Exploration of Neuroscience

Open Exploration

Open Access Review

Cerebral amyloid angiopathy: updates on pathophysiology, diagnosis, and management

Trinity Willsey[1], Charles Faselis[2,3,4], Ali Ahmed[2,3,5], Mo-Kyung Sin[1*]

[1]College of Nursing and Health Sciences, Seattle University, Seattle, WA 98122, USA
[2]Department of Medicine, Veterans Affairs Medical Center, Washington, DC 20422, USA
[3]College of Medicine, George Washington University, Washington, DC 20052, USA
[4]College of Medicine, Uniformed Services University, Bethesda, MD 20814, USA
[5]College of Medicine, Georgetown University, Washington, DC 20057, USA

***Correspondence:** Mo-Kyung Sin, College of Nursing and Health Sciences, Seattle University, 901 12th Ave. P.O.Box 222000, Seattle, WA 98122, USA. sinm@seattleu.edu
Academic Editor: Aurel Popa-Wagner, University of Medicine and Pharmacy Craiova, Romania
Received: August 30, 2025 **Accepted:** December 3, 2025 **Published:** January 5, 2026

Cite this article: Willsey T, Faselis C, Ahmed A, Sin MK. Cerebral amyloid angiopathy: updates on pathophysiology, diagnosis, and management. Explor Neurosci. 2026;5:1006121. https://doi.org/10.37349/en.2026.1006121

Abstract

Cerebral amyloid angiopathy (CAA), characterized by amyloid β deposition in cerebral vasculature, is increasingly recognized as a major contributor to both cognitive decline and lobar intracerebral hemorrhage (ICH) in older adults and often coexists with Alzheimer's disease (AD). Understanding CAA is a crucial step for improving health outcomes and the development of effective therapies. However, significant gaps remain in our understanding of CAA's pathophysiology, diagnostic approaches, biomarker development, and clinical management. A comprehensive review is therefore essential to synthesize existing knowledge and highlight key directions for future research. This review goes beyond prior summaries by critically synthesizing recent evidence on diagnostic innovations—including the Boston criteria v2.0 and emerging plasma biomarkers—and addressing pressing clinical dilemmas such as anticoagulation management in patients with coexisting atrial fibrillation and CAA. It also highlights ongoing research into multimodal diagnostic frameworks and precision treatment strategies aimed at bridging current diagnostic and therapeutic gaps. Together, these updates underscore how advancing biomarker validation, individualized risk stratification, and amyloid-targeted approaches may shape future CAA management and prevention.

Keywords

cerebral amyloid angiopathy, clinical presentation, diagnosis, management, pathophysiology, review

Introduction

Cerebral amyloid angiopathy (CAA) is a common but often unrecognized cerebrovascular condition in older adults and plays a critical role in both neurodegenerative and hemorrhagic brain pathology. It has a

prevalence of about 50–93.6% in people with Alzheimer's disease (AD) and approximately 30% of older adults without AD or other neuropathological abnormalities [1, 2]. Both CAA and AD share the same amyloid β (Aβ) pathology but have different anatomic distributions (cerebral blood vessels vs. the brain parenchyma) in Aβ deposits and different forms of Aβ (Aβ40 vs. Aβ42). The presence of CAA can lead to microhemorrhages or macrohemorrhages, potentially resulting in further cognitive impairment and even death [3–5]. CAA can be asymptomatic, but the disrupted integrity of the vessel wall from the amyloid deposits can also lead to several clinical symptoms, such as microbleeds, lobar hemorrhage (e.g., stroke), cognitive impairment, transient focal neurological episodes (TFNEs), and superficial siderosis. Risk factors for CAA include advancing age and the presence of *APOE ε4* or *ε2* allele. The gold standard for CAA diagnosis is through post-mortem histopathology, but that is not clinically feasible in living patients. Imaging-based Boston criteria are commonly used in living patients and have a high level of certainty. Considering the high prevalence of CAA in people with AD and similar amyloid accumulation pathology, CAA may hold a crucial role in AD management. However, current knowledge and research are limited in understanding its pathophysiology, diagnostics, reliable biomarkers, and clinical management for CAA. A comprehensive review might be a necessary step for synthesizing what is known and identifying directions for future research. This paper provides a comprehensive review of CAA pathophysiology, clinical manifestations, risk factors, diagnosis, management strategies, and directions for future research to better understand and manage CAA.

Pathophysiology

While AD primarily involves Aβ42 accumulation in the brain parenchyma, CAA involves Aβ40 accumulation in the cerebral blood vessels. CAA mainly results from impaired clearance of Aβ from the brain interstitial fluid, leading to progressive cognitive impairment and even death [6, 7]. CAA develops through the following stages: 1) accumulation of Aβ, primarily Aβ40, in cerebral vasculature such as the media, small- to medium-sized cerebral arteries, arterioles, veins, and capillaries, particularly in cortical and leptomeningeal brain vessels, 2) impaired vascular fragility, especially in posterior brain regions (e.g., occipital lobe), due to Aβ40-induced damage to vascular smooth muscle and endothelial cells, 3) non-hemorrhagic brain injury such as white matter hyperintensities (WMHs) and ischemic lesions from impaired cerebral blood flow regulations, and 4) appearance of hemorrhagic brain lesions [cortical superficial siderosis (cSS), microbleeds, intracerebral hemorrhage (ICH)] from vessel wall breakdown [8–16]. cSS occurs in approximately 60% of people with histopathologically-confirmed cases of CAA [17] and is associated with higher odds of recurrent ICH [18]. Both microbleeds and lobar ICH occur in about 50% to 57% of people with CAA [18, 19]. Elimination of the accumulated Aβ through hemorrhage may lead to a process of pathological vessel remodeling [20]. Genetic factors, such as mutations in the amyloid precursor protein (*APP*) gene or *APOE ε4*/*APOE ε2* alleles, exacerbate Aβ accumulation. *APOE ε4* is a major risk factor for CAA formation and progression [21–24]. It hampers Aβ clearance, promoting breakdown of blood vessels and increasing the risk of lobar ICH [23, 25]. Whereas *APOE ε2* is associated with increased risk for CAA-related ICH in the presence of CAA [23, 26] and WMH multispot pattern [27]. Individuals carrying the *APOE ε2* allele were found to have worse clinical outcomes compared to non-carriers, including higher mortality and poorer functional recovery after ICH [28] and a higher risk of lobar ICH (OR: 3.8, 95% CI: 1.0–14.6) if on a warfarin regimen [29]. Table 1 below describes the differences between CAA and AD.

Clinical presentations

The clinical manifestations of CAA range widely, varying from asymptomatic cases to devastating hemorrhagic strokes. It predominantly affects older adults and primarily reflects the consequences of Aβ deposition in cortical and leptomeningeal blood vessels, which weakens vascular integrity and predisposes to bleeding and ischemic change [35, 36]. The most characteristic presentation is spontaneous lobar ICH, which carries a high risk of recurrence. The recurrence rate of ICH in CAA is among the highest of all stroke subtypes, underscoring the importance of early recognition, accurate diagnosis, and tailored management strategies [36].

Table 1. Differences between CAA and AD [30–34].

