Supplementary Table 1. Epidemiology and risk factors of acute cerebral small vessel disease (aCSVD)

	Ischemic aCSVD	**Hemorrhagic aCSVD**	
	Lacunar stroke	**Hypertensive ICH**	**CAA-related ICH**
Epidemiology			
Incidence	The annual incidence of ischemic aCSVD varies among races and regions, ranging from 13 to 40 per 100 000 people.[1, 2]	The annual incidence of ICH ranges from 20 to 30 per 100 000 people, increasing with advanced age and varying across ethnicities and geography and reaching the highest rate of 51.8 per 100 000 person-years in Asian people.[1-3]	
Etiology	1) small vessel disease: main etiology 2) branch atheromatous disease: 26%. 3) cardioembolism: 10% to 15% 4) others: artery-to-artery embolism, microdissection, inflammatory arteritis, etc (very small percentage).[4, 5]	Hypertensive angiopathy was the most common cause, followed by CAA. CAA is a major cause of ICH among elderly patients.[6] More than 50% of primary ICH are associated with hypertension, and CAA accounts for approximately 30%.[7]	
Prognosis	Patients with ischemic aCSVD often have favorable survival and disability outcomes only during the first few years after a stroke. However, in the long term, these patients exhibit a similar risk of recurrence and an even greater risk of cognitive dysfunction than patients with other stroke subtypes.[8, 9]	Hemorrhagic aCSVDs can be life-threatening, with 1-year and 5-year survival rates of 46% and 29%, respectively, leading to a high prevalence of dependency. Lobar ICH reportedly has a greater annual risk of recurrence than nonlobar ICH (7.4% vs. 1.3%).[10]	
Risk factors[4, 11-17]			
Aging	++	+	++
Smoking	+	?	?
Excessive alcohol consumption	+	+	?
Hypertension	++	++	+

Diabetes	+	+	-
ApoE	?	?	++

++: strongly related; +: related; -: unrelated; ?: uncertain/unknown

* The risk factors for aCSVD are still not completely understood. Although some risk factors (e.g., evidence of cardioembolic sources and ischemic heart disease) are suggested to differ among stroke subtypes, hypertension and diabetes appear equally common in both lacunar and nonlacunar ischemic stroke patients.[18]

CAA: cerebral amyloid angiopathy; ICH: intracerebral hemorrhage; ApoE: apolipoprotein E.

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Supplementary Table 2. Differentiation of several concepts

Terminology	Definition	Explanation
Acute ischemic cerebral small vessel disease (ischemic aCSVD)	Ischemic aCSVD defines the ischemic stroke events occurring in the past few weeks, with imaging changes in the territory of small arteries and arterioles compatible with the clinical symptoms. We propose that the imaging criterion to diagnose ischemic aCSVD is the presence of a recent small subcortical infarct (RSSI, see below) without obvious stenosis of ipsilateral parental arteries detected on conventional angiography. Some determined causes should be excluded, such as embolism and inflammatory arteritis.	• This is a clinical concept of a stroke subtype involves symptoms and imaging features • Assessment of the parental artery using conventional examination is required for diagnosis. • A synonym of lacunar stroke or ischemic stroke due to small artery disease • Transient ischemic attack is not included in ischemic aCSVD.
RSSI	A RSSI describes neuroimaging evidence of a recent infarction (around 3 weeks) in the territory of one perforating artery, with imaging features and clinical symptoms consistent with a lesion.[1]	• One of the imaging features of CSVD proposed in the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)[2] • To distinguish from covert lesions, clinical symptoms corresponding to RSSI were emphasized in STRIVE-2[1] • A maximal axial lesion diameter of 20 mm is still a size criterion for RSSI
Lacunar stroke/acute lacunar infarct	Lacunar stroke or acute lacunar infarct describes ischemic strokes presenting with lacunar syndromes (such as pure motor stroke, pure sensory stroke, sensori-motor stroke, and ataxic hemiparesis) with an infarct lesion size ranging from relatively large (15 to 20 mm) to very small (3 to 4 mm). [3] Most lacunar strokes are thought to be caused by intrinsic disease of a single perforating artery.	• A concept proposed by Miller Fisher in 1982[3] • One of the stroke subtypes in Oxfordshire Community Stroke Project (OCSP) classification. In OCSP, patients were allocated to different subgroups according to symptoms and signs.[4]
Ischemic stroke due to small artery occlusion	Ischemic stroke due to small artery occlusion represents patients with traditional lacunar syndromes and lack of evidence of cerebral cortical dysfunction. The diameter of the lesion is less than 15 mm as evaluated by CT or MRI. There is an absence of obvious	• One of the stroke subtypes in Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification • Diagnosis is based on clinical features and work-up results.[5] • Some patients with aCSVD (branch atheromatous disease [BAD]-related

