Diagnosis and management of cerebral amyloid angiopathy: a scientific statement from the International CAA Association and the World Stroke Organization

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Diagnosis and management of cerebral amyloid angiopathy: a scientific statement from the International CAA Association and the World Stroke Organization

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Abstract

Cerebral amyloid angiopathy (CAA) is a well-recognized and challenging disease for neurologists and other clinicians caring for the rapidly aging worldwide population. CAA is a major cause of spontaneous lobar intracerebral hemorrhage (ICH), and can also cause transient focal neurological episodes, and convexity subarachnoid hemorrhage, CAA-associated ICH has a high mortality, morbidity, and recurrence rate. CAA can affect a wide range of clinical decisions including use of antithrombotic medications, safety for anti-β-amyloid peptide (Aβ) immunotherapy, and need for anti-inflammatory or immunosuppressive treatment. We present guidelines, intended to inform the approach to individuals with suspected CAA, written on behalf of the International CAA Association and the World Stroke Organization (WSO). We cover five areas selected for their relevance to practice: (1) diagnosis, testing, and prediction of intracerebral hemorrhage risk; (2) antithrombotic agents and vascular interventions; (3) vascular risk factors and concomitant medications; (4) treatment of CAA manifestations; and (5) diagnosis and treatment of CAA-related inflammation and vasculitis. The statement has been reviewed and approved by the Executive Committee of the WSO, and the International CAA Association.

Keywords
brain bleed, brain microbleeds, cerebral hemorrhage, leukoaraiosis, MRI, antithrombotic

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Introduction

Cerebrovascular amyloid deposition (cerebral amyloid angiopathy, CAA) is now a well-recognized and challenging disease for neurologists and other clinicians caring for the rapidly aging worldwide population. As a major cause of spontaneous intracerebral hemorrhage (ICH), CAA is a primary driver for a stroke subtype with among the highest mortality, morbidity, and recurrence rate across the stroke spectrum. And as an advanced cerebral small vessel pathology, CAA can tangibly affect a wide range of clinical decisions including use of antithrombotic medications, safety for anti-β-amyloid peptide (Aβ) immunotherapy, and need for anti-inflammatory or immunosuppressive treatment.

These guidelines, written on behalf of the International CAA Association, represent a series of clinical considerations and recommendations. They are grouped into five areas selected for their relevance to practice: (1) diagnosis,

testing, and prediction of ICH risk; (2) antithrombotic agents and vascular interventions; (3) vascular risk factors and concomitant medications; (4) treatment of CAA manifestations; and (5) diagnosis and treatment of CAA-related inflammation and vasculitis. The five themes, and the specific recommendations within each, evolved over two International CAA Association conferences (November 2022, Perth, Western Australia and October 2024, Munich, Germany) and were formulated and adopted by the writing group through iterative discussions and consensus. The considerations and recommendations are based on published literature or on the expert opinion of the writing group when there were insufficient published data. Each recommendation is accompanied by a Strength of Recommendation (SOR) rating of either Strong or Weak that is intended to reflect both an assessment of the evidence base supporting the recommendation and the authors' opinion of the clinical importance of the recommended action. The document specifically pertains to the predominant forms of CAA driven by cerebrovascular Aβ deposition as opposed to the considerably less common non-Aβ CAAs.[1]

The writing group emphasizes that the listed recommendations represent general considerations that are intended to inform the approach to individuals with suspected CAA but cannot substitute for clinical judgment in any specific patient or medical situation. A second notable caveat to the International CAA Association recommendations is that they reflect available data as of the date of publication and will almost certainly change as new data emerge. The members of the International CAA Association will therefore seek to provide updated recommendations on the organization's website (caaforum.org), in updated guidelines, or both, in the future.

Basic concepts and suggested terminology

CAA can be used as both a descriptive histopathologic term describing cerebrovascular Aβ deposition and a diagnostic clinical entity with etiologic and prognostic implications for an individual's medical course. Clinical-radiological diagnostic criteria for CAA such as the Boston[2] and Edinburgh[3] criteria straddle the two senses of the term in that they are based on specific clinical presentations of CAA (as listed below) but are validated against advanced CAA neuropathology as the diagnostic reference standard. The term CAA is accordingly used in these guidelines to represent high likelihood of advanced CAA pathology with