Features	CAA	AD
Pathophysiology	Aβ40 accumulation in small- to medium-sized blood vessels, dominantly in the cortex and leptomeningeal vessels	Aβ42 plaques and tau accumulation in the brain parenchyma
Imaging (MRI) features	Microbleeds, cortical superficial siderosis, lobar hemorrhages, white matter hyperintensities	Hippocampal atrophy, white matter hyperintensities
Biomarkers (CSF, plasma)	Lower Aβ40 levels	Lower Aβ42 levels
Clinical presentations	Lobar intracerebral hemorrhage, transient focal neurological episodes, cognitive impairment	Cognitive decline, language difficulties, executive dysfunction

CAA: cerebral amyloid angiopathy; AD: Alzheimer's disease; Aβ: amyloid β; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid.

These hemorrhages typically occur in the cortical or subcortical regions and are most often located in the posterior areas of the brain, such as the occipital and parietal lobes. Unlike deep hemispheric hemorrhages associated with hypertension, CAA-related ICHs are typically cortical-based, and frequently recurrent. They occur due to Aβ deposition in the cortical and leptomeningeal vessels, leading to vessel fragility and rupture [37]. The lobar distribution of these hemorrhages is a distinguishing feature of CAA and helps differentiate it from other small vessel pathologies such as hypertensive arteriopathy. These lobar hemorrhages are associated with significant morbidity and mortality, often leading to long-term neurological disability and increased healthcare burden [12, 38].

Another notable clinical feature of CAA is TFNEs, also referred to as "amyloid spells" [39]. These episodes are characterized by brief, recurrent, and stereotyped neurological symptoms, such as sensory disturbances, motor deficits, or visual phenomena. Although they often mimic transient ischemic attacks (TIAs), TFNEs typically differ in their slow progression, affecting adjacent cortical areas in a sequential manner and spreading pattern. This evolution pattern is more characteristic of CAA and is rarely seen in vascular TIAs. TFNEs are distinguished by their association with cSS and convexity subarachnoid hemorrhage (cSAH) on neuroimaging, both of which are key markers of underlying CAA pathology [30]. The prevailing hypothesis is that these episodes result from cortical spreading depolarizations or small cortical hemorrhages, leading to temporary disruptions in neuronal activity of cortical territories. Importantly, the presence of TFNEs—particularly when associated with cSS—is associated with increased risk of major lobar ICH, making them valuable early warning signs for clinicians. Due to their subtle presentation and overlap with other conditions, TFNEs are often under-recognized, yet they represent a hallmark clinical manifestation of CAA that warrants further diagnostic evaluation [40].

Cognitive impairment is also prevalent among individuals with CAA, ranging from mild cognitive impairment to dementia [12, 41]. The cognitive deficits are often multifactorial, resulting from a combination of microhemorrhages, cortical microinfarcts, and white matter changes. Patients with CAA may experience a gradual decline in cognitive function, a step-wise deterioration following recurrent hemorrhages, or a rapidly progressive decline in cases of CAA-related inflammation (CAA-ri) [12]. The accumulation of Aβ in cerebral vessels contributes to chronic cerebral hypoperfusion and microinfarctions, leading to deficits in executive function, processing speed, and memory [42, 43]. This cognitive decline can occur independently or concomitantly with AD, complicating the clinical picture. Seizures and headaches are less common but may occur, particularly in CAA-ri [44].

CAA-ri is a rare but distinct subtype of CAA characterized by an immune-mediated inflammatory response to vascular Aβ deposits. It encompasses two subtypes: inflammatory CAA and Aβ-related angiitis [45, 46]. It is a rare syndrome of reversible encephalopathy, and unlike sporadic CAA, which typically progresses gradually, CAA-ri often presents with subacute or rapidly progressive cognitive decline, seizures, headaches, behavioral changes, or focal neurological deficits [45, 47]. Magnetic resonance imaging (MRI) findings in CAA-ri are notably different, with characteristic asymmetric cortical or subcortical T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities reflecting vasogenic edema—often described as "gyral edema"—which is not typically seen in non-inflammatory CAA [45, 46, 48]. Unlike the hemorrhagic markers predominant in sporadic CAA (e.g., lobar microbleeds, cSS), CAA-ri may also show

leptomeningeal enhancement or patchy contrast enhancement on MRI. Prompt recognition is critical because, unlike classic CAA, CAA-ri responds to immunosuppressive treatment—typically corticosteroids—with many patients experiencing clinical and radiological improvement [46, 48]. Brain biopsy is sometimes required to confirm the diagnosis, particularly when imaging is inconclusive. Early treatment can significantly alter the disease trajectory and prevent irreversible deficits [46, 48].

Neuroimaging often reveals cerebral microbleeds (CMBs) and cSS in patients with CAA. CMBs are small, chronic hemorrhages visible on susceptibility-weighted imaging (SWI) or T2*-weighted MRI sequences, predominantly located in lobar regions [41, 49]. cSS, indicative of chronic bleeding into the subarachnoid space, appears as linear hypointensities on MRI and is associated with an increased risk of future ICH [39].

Diagnostic approaches

Accurate diagnosis of CAA relies on a combination of clinical assessment supported by neuroimaging and, in some cases, cerebrospinal fluid (CSF) biomarkers. The Boston criteria, recently updated to version 2.0, provide a framework for diagnosing probable CAA based on clinical and imaging findings without the need for histopathological confirmation [30]. MRI is the modality of choice, with SWI sequences being particularly sensitive in detecting CMBs and cSS, hallmark features of CAA [49].

MRI

An MRI serves as the primary non-invasive diagnostic tool for CAA, offering high sensitivity in detecting characteristic vascular changes. ICH, CMBs, and cSS are characteristic findings of CAA on MRI [30, 50]. Additional MRI markers associated with CAA include WMHs and enlarged perivascular spaces in the centrum semiovale, and cortical atrophy. These findings, while not specific to CAA, can support the diagnosis when present in conjunction with other imaging features [30]. Definitive diagnosis of CAA is established through histopathological examination, typically via post-mortem analysis. Less commonly, brain biopsies may be considered in select cases, particularly when CAA-ri is suspected, to guide immunosuppressive therapy [30]. However, due to the invasive nature and limited feasibility of obtaining brain tissue samples, histopathological confirmation is rarely performed in clinical practice. A summary of key MRI findings indicative of CAA is included in Table 2 below.

Table 2. Key MRI findings indicative of CAA.

Typical findings	Key notes/Significance
Lobar intracerebral hemorrhages (ICHs)	Spontaneous hemorrhages in the cortical or subcortical regions, often multiple and recurrent
Cerebral microbleeds (CMBs)	Small, round hypointense lesions predominantly in lobar regions, best visualized using gradient-echo T2*-weighted or susceptibility-weighted imaging (SWI) sequences [49]
Cortical superficial siderosis (cSS)	Linear hypointensities along the cortical surface, representing chronic blood product deposition, detectable via SWI [36]
White matter hyperintensities (WMHs)	Areas of increased signal intensity on fluid-attenuated inversion recovery (FLAIR) sequences, indicating chronic small vessel ischemic changes [51], multiple punctuate subcortical FLAIR hyperintensities (i.e., a multispot pattern) [52]
Enlarged perivascular spaces (EPVS)	Dilated spaces surrounding small blood vessels, more prominent in the centrum semiovale, observable on T2-weighted images

MRI: magnetic resonance imaging; CAA: cerebral amyloid angiopathy.

SWI and T2*-weighted sequences are particularly effective in detecting CMBs, cSS, and cortical subarachnoid hemorrhages (SAHs), while FLAIR sequences are optimal for identifying WMHs [49].