	stenosis of the ipsilateral parental arteries (no more than 50%), or potential cardiac sources of embolism.	stroke patients, see below) may be categorized into large artery atherosclerosis subgroup or stroke of undetermined etiology using TOAST classification.
BAD	It is a pathological concept referring to an occlusion or stenosis at the orifice of the perforating artery due to the atheromatous plaque within the parental artery, a junctional plaque or a microatheroma. [6]	• BAD is one of the critical mechanisms of ischemic aCSVD which involves large artery atherosclerosis. [7]
Cerebral microinfarct (CMI)	CMIs are small subcortical or tiny cortical ischemic lesions. Larger CMIs (0.5 to 4.0 mm) can be detected using conventional structural MRI and as hyperintense lesions on diffusion weighted imaging (DWI). Most of them are asymptomatic and suggested to increase the risk of cognitive decline.[8]	• Whether CMI is one of the subtypes of aCSVD is undetermined.

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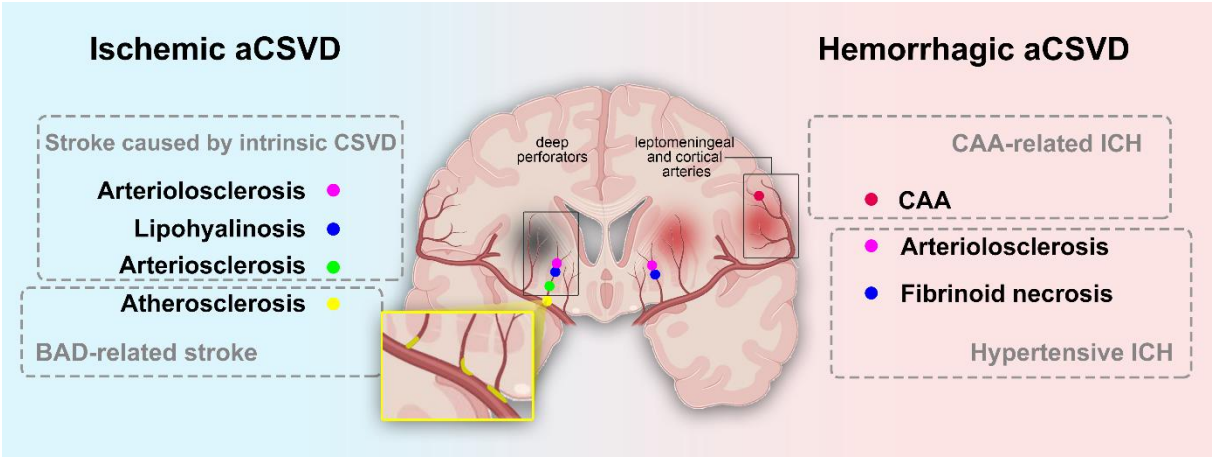
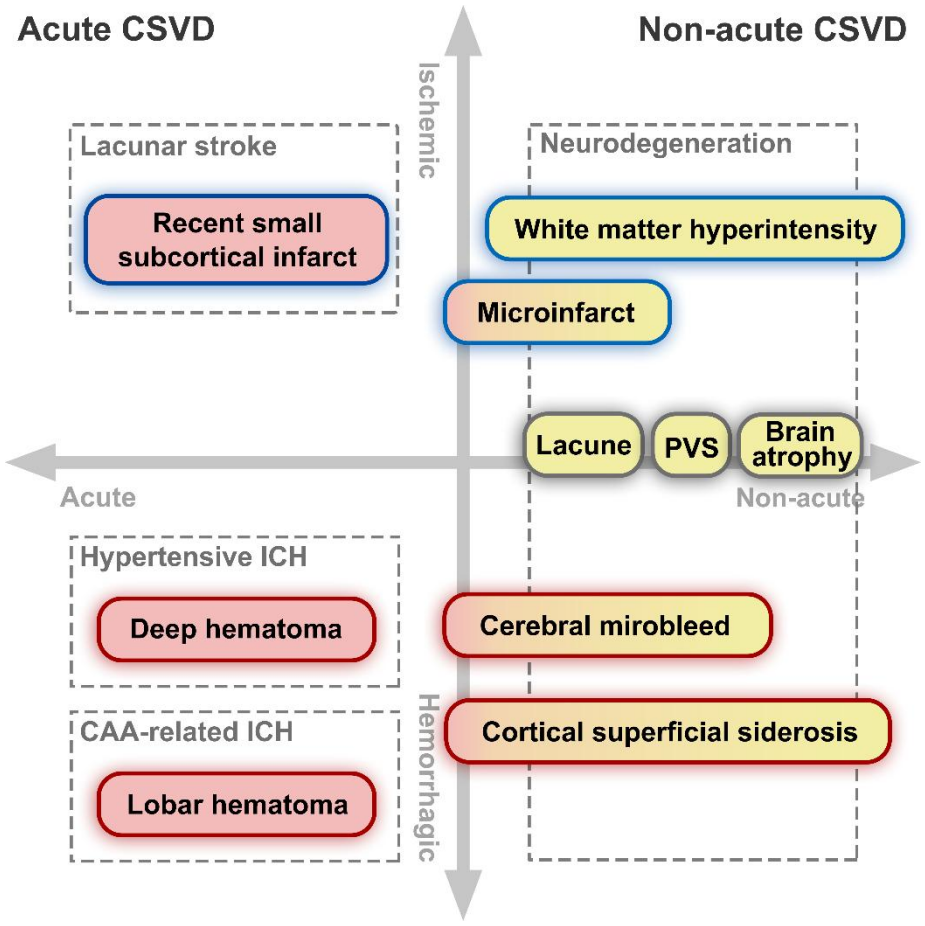
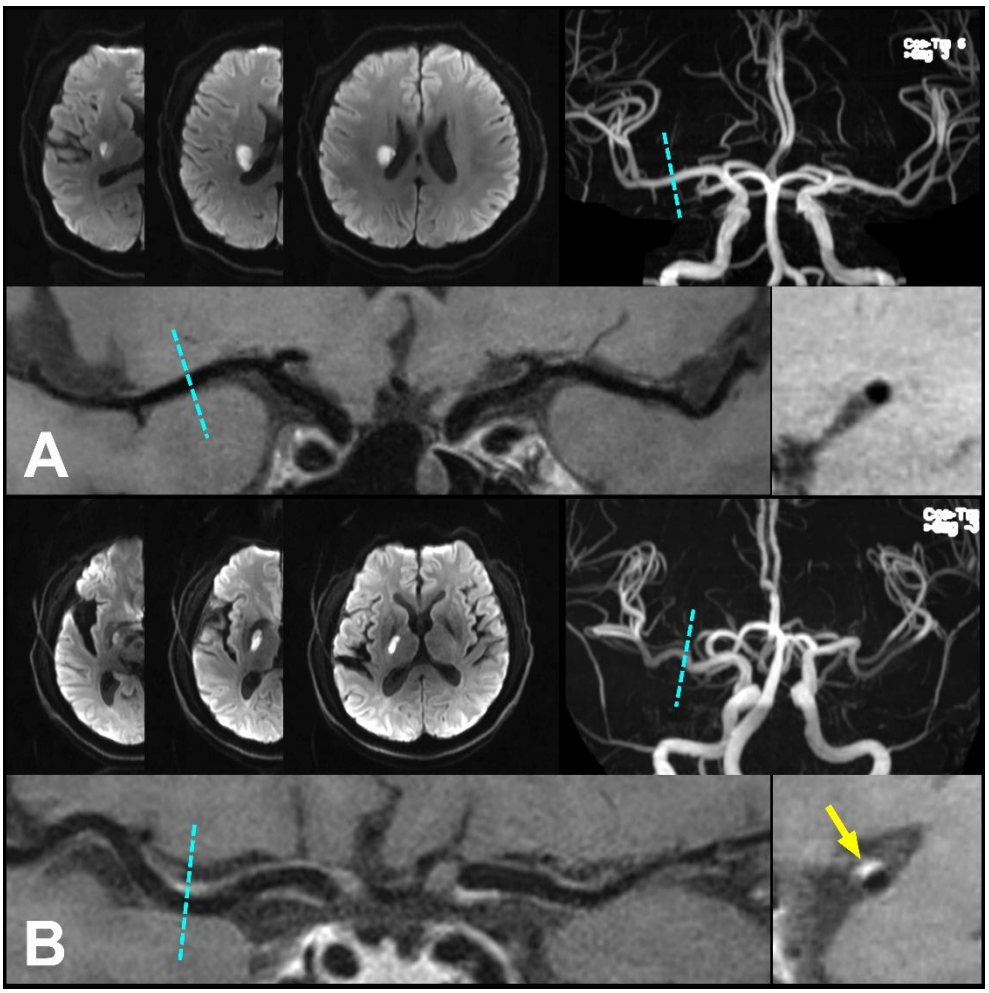
Supplementary Figure 1. Heterogeneous pathogenesis of acute cerebral small vessel disease (aCSVD). Schematic illustration showing the predilection of different small vessels (dots) and lesion sites affected by various pathological processes. Plaque distributions near perforating arteries in branch atheromatous disease are shown in the yellow frame. Ischemic aCSVD and hypertensive intracerebral hemorrhage (ICH) often lead to subcortical lesions, while cerebral amyloid angiopathy (CAA)-related ICH usually manifests as lobar hematoma. (Figure created with biorender.com.)