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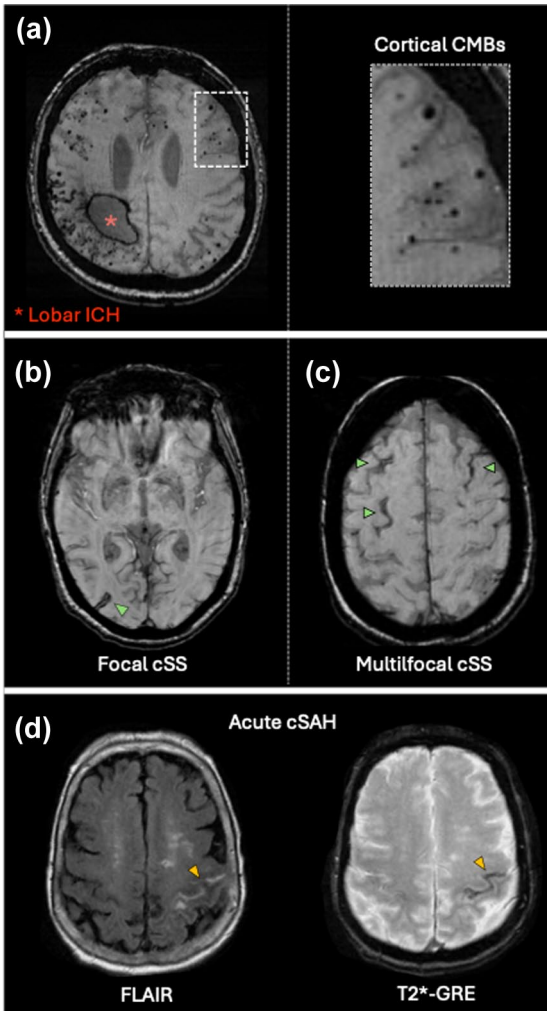
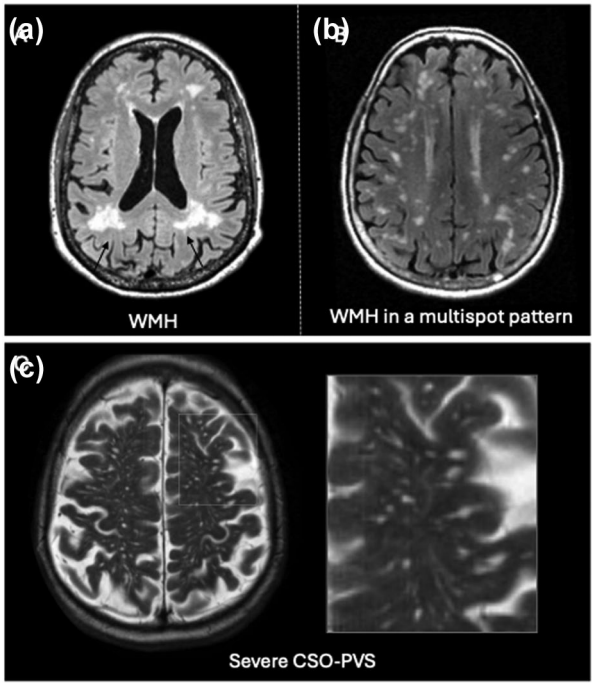
Figure 1. Representative example of hemorrhagic MRI markers of cerebral amyloid angiopathy. (a) Axial SWI demonstrating a subacute lobar hemorrhage (red asterisk) with multiple strictly lobar, mostly cortical, cerebral microbleeds (CMBs) (magnified in the inset). (b–c) Axial SWI examples of cSS in patients with cerebral amyloid angiopathy: a single sulcus with cSS (arrowhead, B), and three affected sulci (arrowheads, C). (d) Acute convexity subarachnoid hemorrhage (linear hypertense signal) on axial FLAIR with corresponding T2*-GRE curvilinear hyposignal along the left central sulcus, in a patient presenting with cerebral amyloid angiopathy-related transient focal neurological episodes. Of note, within the Boston criteria v2.0, acute convexity subarachnoid hemorrhage is treated and rated as a hemorrhagic equivalent of cSS (the chronic form of the same lesion). Images modified from *Int J Stroke*. 2019 Dec;14(9):956-971.



Source. Images modified from Charidimou et al.[8]

Figure 2. Non-hemorrhagic white matter markers included in the Boston criteria v2.0 (b and c). (a) Axial FLAIR sequence showing white matter hyperintensities of presumed vascular origin, with posterior (occipital) predominance (b) White matter hyperintensities in a multispot pattern, corresponding to more than 10 small (circular or ovoid) spots of hyperintensities in the subcortical white matter. (c) Axial section of a T2-weighted sequence at the level of centrum semiovale, magnified in the inset, showing innumerable MRI-visible perivascular spaces (CSF-like contrast, dots or lines in shape, following the path of small caliber penetrating arteries). Images modified from *Int J Stroke*. 2019 Dec;14(9):956-971.



Source. Images modified from Charidimou et al.[8]

the potential for causing or contributing to clinical symptoms. The diagnosis does not necessarily implicate CAA as the sole or primary cause of clinical symptoms, as CAA may often coexist with other neuropathologies in conditions such as cognitive impairment.[4] It also does not indicate a uniformly high risk for future ICH, as this risk can vary substantially among CAA patients (see "Diagnosis, testing, and prediction of ICH risk").

The pathogenesis of CAA[5] appears to occur via a pathway involving accumulation of Aβ in the media and adventitia of arterioles and capillaries of the leptomeninges and cerebral/cerebellar cortex followed by loss of vascular cells and impaired vascular physiology and non-hemorrhagic forms of brain injury such as white matter hyperintensities and microinfarcts. Hemorrhagic forms of brain injury such as cerebral microbleeds (CMB), convexity subarachnoid hemorrhage (cSAH) and its chronic counterpart cortical superficial siderosis (cSS), and ICH (collectively referred to in this document as lobar hemorrhagic lesions, Figure 1) appear to occur at the later stages of CAA progression. Recognized clinical manifestations of CAA in addition to ICH, cSAH, and cognitive decline are transient focal neurologic episodes[6] (TFNEs) and the

autoimmune syndrome of CAA-related inflammation (CAA-ri).[7] The most recent version 2.0 of the Boston criteria for CAA[2] expanded the MRI diagnostic markers for probable CAA to include not only multifocal hemorrhagic lesions but also presence of one hemorrhagic and one non-hemorrhagic marker (severe enlarged perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern, Figure 2), potentially identifying slightly earlier stages of symptomatic CAA.[5]