The Boston criteria, recently updated to version 2.0 in 2022 [30, 53], provide a standardized framework for the in vivo diagnosis of CAA based on clinical presentation and MRI findings.

The updated criteria incorporate emerging MRI markers to enhance diagnostic sensitivity without compromising specificity, facilitating more accurate identification of probable CAA cases [30].

The Edinburgh criteria, based on CT features [54], are an alternative approach to diagnose CAA when MRI is not suitable in cases like people with claustrophobia or with non-MRI compatible implanted devices [54–56]. The simplified Edinburgh criteria are mainly used to diagnose CAA-related lobar ICH and include two key CT findings: SAH and finger-like projections (FLP) [57, 58]. It categorizes patients into three groups: high, medium, and low risk (Table 3). The criteria incorporate *APOE ε4* genotyping for a more complete assessment.

Table 3. Edinburgh criteria for CAA diagnosis [57, 58].

Diagnosis	Findings
High risk for CAA	Lobar ICH + finger-like projections (FLP) + subarachnoid hemorrhage (SAH)
Medium risk for CAA	Lobar ICH + either FLP or SAH
Low risk for CAA	Lobar ICH with absence of both FLP and SAH

CAA: cerebral amyloid angiopathy; ICH: intracerebral hemorrhage.

Current research has developed a web-based tool, the Florey CAA Score (FCAAS), to predict CAA severity [59]. In a pilot study based on the Religious Orders Study and the Rush Memory and Aging Project (ROSMAP), the Latino CORE Study (LATC), and the Minority Aging Research Study (MARS), the FCAAS obtained an AUC-ROC of 0.82 (0.71–0.85), suggesting its potential for clinical use in CAA risk stratification and in predicting amyloid-related imaging abnormalities.

Biomarkers

CSF. CSF biomarkers have emerged as valuable tools in differentiating CAA from other neurodegenerative conditions. Research into CSF biomarkers has revealed that patients with CAA often exhibit reduced levels of Aβ40 and Aβ42, with some studies noting elevated total tau (t-tau) and phosphorylated tau (p-tau) levels [60]. Another study reported no discriminatory capacity of CSF Aβ40 and Aβ42 levels for CAA and AD [61], limiting clinical utility. The discrepancy in the study findings underscores the importance of identifying other confirmative biomarkers useful in clinical routine.

Plasma biomarkers. The development of plasma-based biomarkers for CAA is a promising area of research aimed at enabling non-invasive diagnosis and disease monitoring. Compared to CSF analysis, plasma biomarkers offer a more accessible and less invasive alternative, with growing potential for early screening in both clinical and community settings. Studies have shown that individuals with CAA often demonstrate reduced plasma levels of Aβ40 and Aβ42, as well as altered Aβ40/Aβ42 ratios—biochemical changes that reflect impaired amyloid clearance from the brain [31, 32]. In a 2025 review [62], consistent trends were identified in decreased Aβ peptides in CAA, suggesting peripheral blood measures may mirror cerebral amyloid deposition. Additionally, elevations in p-tau217, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) have been reported in CAA patients, especially those with signs of inflammation or neurodegeneration [44, 62, 63].

While plasma biomarkers represent a major advance toward non-invasive CAA detection, current evidence remains heterogeneous. Variability in assay techniques, study populations, and analytical sensitivity has led to inconsistent findings across cohorts [44, 62, 63]. Moreover, the overlap of CAA-related signatures with those seen in AD complicates their diagnostic specificity. Standardization of assay methods and longitudinal validation studies are needed before these markers can be integrated into clinical practice. Ongoing early-phase clinical trials are currently assessing the prognostic value of combined plasma biomarkers—such as Aβ42/40 ratio, GFAP, and NfL—in predicting hemorrhagic complications during anti-amyloid therapy, reflecting growing translational momentum in this field [44, 62, 63].

While these biomarkers are not yet used routinely in clinical practice, they show potential for risk stratification and longitudinal monitoring, particularly in patients undergoing anti-amyloid therapies or with coexisting AD [62]. As ultra-sensitive detection technologies like Simoa improve reliability, plasma biomarkers may soon complement imaging and CSF studies in diagnosing and tracking CAA progression [44]. Potential candidates include reduced Aβ40 and Aβ42 levels, altered Aβ40/Aβ42 ratios, and elevated

levels of p-tau217, NfL, and GFAP [62]. While these markers show promise for non-invasive diagnosis and early detection of CAA, further studies are needed to validate their clinical utility.

Proteomics analysis. Proteomics analysis using human plasma or brain samples to identify key molecules and pathways involved in CAA pathogenesis is an emerging area for the development of novel therapeutic targets for CAA [64]. Proteomics analysis of microdissected vessels in the leptomeningeal and cortical regions identified APOE and clusterin as upregulated molecules associated with CAA [65]. Clusterin, known as apolipoprotein J and highly present in tissues, has a role in cell survival and death [66] as well as suppression of Aβ aggregation and Aβ fibril formation [67]. Other studies also identified tissue inhibitor of metalloproteinase 3 (TIMP3) and clusterin as upregulated proteins from autopsied human leptomeningeal arteries [68]. TIMP3, a 25 kDa protein found in the central nervous system, plays a role in extracellular matrix homeostasis by inhibiting matrix metallopeptidases 9 activity [68]. Another study based on plasma-based proteomics analysis identified 166 differently expressed proteins in CAA and six hub proteins, including apolipoprotein A-IV (ApoA-IV) and fibulin-5, in 146 patients with probable CAA and 128 controls [69]. Considering the promising role of proteomics in CAA, more studies are needed to better understand CAA pathogenesis and develop targeted therapeutic strategies.

Despite the promise of proteomics in revealing novel molecular pathways, these findings should be interpreted cautiously. Differences in tissue preparation, analytical pipelines, and sample sources (autopsy vs. plasma) contribute to inter-study variability. Most proteomic analyses remain exploratory and underpowered, limiting reproducibility. Larger multicenter validation studies and integration with imaging or genetic data are essential to confirm their clinical applicability. Several ongoing initiatives, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the MarkVCID consortium, are expanding proteomic profiling to identify candidate markers relevant to CAA progression and treatment response [65, 68–71].

Risk factors for CAA

Advancing age is the most significant risk factor for CAA, with prevalence increasing markedly in individuals over 70 years [1, 2]. Genetic predisposition also plays a role; the *APOE ε4* allele correlates with increased amyloid deposition and cognitive decline, while the presence of the *APOE ε2* allele is associated with a higher risk of lobar ICH and cSS [37, 72–74]. A study from the National Alzheimer's Coordinating Center (NACC) reported *APOE ε4* carriers having a higher risk for CAA development [$\chi^2(3) = 150.6$, $p < 0.001$] [75]. Another study also reported *APOE ε4/APOE ε4* carriers having severe CAA in the meninges of the occipital lobe among 371 autopsy samples [76]. A study from the ROSMAP demonstrated that *APOE ε4* carriers showed threefold higher odds (OR = 3.55, 95% CI = 2.73–4.63, $p < 0.001$) of having more severe meningeal/parenchymal CAA than the *APOE ε3/APOE ε3* carriers [72]. While hypertension is a well-established risk factor for deep hemispheric hemorrhages [12], its role in CAA-related lobar hemorrhages is less clear. Some studies suggest that hypertension may exacerbate the risk of hemorrhagic events in CAA, although the association is not as robust as with other forms of small vessel disease [12, 13]. CAA and AD frequently co-occur, with amyloid pathology contributing to both conditions. While CAA can develop independently of AD, its presence often modifies the clinical trajectory of cognitive decline and increases the risk of cerebral hemorrhages [44]. Table 4 below is the list of key studies in CAA.

