessel disease: cerebral microbleeds (CMB), cortical superficial siderosis (cSS), enlarged perivascular spaces (EPVS), lacunes, white matter hyperintensities (WMH) and recent small subcortical infarction (RSSI).

Figure 6: Comparison of haemorrhagic small vessel disease markers at 3 and 7 Tesla: Clear separation of different cerebral microbleeds (CMB) at 7 Tesla allowing detection of additional cortical CMBs invisible on 3T (right panels) and differentiation of cortical from juxtacortical location (left panels).

11. Tables

Table 1: Overview of different small vessel disease scales and scores

Acronym	Author	Main aspects	Comments
DIAGRAM	Hilkens et al.[13]	- Aim: to identify predictors for a macrovascular ICH cause - DIAGRAM + score: Predictors for a macrovascular ICH cause are age 18-50 years, inconclusive CT-angiography (CTA) or CTA with evidence of a macrovascular cause, lobar or posterior fossa ICH and absence of signs of SVD on non-contrast CT (NCCT). - DIAGRAM score: In low-resource settings, the workup can be limited to NCCT without CTA, including age, absence of signs of SVD and ICH location.	- Derivation cohort only included patients with non-traumatic ICH up to 70 years of age[1], which was not the case in validation cohort[22] - Patients with structural cause of ICH (e.g. known vascular malformation or brain tumors), deep supratentorial and posterior fossa ICH > 45 years and patients on therapeutic anticoagulation (INR > 2.5) were excluded from the derivation cohort
MARS	Gregoire et al.[66]	- Aim: To develop a rating instrument assessing cerebral microbleed (CMB) location and count. - Microbleed location and count are assessed separately for both hemispheres and according to three main categories (deep, lobar, infratentorial), which are then divided in anatomical sublocations. - Inter- and intra-rater-agreement are good for definite CMBs.	- The paper includes an illustrative chart to facilitate rating
cSS multifocality score	Charidimou et al.[77]	- Aim: To identify and quantify multiple, concurrent regions of cortical superficial siderosis, which is a mainstay in the diagnosis of CAA[4] - Scoring of cSS is performed separately by hemisphere. 1 point is awarded for a single bleeding source (equivalent to cSS affecting up to 3 adjacent sulci) or 2 for multiple bleeding sources (css affects ≥ 2 separate or > 3 adjacent sulci). The total score is obtained by summing the hemispheres' scores. - Multifocality score is associated with the recurrent ICH risk.	- The paper provides a visual rating aid.
Fazekas scale	Fazekas et al.[89]	- Aim: to identify white matter signal abnormalities on MRI in patients with Alzheimer's disease (AD) compared to normal ageing. - Periventricular and separate deep white matter hyperintensities (WMH) are scored according to a 4-point scale, each (0 = no WMH, 3 = confluent WMH)	- AD was diagnosed clinically based on DSM-III criteria (no autopsy) - In clinical routine, Fazekas separate deep and periventricular WMH are often lumped together as one "Fazekas score" - Only assesses supratentorial WMH
Van Swieten	Van Swieten et al.[90]	- Aim: to develop a scale describing distribution and severity of WMH in anterior and posterior brain regions. - Severity of WMH is graded in four regions (choroid plexus, anterior and posterior cella media, posterior centrum semiovale) according to a 3-point scale (0= no WMH, 2 = confluent WMH). - Interrater reliability was better in MRI ($\kappa_w = 0.78$ for both regions together) than in CT ($\kappa_w = 0.63$).	- Only assesses supratentorial WMH - Although there is a visual rating aid, the location within the particular region is not explicitly mentioned.
PVS grading scale	Doubal et al.[93]	- Aim: to assess enlarged perivascular spaces (ePVS) in different locations separately to account for potential differences in pathophysiology. - Rating is performed for basal ganglia and centrum semiovale separately for each hemisphere according to a 4-point scale. For the total ePVS score, the highest ePVS score for each location is considered, resulting in a maximum of 8 points. - Excellent interrater reliability for basal ganglia ($\kappa = 0.88$) and good interrater reliability for centrum semiovale PVS ($\kappa = 0.78$).	-

CHARTS	Charidimou et al.[108]	- Aim: to develop a reproducible classification instrument for ICH locations. - The haematoma epicentre is determined using a visual rating aid. - ICH is classified into two main locations (lobar versus deep and infratentorial) and an “uncertain” category. Each subcategory is further divided. - Inter- and intrarater agreement are excellent across raters with different levels of experience (Interrater reliability: $\kappa = 0.86$ across three raters for deep and infratentorial versus lobar location, intra-rater reliabilities in the same and across modalities all with $\kappa > 0.8$).	- The paper provides visual rating aids.for ICH epicentres and subcategories.

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