Diagnosis, testing, and prediction of ICH risk

Recommendations for diagnosis, testing and prediction of ICH risk	
Recommendations	**SOR**
1. CAA should be suspected in patients ⩾50 years of age as a potential cause of lobar ICH, cSAH, or TFNE or potential contributor to cognitive decline.	Strong
2. For patients with potential CAA-related clinical and imaging findings who are <50 years of age or have multiple affected first-degree family members, a detailed family history should be taken with consideration of genetic testing for autosomal dominant mutations that cause CAA.	Strong
3. CAA should be considered as a possible cause of unexplained lobar ICH, cSAH, cognitive decline, or TFNE in patients with prior exposure to relevant human cadaveric tissue (including dural grafts, embolization material derived from human dura mater, or growth hormone derived from human cadaveric pituitary glands), including in patients less than 50 years old.	Strong
4. Patients suspected of CAA should have brain MRI with T2*-weighted sequences sensitive to hemorrhagic lesions	Strong
5. The Boston Criteria v2.0 are recommended for diagnosis of CAA (Figure 3)	Strong
6. For patients with a lobar ICH and CT only, where MRI is not feasible, the simplified Edinburgh Criteria are a reasonable alternative for diagnosis	Strong
7. Amyloid biomarker testing, by CSF or PET, is generally not needed to diagnose CAA. However, amyloid biomarker testing could be considered in cases where the Boston criteria cannot be applied (e.g. in patients with mixed lobar and deep ICH or patients less than 50 years old with neurosurgical history) or when competing causes are possible.	Strong Weak
8. For patients with ICH or cSAH otherwise meeting the definition of probable CAA by Boston Criteria, the use of non-invasive CT- or MR-angiography, as indicated by local stroke guidelines, is sufficient to rule out vascular malformations or other secondary causes; intra-arterial digital subtraction angiography is probably not needed.	Strong
9. It is reasonable to incorporate the presence, type and extent of prior hemorrhagic lesions on brain imaging when stratifying risk of future CAA-related ICH. Multiple prior ICHs and multifocal or disseminated cSS appear associated with highest risk of future CAA-related ICH, whereas probable CAA with CMB alone (i.e. without ICH or cSS) appears to be associated with the lowest risk among CAA patients for future ICH.	Strong
10. Testing for APOE genotype is not indicated to diagnose CAA or predict CAA-related ICH risk, except when applying the Edinburgh criteria or evaluating patients with AD for anti-Aβ immunotherapies such as lecanemab or donanemab.	Weak

SOR: Strength of Recommendation.

Synopsis

CAA that is sufficiently advanced to cause hemorrhagic lesions can be diagnosed in life with good accuracy using criteria validated against neuropathology. For optimal sensitivity of the criteria, brain MRI with hemorrhage sensitive (T2*-weighted) sequences is required. However, for patients with ICH who are unable to have MRI, the Edinburgh diagnostic criteria for CAA-associated lobar ICH do a reasonable job of ruling in or out CAA in many patients. Most patients with CAA present with ICH, cSAH (often with anatomically associated TFNE), or cognitive decline, but the clinician should also be aware of less common presentations as an autosomal dominant monogenic hereditary disorder, iatrogenic complication of previous neurosurgery, or as CAA-related inflammation (see "Diagnosis and treatment of CAA-ri and vasculitis"). Emerging evidence suggests that patients with CAA often have low Aβ40 in the cerebrospinal fluid and positive amyloid-PET; however, more research is needed before these tests can be recommended for routine diagnosis. The presence of cSS, particularly when it is disseminated, is the strongest risk factor for future hemorrhagic stroke in patients with CAA.

Figure 3. Framework of the Boston criteria v2.0 for possible and probable sporadic cerebral amyloid angiopathy.

Category	Boston Criteria v2.0 for sporadic Cerebral Amyloid Angiopathy*
Clinical presentation	- Age: ≥50 years - Presentation with at least one of the following: spontaneous intracerebral hemorrhage, convexity subarachnoid hemorrhage, transient focal neurological episodes, cognitive impairment or dementia
Probable CAA	- Meets clinical presentation criteria, and - Brain MRI* demonstrates either: o ≥2 strictly lobar/superficial hemorrhagic lesions, or o One strictly lobar hemorrhagic/superficial lesion plus one white matter feature
Possible CAA (low diagnostic certainty)	- Meets clinical presentation criteria, and - Brain MRI* demonstrates either: o One strictly lobar/superficial hemorrhagic lesion, or o One white matter feature
Additional Criteria	- Absence of spontaneous deep hemorrhagic lesions on T2*-GRE/SWI MRI - Exclusion of other causes of hemorrhagic lesions, based on clinical history, imaging, and additional workup when appropriate - Cerebellar hemorrhagic lesions are not classified as either lobar or deep
***Brain MRI markers definition**	
Hemorrhagic markers	**Lobar (cortical-juxtacortical)/superficial hemorrhagic lesions (T2*-GRE/SWI, ideally SWI @ 3Tesla)** 1) Lobar Intracerebral hemorrhage (acute, subacute or chronic) 2) Lobar cerebral microbleeds 3) Cortical superficial siderosis 4) Convexity subarachnoid hemorrhage (hyperintense on FLAIR if acute)
White matter features	**White matter features** 1) Severe perivascular spaces in the centrum semiovale: >20 visible in one hemisphere on T2-weighted sequences 2) White matter hyperintensities in a multispot pattern: >10 small (~3-25 mm), juxtacortical/subcortical, round/ovoid lesions throughout the brain on FLAIR

*From data based on Charidimou, ..., Greenberg. Lancet Neurology. 2022 Aug;21(8):714-725

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Recommendation-specific supportive text

1. CAA can cause transient focal neurological episodes, lobar intracerebral hemorrhage, and convexity subarachnoid hemorrhage and contribute to cognitive decline (independent of concomitant Alzheimer's disease (AD) pathology).[2]
2. Rare causes of early-onset Aβ-CAA include autosomal dominant genetic mutations in APP and presenilin-2 (and for non-Aβ-CAA transthyretin, BRI2, or cystatin-C(1)). The clinician can therefore also suspect CAA in patients younger than 50, particularly when there is a history of an affected first-degree relative, or when there are multiple affected first-degree relatives.
3. Iatrogenic CAA is caused by seeding of the central nervous system with exogenous Aβ. Cases have been linked to transplanted human dura mater, embolization of lyophilized dura mater, and human cadaveric pituitary-derived growth hormone, typically with a latency period of several decades. Therefore, careful questioning for history of neurosurgery or other potentially relevant procedures is indicated in any person with possible CAA symptoms.[9]
4. Brain MRI is more sensitive for CAA than brain CT, because it can detect prior silent hemorrhagic lesions (CMB and cSS) and centrum semiovale perivascular spaces.[10] The MRI protocol should include a T2*-weighted sequence with high sensitivity for silent hemorrhagic lesions. Sensitivity is enhanced by

higher field strength (e.g. 3.0 Tesla) and susceptibility-weighted imaging (SWI) instead of T2*-weighted gradient-recalled echo (GRE).[11]