Management strategies

Although there are no proven treatments for CAA, current management focuses on preventing complications and exploring experimental therapies aimed at enhancing amyloid clearance and vascular health. Potential promising approaches include Aβ-degrading enzymes [e.g., neprilysin, insulin-degrading enzyme (IDE)], vascular receptor-mediated clearance [e.g., low-density lipoprotein receptor-related protein-1 (LRP1)], and the perivascular drainage pathway (i.e., an Aβ clearance route) [64, 79, 80]. Studies found both neprilysin and IDE promote Aβ degradation and clearance [81–83]. LRP1, highly present in cerebrovascular walls, plays a role in the clearance of Aβ from the brain [84, 85]. Perivascular drainage

Table 4. Key studies in CAA.

Authors	Study objective	Setting/Participants	Results	Notes
Banerjee et al. [60] (2020)	To assess CSF biomarkers in patients with CAA	CAA (*n* = 10), AD (*n* = 20), controls (*n* = 10)	Reduced CSF Aβ40 and Aβ42 levels in CAA compared to AD and controls; tau levels were intermediate	Supports the role of CSF biomarkers in distinguishing CAA from AD
Charidimou et al. [30] (2022)	To validate Boston criteria v2.0 for diagnosing CAA using MRI-neuropathology correlation	Multicenter retrospective study; *n* = 159 in the deviation cohort, *n* = 59 in the temporal validation cohort, *n* = 123 in the geographical validation cohort	Boston criteria v2.0 improved diagnostic sensitivity (74%) and maintained specificity (95%)	Established updated, reliable criteria for in vivo CAA diagnosis
Charidimou et al. [77] (2018)	Meta-analysis of CSF biomarkers in CAA	Pooled data from multiple studies (*n* = 3 studies: *n* = 59 CAA cases, *n* = 94 healthy controls, *n* = 158 AD cases)	Decreased Aβ40 and Aβ42 in CAA; variable tau levels	Confirms CSF profile differs from AD; suggests heterogeneity
Charidimou et al. [41] (2017)	Evaluate the detection and clinical implications of cortical superficial siderosis (cSS) in CAA	Mixed cohort with CAA and related conditions	cSS is strongly associated with the risk of future ICH and TFNEs	cSS is a key imaging marker in the Boston criteria
Kargiotis et al. [49] (2018)	Review of cerebral microbleeds (CMBs): causes, imaging, and clinical relevance	Literature review	Lobar CMBs are prominent in CAA and detectable via SWI/T2* MRI	Useful for differentiating CAA from hypertensive arteriopathy
Muir et al. [44] (2024)	Compare plasma biomarker quantification methods for AD and CAA application	Analytical comparison of biomarker assays	Combining biomarkers (Aβ ratio, p-tau, neuroinflammation, demographic/clinical variables) has the potential to improve the differential diagnosis of AD and CAA	Several methodological issues were identified: suggest using neuropathological gold standard, control for disease stage, essay standardization; sex differences and longitudinal changes
Paniagua Bravo et al. [51] (2014)	Compare MRI techniques for WMH detection	Healthy and clinical populations (*n* = 40 randomly selected patients; *n* = 10 controls)	3D-FLAIR is superior in detecting WMHs compared to other sequences	Informs optimal MRI protocols for identifying WMHs in CAA
Seifert et al. [78] (2025)	Overview of diagnosis and management of CAA-related inflammation (CAA-ri)	Review article	CAA-ri is an immune-mediated variant with distinct imaging and steroid-responsive features	Highlights need to differentiate CAA-ri from sporadic CAA
Sin et al. [62] (2025)	Comprehensive review of plasma biomarkers for CAA in the context of ARIA	Review, including prospective biomarker studies	Plasma GFAP, Aβ42, and t-tau may predict CAA and ARIA risk	Suggests risk prediction with the potential plasma biomarkers for CAA in future studies
Smith et al. [39] (2021)	Characterize TFNEs in CAA and their clinical outcomes	Observational study of CAA patients with TFNEs	TFNEs are predictive of subsequent ICH and cSS	TFNEs should raise suspicion for underlying CAA
Theodorou et al. [37] (2023)	Examine the link between cSS, TFNEs, and lobar hemorrhage in CAA	Case series of CAA patients	TFNEs and cSS often precede symptomatic lobar hemorrhage	Reinforces the importance of early MRI detection of cSS in risk stratification

CAA: cerebral amyloid angiopathy; CSF: cerebrospinal fluid; AD: Alzheimer's disease; Aβ: amyloid β; MRI: magnetic resonance imaging; ICH: intracerebral hemorrhage; TFNEs: transient focal neurological episodes; SWI: susceptibility-weighted imaging; p-tau: phosphorylated tau; WMH: white matter hyperintensity; FLAIR: fluid-attenuated inversion recovery; ARIA: amyloid-related imaging abnormalities; GFAP: glial fibrillary acidic protein; t-tau: total tau.

pathway, also known as intramural periarterial drainage (IPAD), is impaired in CAA, leading to Aβ accumulation in vessel walls. IPAD relies on vascular smooth muscle cell contraction [86]. Potential

strategies to restore IPAD pathway include anti-inflammatory agents or antioxidants, as well as pulsation-based therapies such as physical activity and medications affecting heart rate [86, 87]. Optimizing control of vascular risk factors, such as hypertension, diabetes, and hyperlipidemia, may support perivascular drainage and reduce secondary damage [86].

Experimental medications

As experimental medications, cilostazol (type 3 phosphodiesterase selective inhibitor) [88], taxifolin [89], and minocycline [90] were shown to be effective in improving CAA-related cognitive impairment and reducing CAA-related microhemorrhages in animal models. Human studies are needed to confirm these findings.

CAA management in atrial fibrillation

Atrial fibrillation (AF) is highly prevalent in older adults, and the co-existence of both AF and CAA is rising because of the aging population, posing a clinical dilemma regarding anticoagulant use [14]. Anticoagulants are commonly used treatment options for people with AF to manage cardioembolic stroke risk, whereas anticoagulants use increases the risk of ICH in CAA. Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) is used to estimate the risk of major bleeding for patients with AF and on anticoagulation therapy, whereas the CHA_2DS_2-VASc score is used to predict the risk of stroke in patients with AF [14, 91]. The CHA_2DS_2-VASc score of ≥ 2 is associated with around 2.5% annual stroke risk and is an indication to use direct oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban) or vitamin K antagonists (e.g., warfarin, acenocoumarol, phenprocoumon) for the risk reduction [14].

Clinicians must weigh these competing risks using a risk–benefit decision framework. Patients with high CHA_2DS_2-VASc scores and low HAS-BLED scores generally benefit from anticoagulation, whereas those with multiple CAA-related hemorrhagic markers (e.g., cSS, CMBs) may have prohibitive bleeding risk. In such cases, shared decision-making that includes neurologists, cardiologists, and patients is essential to align treatment with individual risk tolerance and life expectancy.