Supplementary Figure 2. Classification of cerebral small vessel disease (CSVD) imaging features and their relationship with clinical manifestations. Some CSVD lesions can present with acute stroke symptoms (red), whereas others accumulate covertly and result in neurodegenerative symptoms (yellow). The nature of CSVD can lead to both ischemic (blue frame) and hemorrhagic (red frame) consequences. PVS: perivascular space; ICH: intracerebral hemorrhage.



Supplementary Figure 3. An example of vessel wall imaging that helps to differentiate two etiologies of acute ischemic cerebral small vessel disease. Diffusion-weighted imaging and conventional magnetic resonance angiography revealed similar lesions in two patients. Curved multiplanar reconstruction of vessel wall imaging and transverse view of the parental artery revealed a normal vessel wall in patient A and an atherosclerotic plaque in patient B (arrow). Therefore, the infarct lesions of patient A and B were presumed to be caused by intrinsic cerebral small vessel disease (of lipohyalinotic origin) and branch atheromatous disease (of atherosclerotic origin) respectively.



Supplementary Figure 4. Representative cases of acute ischemic cerebral small vessel disease lesions with different morphological fates. An acute infarction in the left corona radiata showed cavitation with a hemosiderin rim adjacent to the lesion (yellow arrow) after 14 months of follow-up (A). A left basal ganglia infarction evolved into white matter hyperintensity after 14 months (B). An acute infarction on the right pons became almost invisible at 13 months after stroke (C).