5. The Boston Criteria 2.0 for probable CAA (Figure 3) have been validated to have good accuracy for diagnosis of moderate-to-severe CAA pathology.[2] When compared against autopsy, the reference standard, the criteria had 74.5% sensitivity (95% CI 65.4–82.7%) and 95.0% specificity (83.1–99.4%). Diagnostic accuracy appears highest for individuals presenting with ICH, lower for non-ICH presentations, and lowest for individuals who do not have clinical symptoms associated with CAA.[2,12,13] According to the criteria, probable CAA is not diagnosed when there are mixed location bleeds (i.e. hemorrhages or microbleeds in both lobar and non-lobar locations); however, the clinician should be aware that patients with mixed bleeds may still have a combination of CAA along with a non-CAA arteriopathy (e.g. from arteriolosclerosis). There is some evidence that patients with mixed bleeds and cortical superficial siderosis or a ratio of lobar to deep microbleeds greater than four are likely to have CAA, but more data with neuropathological correlation are needed.[14]
6. The Edinburgh diagnostic criteria for CAA-associated lobar ICH (Supplemental Table 1) use a combination of presence or absence of finger-like projections, subarachnoid extension of hemorrhage, and APOE genotype to predict moderate or severe CAA pathology in patients with lobar ICH.[3] In the derivation study, the absence of subarachnoid hemorrhage and the absence of an APOE ε4 allele ruled out CAA with 100% sensitivity (95% CI 88–100%), while the presence of subarachnoid hemorrhage and either APOE ε4 allele possession or finger-like projections ruled in CAA with a specificity of 96% (95% CI 78–100%). However, a limitation of these criteria is that APOE testing is not available in most regions. A simplified version of the criteria,[15] omitting APOE testing, can be used to help rule in CAA based on the presence of finger-like projections plus subarachnoid hemorrhage (specificity 87%, 95% CI 79–92%) or to rule out CAA based on the absence of either finger-like projections or subarachnoid hemorrhage (sensitivity 81% (95% CI 71–88%). Another possible limitation of these criteria is their sensitivity may be reduced in low-volume ICH.[16]
7. Amyloid biomarkers have been developed from blood, cerebrospinal fluid, and positron emission tomography (PET). These markers hold promise for diagnosing CAA. In CAA, studies show that there is low CSF Aβ40 and Aβ42,[17,18] and mildly elevated amyloid-PET signal[19] with a higher occipital to global ratio than in AD.[20] However, there are limited data on sensitivity in CAA, the presence of AD pathology may generate false positives for CAA, and current studies have not always produced consistent results. Plasma markers of Aβ are less accurate than CSF, and so far there are limited and inconsistent data on plasma markers in CAA.[21] Additional research is needed to derive specific thresholds for CSF Aβ40 and Aβ42 levels and PET amyloid ligand binding to make diagnoses in individual patients.
8. For patients with ICH or subarachnoid hemorrhage, clinicians should consider alternative diagnoses including vascular malformation, cortical venous thrombosis, or trauma.[22,23] Published ICH guidelines recommend non-invasive angiography in some scenarios, with variable levels of evidence depending on the scenario and the specific guideline.[22–24] Observational data and expert consensus suggests that invasive catheter angiography is probably not needed for patients with an intracerebral hemorrhage or cSAH who meet criteria for probable CAA and don't have evidence of a vascular malformation on non-invasive vascular imaging, such as CT-angiography.
9. Several clinical and MRI features have been associated with future risk of ICH in CAA; however, there are no validated multivariable prediction models to precisely estimate the risk. Multiple prior ICHs and multifocal or disseminated cSS appear associated with highest risk. Probable CAA with CMB only (i.e. without ICH or cSS) appears to be associated with the lowest risk among CAA patients for future ICH. Patients presenting with lobar ICH due to CAA have an average risk for recurrence of 7.4% per year (95% CI 3.2–11.6% per year)[25] and patients presenting with cSAH have an average risk for new hemorrhagic stroke of 21.4% per year (95% CI 16.7–26.9% per year).[26] A meta-analysis showed that cSS is the strongest predictor of new hemorrhagic stroke in patients with CAA, including patients who presented with or without ICH. In that study, the presence of disseminated cSS (meaning that four or more sulci are involved) increased risk of future ICH by 4.28 fold (95% CI 2.91–6.30) while the presence of focal cSS (three or fewer sulci involved) increased risk by 2.11-fold (95% CI 1.31–2.41).[27] Another meta-analysis confined to patients presenting with CAA-related ICH had similar findings: disseminated cSS predicted ICH recurrence (HR 3.59, 95% CI 1.96–6.57) but the risk in patients with focal cortical superficial siderosis, while elevated, was not statistically significant (HR 1.41, 95% CI 0.68–2.95).[28]

In statistical models that don't control for cSS, other factors have been associated with risk for recurrent ICH including APOE genotype, history of prior symptomatic hemorrhage, and number of microbleeds. Models that control for cSS (potentially limited by insufficient sample size) have not confirmed these additional factors as independent predictors of risk.

10. The APOE ε4 and ε2 alleles are associated with higher prevalence and severity of CAA. APOE genotype testing increases the accuracy of the Edinburgh criteria[3] and is also recommended to stratify risk of ARIA in patients being evaluated for treatment with anti-Aβ immunotherapy.