Recommended management strategies for concomitant AF and CAA include cardiovascular risk factor (e.g., hypertension, statin use) modification and left atrial appendage closure [14]. Left atrial appendage closure, which can be done non-surgically with a Watchman device, has demonstrated up to 85% reduction in hemorrhagic stroke [92].

Emerging plasma biomarkers such as NfL, GFAP, and altered Aβ40/Aβ42 ratios may assist in risk stratification and identifying CAA patients at the highest hemorrhagic risk [64–67]. These tools, combined with MRI markers, could enable a more personalized approach to anticoagulation in CAA. Integrating biomarker-based risk assessment into clinical decision-making frameworks may help clinicians optimize stroke prevention while minimizing bleeding complications.

Discussion

This review provides a comprehensive and state-of-the-art review of CAA, focusing on pathophysiology, clinical presentations, diagnostic approaches, risk factors, and management strategies. CAA is a complicated cerebrovascular disease and a major cause of vascular dysfunction, lobar ICH, and cognitive impairment in older adults.

Despite much progress in CAA research, significant limitations remain. Brain histopathology remains the gold standard of CAA diagnosis, but not practical. Both the Boston criteria and the Edinburgh criteria enable early detection of symptomatic CAA but are limited in the identification of asymptomatic CAA. The need for innovative biomarkers in consideration of *APOE* genes to diagnose asymptomatic CAA is emphasized, especially as anti-amyloid therapies become more widely used in AD management.

This review also acknowledges that while plasma biomarker and proteomics studies have yielded valuable insights, their translation to routine practice remains limited by methodological heterogeneity and small cohort sizes. A balanced appraisal underscores that current findings, though encouraging, are preliminary. Future research should emphasize standardization of measurement protocols, replication across diverse populations, and correlation with clinical outcomes. Such rigor will be vital for establishing reliable biomarkers that inform diagnosis, prognosis, and therapeutic monitoring in CAA.

Up-to-date management strategies for CAA include Aβ enzymatic degradation, vascular receptor-mediated, and perivascular drainage [64, 79]. However, age-related decline in enzyme activity and arterial stiffening may limit Aβ breakdown and clearance [93, 94], emphasizing the complexity of Aβ clearance in older adults and the necessity of therapeutic regimens to minimize progression of AD and CAA. Most biomarkers and therapeutic strategies targeting amyloid clearance have been conducted in animal models, underscoring validation studies in human studies. In addition, plasma-based biomarkers and proteomics analysis are gaining recognition as promising avenues for understanding the underlying CAA pathophysiology, refining diagnostic approaches via identifying biomarkers and therapeutic targets, which warrant future studies. Furthermore, current diagnostic gaps in asymptomatic or mixed pathologies (CAA and AD) heighten the need for further studies.

Directions for future research

Future studies should prioritize longitudinal cohort tracking for early detection of asymptomatic CAA and clarify the mechanisms of vessel wall degeneration. Integrating genetic, imaging, and fluid biomarkers into multimodal diagnostic frameworks will be key for improving diagnostic precision. Translational research bridging animal and human studies is also crucial to validate mechanistic insights and develop targeted therapies aimed at halting or reversing amyloid deposition. Ultimately, these efforts will support the creation of comprehensive risk stratification tools that combine genetic, imaging, and clinical data for individualized management.

Conclusions

CAA frequently coexists with AD and contributes significantly to adverse cognitive and cerebrovascular outcomes in older adults. Much progress has been made in diagnosing and managing CAA. The Boston criteria and the Edinburgh criteria are both reliable in vivo methods to diagnose symptomatic CAA. Emerging CSF, plasma, and proteomic biomarkers offer promise for earlier detection. Several experimental agents effective in animal models require validation in human trials. This review provides up-to-date research and future directions for CAA management.

Abbreviations

AD: Alzheimer's disease

AF: atrial fibrillation

Aβ: amyloid β

CAA: cerebral amyloid angiopathy

CAA-ri: cerebral amyloid angiopathy-related inflammation

CMBs: cerebral microbleeds

CSF: cerebrospinal fluid

cSS: cortical superficial siderosis

FCAAS: Florey Cerebral Amyloid Angiopathy Score

FLAIR: fluid-attenuated inversion recovery

GFAP: glial fibrillary acidic protein

HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly

ICH: intracerebral hemorrhage

IDE: insulin-degrading enzyme

IPAD: intramural periarterial drainage

LRP1: low-density lipoprotein receptor-related protein-1

MRI: magnetic resonance imaging

NfL: neurofilament light chain

p-tau: phosphorylated tau

ROSMAP: Religious Orders Study and the Rush Memory and Aging Project

SAHs: subarachnoid hemorrhages

SWI: susceptibility-weighted imaging

TFNEs: transient focal neurological episodes

TIAs: transient ischemic attacks

TIMP3: tissue inhibitor of metalloproteinase 3

WMHs: white matter hyperintensities

Declarations

Author contributions

TW: Investigation, Writing—original draft, Writing—review & editing. CF: Investigation, Writing—review & editing. AA: Investigation, Writing—review & editing. MKS: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

References

1. Walker L, Simpson H, Thomas AJ, Attems J. Prevalence, distribution, and severity of cerebral amyloid angiopathy differ between Lewy body diseases and Alzheimer's disease. Acta Neuropathol Commun. 2024;12:28. [DOI] [PubMed] [PMC]
2. Sin MK, Cheng Y, Roseman JM, Zamrini E, Ahmed A. Relationships between Cerebral Vasculopathies and Microinfarcts in a Community-Based Cohort of Older Adults. J Clin Med. 2023;12:3807. [DOI] [PubMed] [PMC]
3. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways. Nat Rev Neurol. 2020;16: 30–42. [DOI] [PubMed] [PMC]
4. van Veluw SJ, Scherlek AA, Freeze WM, Ter Telgte A, van der Kouwe AJ, Bacskai BJ, et al. Different microvascular alterations underlie microbleeds and microinfarcts. Ann Neurol. 2019;86:279–92. [DOI] [PubMed] [PMC]
5. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann Neurol. 1991;30:637–49. [DOI] [PubMed]
6. Banerjee G, Carare R, Cordonnier C, Greenberg SM, Schneider JA, Smith EE, et al. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. J Neurol Neurosurg Psychiatry. 2017;88:982–94. [DOI] [PubMed] [PMC]
7. Dörner M, Tyndall A, Hainc N, von Känel R, Neumann K, Euler S, et al. Neuropsychiatric symptoms and lifelong mental activities in cerebral amyloid angiopathy – a cross-sectional study. Alzheimers Res Ther. 2024;16:196. [DOI] [PubMed] [PMC]
8. Koemans EA, Chhatwal JP, van Veluw SJ, van Etten ES, van Osch MJP, van Walderveen MAA, et al. Progression of cerebral amyloid angiopathy: a pathophysiological framework. Lancet Neurol. 2023; 22:632–42. [DOI] [PubMed]
9. Greenberg SM, van Veluw SJ. Cerebral Amyloid Angiopathy. Stroke. 2024;55:1409–11. [DOI] [PubMed]
10. Take Y, Chikai Y, Shimamori K, Kuragano M, Kurita H, Tokuraku K. Amyloid β aggregation induces human brain microvascular endothelial cell death with abnormal actin organization. Biochem Biophys Rep. 2022;29:101189. [DOI] [PubMed] [PMC]
11. Khan F, Qiu H. Amyloid-β: A potential mediator of aging-related vascular pathologies. Vascul Pharmacol. 2023;152:107213. [DOI] [PubMed] [PMC]
12. Samarasekera N, Smith C, Al-Shahi Salman R. The association between cerebral amyloid angiopathy and intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2012;83:275–81. [DOI] [PubMed]
13. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701. [DOI] [PubMed]
14. Fusco L, Palamà Z, Scarà A, Borrelli A, Robles AG, De Masi De Luca G, et al. Management of cerebral amyloid angiopathy and atrial fibrillation: We are still far from precision medicine. World J Cardiol. 2024;16:231–9. [DOI] [PubMed] [PMC]
15. Auger CA, Perosa V, Greenberg SM, van Veluw SJ, Kozberg MG. Cortical superficial siderosis is associated with reactive astrogliosis in cerebral amyloid angiopathy. J Neuroinflammation. 2023;20: 195. [DOI] [PubMed] [PMC]

16. Bohr T, Hjorth PG, Holst SC, Hrabětová S, Kiviniemi V, Lilius T, et al. The glymphatic system: Current understanding and modeling. iScience. 2022;25:104987. [DOI] [PubMed] [PMC]
17. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74:1346–50. [DOI] [PubMed] [PMC]
18. Malhotra K, Theodorou A, Katsanos AH, Zompola C, Shoamanesh A, Boviatsis E, et al. Prevalence of Clinical and Neuroimaging Markers in Cerebral Amyloid Angiopathy: A Systematic Review and Meta-Analysis. Stroke. 2022;53:1944–53. [DOI] [PubMed]
19. Jäkel L, De Kort AM, Klijn CJM, Schreuder FHBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis. Alzheimers Dement. 2022;18:10–28. [DOI] [PubMed] [PMC]
20. Kozberg MG, Yi I, Freeze WM, Auger CA, Scherlek AA, Greenberg SM, et al. Blood-brain barrier leakage and perivascular inflammation in cerebral amyloid angiopathy. Brain Commun. 2022;4:fcac245. [DOI] [PubMed] [PMC]
21. Rannikmäe K, Kalaria RN, Greenberg SM, Chui HC, Schmitt FA, Samarasekera N, et al. APOE associations with severe CAA-associated vasculopathic changes: collaborative meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85:300–5. [DOI] [PubMed] [PMC]
22. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol. 2019;15:501–18. [DOI] [PubMed] [PMC]
23. Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, et al. Association of apolipoprotein E ϵ2 and vasculopathy in cerebral amyloid angiopathy. Neurology. 1998;50:961–5. [DOI] [PubMed]
24. Hu H, Wan S, Hu Y, Wang Q, Li H, Zhang N. Deciphering the role of APOE in cerebral amyloid angiopathy: from genetic insights to therapeutic horizons. Ann Med. 2025;57:2445194. [DOI] [PubMed] [PMC]
25. Yang Q, Sun H, Ma X, Tang L, Liu X, Huang X, et al. Apolipoprotein E genotype is associated with island sign in lobar intracerebral hemorrhage. Front Neurol. 2025;16:1540307. [DOI] [PubMed] [PMC]
26. Wu J, Liu Z, Yao M, Zhu Y, Peng B, Ni J. Clinical characteristics of cerebral amyloid angiopathy and risk factors of cerebral amyloid angiopathy related intracerebral hemorrhage. J Neurol. 2024;271:5025–34. [DOI] [PubMed]
27. Ye X, Jia Y, Song G, Liu X, Wu C, Li G, et al. Apolipoprotein E ε2 Is Associated with the White Matter Hyperintensity Multispot Pattern in Spontaneous Intracerebral Hemorrhage. Transl Stroke Res. 2024;15:101–9. [DOI] [PubMed]
28. Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, et al.; International Stroke Genetics Consortium. *APOE* genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurol. 2011;10:702–9. [DOI] [PubMed] [PMC]
29. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology. 2000;55:947–51. [DOI] [PubMed]
30. Charidimou A, Boulouis G, Frosch MP, Baron JC, Pasi M, Albucher JF, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 2022;21:714–25. [DOI] [PubMed] [PMC]
31. Sembill JA, Lusse C, Linnerbauer M, Sprügel MI, Mrochen A, Knott M, et al. Cerebrospinal fluid biomarkers for cerebral amyloid angiopathy. Brain Commun. 2023;5:fcad159. [DOI] [PubMed] [PMC]
32. De Kort AM, Kuiperij HB, Marques TM, Jäkel L, van den Berg E, Kersten I, et al. Decreased Cerebrospinal Fluid Amyloid β 38, 40, 42, and 43 Levels in Sporadic and Hereditary Cerebral Amyloid Angiopathy. Ann Neurol. 2023;93:1173–86. [DOI] [PubMed] [PMC]
33. Charidimou A, Baron JC, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs. Int J Stroke. 2013;8:105–8. [DOI] [PubMed]

34. Verbeek MM, Kremer BP, Rikkert MO, Van Domburg PH, Skehan ME, Greenberg SM. Cerebrospinal fluid amyloid β_{40} is decreased in cerebral amyloid angiopathy. Ann Neurol. 2009;66:245–9. [DOI] [PubMed] [PMC]
35. Wermer MJH, Greenberg SM. The growing clinical spectrum of cerebral amyloid angiopathy. Curr Opin Neurol. 2018;31:28–35. [DOI] [PubMed]
36. Charidimou A, Linn J, Vernooij MW, Opherk C, Akoudad S, Baron JC, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. Brain. 2015; 138:2126–39. [DOI] [PubMed]
37. Theodorou A, Chondrogianni M, Bakola E, Kaloudi G, Foska A, Michalakakou S, et al. Cortical Superficial Siderosis and Transient Focal Neurological Episode Preceding Lobar Hemorrhage in Cerebral Amyloid Angiopathy. Stroke. 2023;54:e48–51. [DOI] [PubMed]
38. Charidimou A, Imaizumi T, Moulin S, Biffi A, Samarasekera N, Yakushiji Y, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. Neurology. 2017;89: 820–9. [DOI] [PubMed] [PMC]
39. Smith EE, Charidimou A, Ayata C, Werring DJ, Greenberg SM. Cerebral Amyloid Angiopathy-Related Transient Focal Neurologic Episodes. Neurology. 2021;97:231–8. [DOI] [PubMed] [PMC]
40. Charidimou A, Peeters A, Fox Z, Gregoire SM, Vandermeeren Y, Laloux P, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke. 2012;43:2324–30. [DOI] [PubMed]
41. Charidimou A, Boulouis G, Xiong L, Jessel MJ, Roongpiboonsopit D, Ayres A, et al. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. Neurology. 2017;88: 1607–14. [DOI] [PubMed] [PMC]
42. Charidimou A, Boulouis G, Greenberg SM, Viswanathan A. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: A meta-analysis. Neurology. 2019;93:e2192–202. [DOI] [PubMed] [PMC]
43. Solis E Jr, Hascup KN, Hascup ER. Alzheimer's Disease: The Link Between Amyloid-β and Neurovascular Dysfunction. J Alzheimers Dis. 2020;76:1179–98. [DOI] [PubMed] [PMC]
44. Muir RT, Ismail Z, Black SE, Smith EE. Comparative methods for quantifying plasma biomarkers in Alzheimer's disease: Implications for the next frontier in cerebral amyloid angiopathy diagnostics. Alzheimers Dement. 2024;20:1436–58. [DOI] [PubMed] [PMC]
45. Chu S, Xu F, Su Y, Chen H, Cheng X. Cerebral Amyloid Angiopathy (CAA)-Related Inflammation: Comparison of Inflammatory CAA and Amyloid-β-Related Angiitis. J Alzheimers Dis. 2016;51:525–32. [DOI] [PubMed]
46. Bozovic I, Jeremic M, Pavlovic A, Jovanovic C, Kresojevic N, Vojvodic N, et al. Cerebral Amyloid Angiopathy-Related Inflammation (CAA-rI): Three Heterogeneous Case Reports and a Focused Literature Review. Brain Sci. 2023;13:747. [DOI] [PubMed] [PMC]
47. Kinnecom C, Lev MH, Wendell L, Smith EE, Rosand J, Frosch MP, et al. Course of cerebral amyloid angiopathy-related inflammation. Neurology. 2007;68:1411–6. [DOI] [PubMed]
48. Charidimou A. Diagnosing Cerebral Amyloid Angiopathy-Related Inflammation. Neurology. 2024;103: e209647. [DOI] [PubMed]
49. Kargiotis O, Safouris A, Magoufis G, Papageorgiou E, Fili M, Psychogios K, et al. Cerebral Microbleeds: Incidence, Imaging Characteristics, Common and Uncommon Causes. J Neurosonol Neuroimag. 2018; 10:80–94. [DOI]
50. Bonnar O, Eyre B, van Veluw SJ. Perivascular brain clearance as a therapeutic target in cerebral amyloid angiopathy and Alzheimer's disease. Neurotherapeutics. 2025;22:e00535. [DOI] [PubMed] [PMC]
51. Paniagua Bravo Á, Sánchez Hernández JJ, Ibáñez Sanz L, Alba de Cáceres I, Crespo San José JL, García-Castaño Gandariaga B. A comparative MRI study for white matter hyperintensities detection: 2D-FLAIR, FSE PD 2D, 3D-FLAIR and FLAIR MIP. Br J Radiol. 2014;87:20130360. [DOI] [PubMed] [PMC]