Management of CAA

Antithrombotic agents and vascular interventions

Recommendations for Management of CAA: Antithrombotic agents and vascular interventions

Recommendations	SOR
1. For all patients with probable CAA, clinicians should individualize the decision to initiate or resume antithrombotic treatment according to the known risks and benefits of antithrombotic treatment, the patient's personalized risks of major ischemic vascular events, future ICH and other hemorrhagic complications, and personal preferences. Future risk of ICH in patients with CAA should be estimated using their individual CAA phenotypic markers (see "Diagnosis, testing, and prediction of ICH risk"). Similarly, risk of major ischemic vascular events should be estimated based on patient characteristics, and if available, on validated scores (e.g. CHA_2DS_2-VASc in patients with atrial fibrillation).	Strong
2. In patients with probable CAA, we do not recommend antiplatelet treatment in the absence of prior symptomatic ischemic stroke, cardiovascular disease, or peripheral vascular disease (i.e. for primary prevention).	Strong
3. In patients with probable CAA who have not experienced a prior symptomatic ICH or cSAH and are not known to have disseminated or multifocal cSS on MRI, antiplatelet or anticoagulation is reasonable where there is an established indication for secondary prevention of major ischemic vascular events or ischemic stroke prevention	Weak
4. In patients with CAA-related ICH and an indication for antithrombotic medication, treatment with antiplatelet monotherapy may be safe and may be considered.	Weak
5. In patients with CAA-related ICH or cSAH and high-risk atrial fibrillation (CHA_2DS_2-VASc $\geq$ 2), it is unclear whether anticoagulation should be resumed or avoided. Based on the current evidence, anticoagulation may be avoided in this situation. If anticoagulation is considered, a direct oral anticoagulant (DOAC) is preferable to a vitamin K antagonist (VKA).	Weak Strong
6. In patients with CAA-related ICH and high-risk atrial fibrillation (CHA_2DS_2-VASc $\geq$ 2), clinicians might consider left atrial appendage closure, although it is unclear whether left atrial appendage closure provides greater net benefit than medical management in this setting.	Weak
7. In patients with probable CAA and a mechanical heart valve and additional cardioembolic risk factors (such as greater age or prior valve-related stroke), VKAs should be considered because the high risk of cardiogenic emboli likely outweighs the risk of ICH. In patients with aortic mechanical valves, no additional risk factors, and recurrent lobar ICH, clinicians might consider antiplatelet treatment in place of VKAs.	Weak Weak
8. In patients with probable CAA and an acute ischemic stroke due to large vessel occlusion, endovascular thrombectomy (EVT) without thrombolysis is the preferred treatment option. In patients with probable CAA and acute ischemic stroke who are not eligible for EVT, clinicians should consider intravenous thrombolysis in the absence of prior history of ICH, because of the known benefits of intravenous thrombolysis, and the limited evidence of the attenuation of net benefit in patients with CAA. However, patients with prior CAA-related ICH are likely at increased risk of hemorrhagic complications.	Weak Weak
9. Multiple other conditions exist for which long-term anticoagulation is indicated, for example, unprovoked or repeated deep venous thrombosis, pulmonary embolism, antiphospholipid syndrome. For these situations, it is reasonable to take an individualized and multidisciplinary approach to weighing the relative risks and benefits.	Weak

SOR: Strength of Recommendation.

Synopsis. For patients with CAA, the decision of whether to initiate or resume antithrombotic treatment or consider alternatives is influenced by the relatively high risk of hemorrhagic complication in comparison with patients without CAA. This decision requires balancing the established benefit of antiplatelet or anticoagulant treatments in preventing future ischemic vascular events against their potential to increase the risk of major bleeding events (including ICH), the required duration of the antithrombotic treatment and the availability of alternatives.

Recommendation-specific supportive text

1. The complexity of balancing relative risks and benefits of treatment options dictates an individualized, situation-specific approach rather than a one-size-fits-all blanket recommendation.
2. The recommendation is based on data from studies of aspirin for primary prevention in people without prior symptomatic vascular disease. In these people, aspirin is of uncertain net value as the reduction in occlusive events is offset by increased major bleeds.[29]
3. The recommendation is based on the results of a pooled analysis of individual patient data from cohort studies in 20 322 adults from 38 cohorts (over 35 225 patient-years of follow-up; median 1·34 years [IQR 0·19–2·44]) adults with recent ischemic stroke or transient ischemic attack.[30] Irrespective of cerebral microbleeds anatomical distribution or burden (available in 12,669 patients, of whom < 4% fulfilled the criteria for probable CAA; personal communication D. Werring), the rate of ischemic stroke exceeded that of intracranial hemorrhage. The recommendation recognizes that the outcome of intracranial hemorrhage may be worse than for ischemic stroke, partially offsetting the higher frequency of the latter relative to the former.

In an MRI sub-study of a randomized controlled trial assessing apixaban versus aspirin in patients with atrial fibrillation (AF) and at least one other risk factor for stroke, there was no increase in the percentage of patients who developed new microbleeds 1 year after treatment (HR 0.9, 95% CI 0.5–1.6).[31] Whether these findings apply to patients with CAA, particularly those with disseminated superficial siderosis, is unknown.

4. In patients with ICH who had previously taken antithrombotic therapy, restarting antiplatelet therapy had no significant effect on recurrent ICH or all major vascular events in a pilot-phase trial.[32] In explanatory subgroup analysis there was no significant heterogeneity in treatment effect for patients with lobar versus those with non-lobar location of the ICH,[33] presence of focal/disseminated superficial siderosis, or probable CAA according to the modified Boston or Edinburgh criteria for CAA.[34] These findings provide some reassurance about the use of antiplatelet therapy after ICH if indicated for secondary prevention of major ischemic vascular events, including patients with lobar ICH due to CAA, with the caveat that the confidence intervals in these exploratory CAA subgroups were wide.
5. Risk of non-fatal stroke or vascular death in AF patients following anticoagulation-related ICH is high, both when treated with a DOAC and when anticoagulation is avoided.[35,36] As patients with ICH were excluded from the pivotal DOAC non-valvular AF trials,[37–41] it is uncertain whether their reported safety and efficacy relative to VKA[38–41] and aspirin[37] generalizes to ICH survivors, including CAA-related ICH.