52. Charidimou A, Boulouis G, Haley K, Auriel E, van Etten ES, Fotiadis P, et al. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. Neurology. 2016;86:505–11. [DOI] [PubMed] [PMC]
53. Greenberg SM, Charidimou A. Diagnosis of Cerebral Amyloid Angiopathy: Evolution of the Boston Criteria. Stroke. 2018;49:491–7. [DOI] [PubMed] [PMC]
54. Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. Lancet Neurol. 2018;17:232–40. [DOI] [PubMed] [PMC]
55. Hillal A, Apostolaki-Hansson T, Ramgren B, Hansen B, Norrving B, Wassélius J, et al. The probability of cerebral amyloid angiopathy according to the Simplified Edinburgh CT criteria in a large, unselected lobar intracerebral hemorrhage population. Neuroradiology. 2025;67:823–31. [DOI] [PubMed] [PMC]
56. Zhang M, Che R, Liu X, Hou C, Wang Z, Hu S, et al. Clinical diagnosis of cerebral amyloid angiopathy related hemorrhage in China: Simplified Edinburgh criteria and Boston criteria version 2.0. Eur Stroke J. 2025;10:1373–82. [DOI] [PubMed] [PMC]
57. Rodrigues MA, Seiffge D, Samarasekera N, Moullaali TJ, Wardlaw JM, Schreiber S, et al.; Edinburgh CAA criteria prognosis collaborators. Association between the Edinburgh CT and genetic diagnostic criteria for cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage and recurrent intracerebral haemorrhage: an individual patient data meta-analysis. Lancet Neurol. 2025;24:828–39. [DOI] [PubMed]
58. Sembill JA, Knott M, Xu M, Roeder SS, Hagen M, Sprügel MI, et al. Simplified Edinburgh CT Criteria for Identification of Lobar Intracerebral Hemorrhage Associated With Cerebral Amyloid Angiopathy. Neurology. 2022;98:e1997–2004. [DOI] [PubMed]
59. Chu C, Wang Y, Ma L, Mutimer CA, Ji G, Shi H, et al. Developing and validating a prediction tool for cerebral amyloid angiopathy neuropathological severity. Alzheimers Dement. 2025;21:e14583. [DOI] [PubMed] [PMC]
60. Banerjee G, Ambler G, Keshavan A, Paterson RW, Foiani MS, Toombs J, et al. Cerebrospinal Fluid Biomarkers in Cerebral Amyloid Angiopathy. J Alzheimers Dis. 2020;74:1189–201. [DOI] [PubMed] [PMC]
61. Margraf NG, Jensen-Kondering U, Weiler C, Leypoldt F, Maetzler W, Philippen S, et al. Cerebrospinal Fluid Biomarkers in Cerebral Amyloid Angiopathy: New Data and Quantitative Meta-Analysis. Front Aging Neurosci. 2022;14:783996. [DOI] [PubMed] [PMC]
62. Sin MK, Dage JL, Nho K, Dowling NM, Seyfried NT, Bennett DA, et al. Plasma Biomarkers for Cerebral Amyloid Angiopathy and Implications for Amyloid-Related Imaging Abnormalities: A Comprehensive Review. J Clin Med. 2025;14:1070. [DOI] [PubMed] [PMC]
63. Rasing I, Voigt S, Koemans EA, de Kort AM, van Harten TW, van Etten ES, et al. Serum and cerebrospinal fluid neurofilament light chain and glial fibrillary acid protein levels in early and advanced stages of cerebral amyloid Angiopathy. Alzheimers Res Ther. 2024;16:86. [DOI] [PubMed] [PMC]
64. Inoue Y, Ando Y, Misumi Y, Ueda M. Current Management and Therapeutic Strategies for Cerebral Amyloid Angiopathy. Int J Mol Sci. 2021;22:3869. [DOI] [PubMed] [PMC]
65. Endo Y, Hasegawa K, Nomura R, Arishima H, Kikuta KI, Yamashita T, et al. Apolipoprotein E and clusterin inhibit the early phase of amyloid-β aggregation in an in vitro model of cerebral amyloid angiopathy. Acta Neuropathol Commun. 2019;7:12. [DOI] [PubMed] [PMC]
66. Humphreys DT, Carver JA, Easterbrook-Smith SB, Wilson MR. Clusterin has chaperone-like activity similar to that of small heat shock proteins. J Biol Chem. 1999;274:6875–81. [DOI] [PubMed]
67. Narayan P, Meehan S, Carver JA, Wilson MR, Dobson CM, Klenerman D. Amyloid-β oligomers are sequestered by both intracellular and extracellular chaperones. Biochemistry. 2012;51:9270–6. [DOI] [PubMed] [PMC]