There are five completed randomized trials (one unpublished).[35,36,42,43] Four of these were included in a recent individual patient data meta-analysis of a total of 412 participants (310 [75%] aged 75 years or older and 163 [40%] with CHA2DS2-VASc score > 4).[44] The intervention was a DOAC in 209 (99%) of 212 participants who were assigned to start oral anticoagulation, and the comparator was antiplatelet monotherapy in 67 (33%) of 200 participants assigned to avoid oral anticoagulation. All trials sought and recorded major adverse cardiovascular events between 2–6 years of maximum follow-up. The primary outcome of any stroke or cardiovascular death occurred in 29 (14%) of 212 participants who were assigned to start oral anticoagulation versus 43 (22%) of 200 who were assigned to avoid oral anticoagulation (pooled HR 0·68 [95% CI 0·42–1·10]; $I^2 = 0\%$). Oral anticoagulation reduced the risk of ischemic major adverse cardiovascular events (nine [4%] of 212 vs 38 [19%] of 200; pooled HR 0·27 [95% CI 0·13–0·56]; $I^2 = 0\%$). Hemorrhagic major adverse cardiovascular events occurred in 15 (7%) of 212 participants assigned to start oral anticoagulation vs nine (5%) of 200 assigned to avoid oral anticoagulation (pooled HR 1·80 [95% CI 0·77–4·21]; $I^2 = 0\%$). Death from any cause occurred in 38 (18%) of 212 participants assigned to start oral anticoagulation vs 29 (15%) of 200 of 212 participants assigned to avoid oral anticoagulation (1·29 [0·78–2·11]; $I^2 = 50\%$). Death or dependence after 1 year occurred in 78 (53%) of 147 participants assigned to start oral anticoagulation with available data vs 74 (51%) of 145 participants assigned to avoid oral anticoagulation with available data (pooled odds ratio 1·12 [95% CI 0·70–1·79]; $I^2 = 0\%$). There was no significant interaction between ICH location and the primary outcome (p-interaction = 0.98), although power to detect an interaction was limited. Recently, the results of PRESTIGE-AF[42] (n = 319), further supported the protective effect of DOACs on the occurrence of ischemic stroke (1/158 participants assigned to DOAC, 20/161 participants assigned to avoiding anticoagulant; HR 0.05, 95% CI 0.01–0.36), but at the cost of an increased risk of ICH (11/158 in DOAC group, 1/161 in no anticoagulant group; HR 10.89, 95% CI 1.95–60.72). The HR for recurrent ICH did not reach the pre-specified HR "non-inferiority" margin of 1.735. Completion of ongoing trials and further individual patient data meta-analysis should enable subgroup analyses, including in patients with ICH due to CAA.

In one of the ongoing trials, ENRICH-AF, the Data Safety Monitoring Board recommended in 2023 that participants with lobar ICH or convexity SAH should have the study drug terminated as soon as possible and that no further

patients with lobar ICH or acute convexity SAH should be enrolled.[45] This recommendation was based on observation of an unacceptably high risk of recurrent hemorrhagic stroke among those assigned to edoxaban in those with lobar ICH (n=174, 25%) or convexity SAH (n=34, 5%) as their qualifying event, among a total of 699 participants included at that time. Other trials continue to include these patients and subgroup analyses of participants with CAA are awaited.

If anticoagulation were to be considered following CAA-related ICH, it is reasonable to begin within weeks after the ICH, but there is no evidence from randomized controlled trials to inform the precise timing.

6. Left atrial appendage closure has not been reported in randomized controlled trials in patients with ICH in general, patients with CAA-related ICH, or CAA without ICH. Accordingly, it is unknown whether the relative safety and efficacy of left atrial appendage closure compared to anticoagulation generalizes to patients with CAA or CAA-related ICH, who have high risks of recurrent ICH and major ischemic events. The procedural risk of left atrial appendage closure has decreased since its introduction, and the antithrombotic regime after the procedure is increasingly moderated toward less intense regimes.[46,47] The immediate risk of the procedure and the risk of subsequent short-term dual antiplatelet regime (or DOAC) followed by longer single antiplatelet treatment should be weighed against the estimated benefit and risk of lifelong anticoagulation or other antithrombotic regimens.
7. Risk for cardioembolic stroke associated with mechanical heart valves appears increased by additional factors such as age and prior ischemic stroke.[48] When resuming VKAs following CAA-related ICH, it is reasonable to begin within weeks after ICH, but there is no evidence from randomized trials to inform precise timing. The alternative of surgically exchanging the mechanical valve with a bioprosthetic valve is unattractive because of the high risk of such operation and should be considered only in exceptional circumstances, for example, individuals with recurrent CAA-related ICH and acceptable surgical risk.
8. There is currently no evidence to exclude patients from endovascular thrombectomy based on the presence of CMBs.[49] Expert opinion is divided on whether to avoid intravenous thrombolysis altogether in patients with prior CAA-related ICH versus deciding on a case-by-case basis. Patients with intracranial hemorrhage (including ICH) were excluded from the randomized controlled trials assessing intravenous thrombolysis. Currently, ICH (irrespective of its cause) >3 months previously is not considered an absolute contraindication in many practices. In patients with a known history of CAA who present with symptoms of acute stroke, the possibility of TFNE should be considered and their neuroimaging carefully examined for cSAH. Patients with CMBs appear to have an increased risk of ICH after intravenous thrombolysis,[50,51] and a higher risk of poor functional outcome relative to those without CMBs.[50] The risk of ICH increases with the number of CMBs.[50] However, there is no evidence that intravenous thrombolysis should be withheld from otherwise eligible patients solely because of CMBs, including patients with strictly lobar CMBs indicative of CAA.[51]
9. There are less data to guide anticoagulation for the range of indications outside of AF and thus greater need for an individualized approach. A guiding principle is that shorter duration and lower intensity of anticoagulation help to mitigate ICH risk.