68. Manousopoulou A, Gatherer M, Smith C, Nicoll JAR, Woelk CH, Johnson M, et al. Systems proteomic analysis reveals that clusterin and tissue inhibitor of metalloproteinases 3 increase in leptomeningeal arteries affected by cerebral amyloid angiopathy. Neuropathol Appl Neurobiol. 2017;43:492–504. [DOI] [PubMed] [PMC]
69. Xu J, Su Y, Sha Y, Fu J, Yan T, Xu F, et al. Circulating proteomic biomarkers for cerebral amyloid angiopathy screening and risk stratification. Alzheimers Dement. 2025;21:e70044. [DOI] [PubMed] [PMC]
70. Lennon MJ, Karvelas N, Ganesh A, Whitehead S, Sorond FA, Durán Laforet V, et al. The future of biomarkers for vascular contributions to cognitive impairment and dementia (VCID): proceedings of the 2025 annual workshop of the Albert research institute for white matter and cognition. Geroscience. 2025;47:6177–90. [DOI] [PubMed] [PMC]
71. Weiner MW, Kanoria S, Miller MJ, Aisen PS, Beckett LA, Conti C, et al.; Alzheimer's Disease Neuroimaging Initiative. Overview of Alzheimer's Disease Neuroimaging Initiative and future clinical trials. Alzheimers Dement. 2025;21:e14321. [DOI] [PubMed] [PMC]
72. Yu L, Boyle PA, Nag S, Leurgans S, Buchman AS, Wilson RS, et al. *APOE* and cerebral amyloid angiopathy in community-dwelling older persons. Neurobiol Aging. 2015;36:2946–53. [DOI] [PubMed] [PMC]
73. Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN. Apolipoprotein E-ϵ4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. Am J Pathol. 1996;148:2083–95. [PubMed] [PMC]
74. Olichney JM, Hansen LA, Galasko D, Saitoh T, Hofstetter CR, Katzman R, et al. The apolipoprotein E epsilon 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. Neurology. 1996;47:190–6. [DOI] [PubMed]
75. Vidoni ED, Yeh HW, Morris JK, Newell KL, Alqahtani A, Burns NC, et al. Cerebral β-Amyloid Angiopathy Is Associated with Earlier Dementia Onset in Alzheimer's Disease. Neurodegener Dis. 2016;16: 218–24. [DOI] [PubMed] [PMC]
76. Chui HC, Ramirez-Gomez L. Clinical and imaging features of mixed Alzheimer and vascular pathologies. Alzheimers Res Ther. 2015;7:21. [DOI] [PubMed] [PMC]
77. Charidimou A, Friedrich JO, Greenberg SM, Viswanathan A. Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy: A meta-analysis. Neurology. 2018;90:e754–62. [DOI] [PubMed] [PMC]
78. Seifert RM, Klingebiel R, Schäbitz WR. Diagnosis, pathomechanisms and therapy of cerebral amyloid angiopathy-related inflammation (CAA-ri). Neurol Res Pract. 2025;7:26. [DOI] [PubMed] [PMC]
79. van Veluw SJ, Benveniste H, Bakker ENTP, Carare RO, Greenberg SM, Iliff JJ, et al. Is CAA a perivascular brain clearance disease? A discussion of the evidence to date and outlook for future studies. Cell Mol Life Sci. 2024;81:239. [DOI] [PubMed] [PMC]
80. Saxena SK, Ansari S, Maurya VK, Kumar S, Sharma D, Malhotra HS, et al. Neprilysin-Mediated Amyloid Beta Clearance and Its Therapeutic Implications in Neurodegenerative Disorders. ACS Pharmacol Transl Sci. 2024;7:3645–57. [DOI] [PubMed] [PMC]
81. Vekrellis K, Ye Z, Qiu WQ, Walsh D, Hartley D, Chesneau V, et al. Neurons regulate extracellular levels of amyloid β-protein via proteolysis by insulin-degrading enzyme. J Neurosci. 2000;20:1657–65. [DOI] [PubMed] [PMC]
82. Miller BC, Eckman EA, Sambamurti K, Dobbs N, Chow KM, Eckman CB, et al. Amyloid-β peptide levels in brain are inversely correlated with insulysin activity levels *in vivo*. Proc Natl Acad Sci U S A. 2003; 100:6221–6. [DOI] [PubMed] [PMC]
83. Stargardt A, Gillis J, Kamphuis W, Wiemhoefer A, Kooijman L, Raspe M, et al. Reduced amyloid-β degradation in early Alzheimer's disease but not in the APPswePS1dE9 and 3xTg-AD mouse models. Aging Cell. 2013;12:499–507. [DOI] [PubMed]

84. Kanekiyo T, Cirrito JR, Liu CC, Shinohara M, Li J, Schuler DR, et al. Neuronal clearance of amyloid-β by endocytic receptor LRP1. J Neurosci. 2013;33:19276–83. [DOI] [PubMed] [PMC]
85. Kanekiyo T, Liu CC, Shinohara M, Li J, Bu G. LRP1 in brain vascular smooth muscle cells mediates local clearance of Alzheimer's amyloid-β. J Neurosci. 2012;32:16458–65. [DOI] [PubMed] [PMC]
86. Aldea R, Weller RO, Wilcock DM, Carare RO, Richardson G. Cerebrovascular Smooth Muscle Cells as the Drivers of Intramural Periarterial Drainage of the Brain. Front Aging Neurosci. 2019;11:1. [DOI] [PubMed] [PMC]
87. Muñoz E, Valero RA, Quintana A, Hoth M, Núñez L, Villalobos C. Nonsteroidal anti-inflammatory drugs inhibit vascular smooth muscle cell proliferation by enabling the Ca^{2+}-dependent inactivation of calcium release-activated calcium/orai channels normally prevented by mitochondria. J Biol Chem. 2011;286:16186–96. [DOI] [PubMed] [PMC]
88. Maki T, Okamoto Y, Carare RO, Hase Y, Hattori Y, Hawkes CA, et al. Phosphodiesterase III inhibitor promotes drainage of cerebrovascular β-amyloid. Ann Clin Transl Neurol. 2014;1:519–33. [DOI] [PubMed] [PMC]
89. Saito S, Yamamoto Y, Maki T, Hattori Y, Ito H, Mizuno K, et al. Taxifolin inhibits amyloid-β oligomer formation and fully restores vascular integrity and memory in cerebral amyloid angiopathy. Acta Neuropathol Commun. 2017;5:26. [DOI] [PubMed] [PMC]
90. Yan P, Zhu A, Liao F, Xiao Q, Kraft A, Gonzales E, et al. Minocycline reduces spontaneous hemorrhage in mouse models of cerebral amyloid angiopathy. Stroke. 2015;46:1633–40. [DOI] [PubMed] [PMC]
91. Bianconi E, Del Freo G, Salvadori E, Barbato C, Formelli B, Pescini F, et al. Can CHA_2DS_2-VASc and HAS-BLED Foresee the Presence of Cerebral Microbleeds, Lacunar and Non-Lacunar Infarcts in Elderly Patients With Atrial Fibrillation? Data From Strat–AF Study. Front Neurol. 2022;13:883786. [DOI] [PubMed] [PMC]
92. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al.; PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J Am Coll Cardiol. 2017;70:2964–75. [DOI] [PubMed]
93. Morrone CD, Liu M, Black SE, McLaurin J. Interaction between therapeutic interventions for Alzheimer's disease and physiological Aβ clearance mechanisms. Front Aging Neurosci. 2015;7:64. [DOI] [PubMed] [PMC]
94. Hawkes CA, Jayakody N, Johnston DA, Bechmann I, Carare RO. Failure of perivascular drainage of β-amyloid in cerebral amyloid angiopathy. Brain Pathol. 2014;24:396–403. [DOI] [PubMed] [PMC]