Vascular risk factors and concomitant medications

Recommendations for Management of CAA: Vascular risk factors and concomitant medications	
Recommendations	**SOR**
1. In patients with ICH attributed to CAA, blood pressure (BP) should be regularly monitored to maintain a long-term target of ⩽130/80 mm Hg to reduce risk of ICH recurrence. Home BP monitoring may be helpful to empower patients, improve medication adherence, and allow more frequent and accurate BP measurements to avoid BP variability.	Strong
2. There are insufficient data to assess the benefits versus risks of lipid-lowering agents, (including statins) relative to prevention of cardiovascular events and hemorrhage occurrence in patients with CAA. Pending data from randomized trials, it may be reasonable to continue lipid-lowering therapy in high-risk patients with an established cardiovascular indication and to discontinue therapy when the indication is for primary prevention only.	Weak
3. The risks of continuation or initiation of selective serotonin reuptake inhibitors (SSRIs) on hemorrhage occurrence in patients with CAA are uncertain. It may be reasonable to use SSRIs in CAA patients with significant depressive symptoms.	Weak
4. Regular long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with CAA should be avoided because of increased ICH risk.	Weak
5. In patients with CAA, healthy lifestyle modifications including avoidance of excessive alcohol consumption and smoking cessation are advisable to reduce stroke risk	Strong

SOR: Strength of Recommendation.

Synopsis. The prevalence of vascular risk factors among patients with CAA is high,[52] and patients with CAA are at risk for both (recurrent) ICH, ischemic stroke, and cognitive decline. Uncontrolled hypertension is a major risk factor for hemorrhagic and ischemic stroke.[53] It is, therefore, important to closely monitor BP and aggressively treat hypertension. Observational non-randomized data and meta-analyses have linked statins,[54–57] SSRIs[58,59] and NSAIDs[60,61] to increased risk of hemorrhage occurrence/recurrence. More research is needed to confirm and refine these potential risks. Avoidance of smoking and excessive alcohol consumption have overall health benefits.

Recommendation-specific supportive text

1. Long-term BP control is inadequate in ICH patients, including those with CAA,[62] and is associated with higher risk for ICH recurrence.[63,64] In a prospective cohort study of ICH patients, < 50% of patients achieved consistent BP control based on AHA/ASA guidelines during a median follow-up of 36.8 months, and the hazard ratio (HR) for a recurrent lobar ICH was 3.53 (95% CI, 1.65–7.54).[64] In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, BP lowering with perindopril plus indapamide significantly reduced the overall stroke risk during a mean follow-up of 3.9 years. BP lowering was beneficial across all stroke types, particularly ICH. The adjusted HR of first ICH was 0.44 (95% CI, 0.28–0.69).[65] This reduction appeared to apply to lobar and deep ICH and mainly concerned patients whose qualifying events was an ICH; the HR for ICH recurrence among subjects with prior ICH relative to a first ICH in subjects with prior ischemic stroke was 6.60 (95% CI, 4.50–9.68).[66] In a secondary analysis, active treatment reduced the risk of probable CAA-related ICH (defined by Boston criteria using CT imaging) by 77% (95% CI, 19–93%), that of hypertension-related ICH by 46% (95%CI, 4–69%) and unclassified ICH by 43% (95%, −5%, 69%).[67] The recommendation for a target BP of ⩽130/80 mm Hg is based on data from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)[68] and Secondary Prevention of Small Subcortical Strokes (SPS3)[69] trials and the AHA/ASA ICH management guidelines.[22]

Home BP monitoring may be helpful to empower patients, improve compliance, and allow more frequent and accurate BP measurements to avoid BP variability. Screening for and treatment of obstructive sleep apnea[70] and lifestyle modifications should be considered as adjunctive to pharmacotherapy for BP management.

2. Aggregate randomized data do not show significant increase in ICH risk with statins in patients without a history of stroke, but there are limited data on statins or other lipid-lowering drugs in patients with CAA or history of ICH.[71,72] For example, trials of PCSK-9 inhibitors excluded patients with history of ICH. Some studies reported an association between statin use and the prevalence of lobar CMB or the occurrence of lobar ICH, particularly in patients carrying APOE-ε4 and APOE-ε2 genotypes.[56,73,74] Results from observational non-randomized studies examining the association between statin therapy, lipid-lowering, and ICH risk have been inconsistent.[54–57,75,76] Other single-center, observational, non-randomized, studies have suggested that pre-ICH use of statins is associated with improved recovery and that statin discontinuation during hospitalization is associated with increased in-hospital mortality.[77,78] However, selection bias and confounding-by-indication limit the interpretation of these studies. Randomized trials addressing this uncertainty are ongoing. At present, the decision to use statins in CAA patients must consider the risk of ischemic events versus the potential risk of ICH.
3. CAA patients are at high risk of depressive symptoms. SSRIs are effective in treating depression and anxiety, however, there are inconsistent data regarding their association with ICH risk.[58,59,79] A switch to another class of antidepressants could be considered, balancing the possibility of increased ICH risk against the important quality of life considerations in adequately treating depression.
4. Observational studies and meta-analyses reported increased risk of ICH with NSAIDs-use.[60,61] Randomized data from ICH patients are lacking. If safer alternatives are available, frequent/daily use of NSAIDs is not recommended.
5. Excessive alcohol use (⩾2 drinks per day) has been linked to elevated BP and increased ICH risk.[30–31] Healthy lifestyle, including reduction in alcohol consumption, smoking cessation, healthy diet, and physical activity, has multiple positive effects and can lead to reduced BP and risk of stroke and cardiovascular disease.

Treatment of CAA manifestations

Recommendations for Management of CAA: Treatment of CAA manifestations	
Recommendations	**SOR**
A. TFNEs	
1. CAA should be suspected in patients 50 years of age or older presenting with TFNEs.	Strong
2. In patients with acute presentations of CAA-related TFNEs and imaging evidence of acute cSAH, management should follow principles and guidelines similar to those for acute ICH. This includes acute blood pressure lowering (e.g. targeting a systolic blood pressure of 130–140 mm Hg), anticoagulation reversal, and avoiding antithrombotic (antiplatelet and anticoagulant) medications for 24–48 h before reassessment.	Weak
3. While CAA-related TFNEs are usually self-limited, in patients with multiple attacks causing distress, it is reasonable to consider a short course (e.g. 3–6 months) of an antiseizure drug, particularly those also effective against migraine (e.g. topiramate, lamotrigine, and levetiracetam).	Weak
4. Patient with CAA-related TFNEs particularly if associated with cSS/cSAH, are at high risk for future intracranial hemorrhage (ICH or cSAH) and should be treated like other high-risk CAA patients (see "Recommendations for Management of CAA" sections above).	Strong
B. Anti-Aβ immunotherapy	
5. CAA appears to be associated with increased risk for adverse effects of anti-Aβ immunotherapy. As such, these treatments should not be used for the purpose of treating CAA outside the context of a research trial.	Strong
6. In line with appropriate use recommendations, patients with early AD who are eligible for passive immunotherapy with monoclonal antibodies targeting **Aβ** who have prior ICH or cSAH, >4 CMBs, or foci of cSS should be excluded from treatment	Strong
C. Special considerations for management of CAA-related ICH	
7. Standard acute ICH management guidelines apply to CAA-related lobar ICH.	Strong
8. In patients who are eligible for hematoma evacuation, CAA should not be considered a contraindication. When hematoma evacuation is performed, a tissue sample should be obtained for histopathological analysis	Strong Strong

SOR: Strength of Recommendation.

Synopsis. The treatment of CAA manifestations requires a tailored approach with specific considerations based on clinical presentation. For CAA-TFNEs, maintaining a high index of suspicion and differentiating them from transient ischemic attacks (TIAs) through clinical judgment and appropriate neuroimaging is essential. Early recognition and management are particularly crucial in patients presenting with acute cSAH. While TFNEs are often self-limited, symptomatic management may be considered in select cases. CAA-related cognitive impairment represents another key clinical entity, frequently in accompaniment with neurodegenerative pathologies such as AD. Although no disease-modifying treatments exist for CAA, symptomatic therapies, such as cholinesterase inhibitors, may offer modest benefit.[80] A major emerging concern is the interaction between CAA and anti-Aβ immunotherapies in patients with concomitant AD and CAA, given the increased risk of amyloid-related imaging abnormalities (ARIA). Current evidence suggests that AD patients with a significant CAA burden are at heightened risk for ARIA, necessitating careful eligibility assessment before initiating these treatments. Until further evidence is available, anti-Aβ monoclonal antibodies should not be used as a treatment for CAA outside of research settings. Finally, acute management of CAA-ICH should align with established stroke guidelines. Notably, CAA should not be considered a contraindication for hematoma evacuation in eligible patients. When hematoma evacuation is performed, obtaining tissue for histopathological analysis can provide valuable diagnostic insights to support a CAA diagnosis.

Recommendation-specific supportive text

A.

1. CAA-related TFNEs are brief, transient, and often stereotyped focal neurological episodes that occur in patients with CAA.[6,81,82] They typically present with motor, somatosensory, or visual disturbances and can be mistaken for TIAs or focal seizures. However, unlike TIAs, TFNEs frequently exhibit a spreading progression of symptoms across contiguous cortical territories over minutes, often lasting less than 30 min, with a high recurrence rate.[83] Recognizing these episodes as CAA-related is crucial, as misdiagnosis can lead to inappropriate initiation of antithrombotic therapy. CAA-related TFNEs definition and diagnostic criteria have been suggested, in order to avoid both misdiagnosis and overdiagnosis.[6]
2. TFNEs are closely associated with acute cSAH, and patients experiencing these episodes have a substantially increased risk of subsequent ICH.[81] In a meta-analysis, 24.5% of patients

with TFNEs developed symptomatic ICH within eight weeks,[26] highlighting the urgency of appropriate acute management. Blood pressure management is reasonable, as acute cSAH may progress to ICH, with observational data suggesting that early expansion of cSAH to parenchymal hemorrhage can occur within 24 h. While no randomized trials have directly evaluated blood pressure targets in TFNEs, the general consensus is to apply ICH guidelines, lowering systolic blood pressure to below 140 mm Hg within the first 6 h if tolerated, with a long-term systolic blood pressure target of 130 mm Hg.

3. Although TFNEs are not epileptic in nature, their symptoms overlap with spreading cortical depolarization phenomena observed in migraine and epilepsy.[6] Clinical experience suggests that antiseizure medications or migraine-preventive agents like topiramate, lamotrigine or levetiracetam may reduce the frequency and severity of recurrent TFNEs.[6] However, no randomized trials have evaluated antiseizure therapy for TFNEs, and treatment should be individualized based on symptom burden.
4. The presence of TFNEs in conjunction with cSS or cSAH, is a strong predictor of future ICH, with an estimated annual hemorrhage risk of about 19% in patients fulfilling the Boston Criteria for probable CAA.[84] Given the high risk of hemorrhagic complications, these patients should be managed similarly to those with spontaneous ICH, with aggressive blood pressure control and avoidance of antithrombotic agents unless outweighed by the clinical benefits.[6]

B.

5. Anti-Aβ monoclonal antibodies, such as lecanemab and donanemab, have been approved by the US Food and Drug Administration (and the European Medicines Agency for lecanemab) for the treatment of early AD. However, these therapies carry a significant risk for ARIA.[85,86] The pathophysiological mechanisms of ARIA are not fully understood, but may in part be due to antibodies binding to Aβ in the cerebral vessels, particularly small vessels affected by pre-existing CAA.[87,88] Given potentially devastating complications associated with severe ARIA and the lack of evidence supporting disease-modifying effects in CAA, the use of anti-Aβ immunotherapy for CAA itself is not recommended outside the context of a clinical trial.[89]
6. In patients with early AD who are eligible for passive immunotherapy with monoclonal antibodies targeting Aβ (e.g. lecanemab and donanemab), the presence of concomitant CAA appears to be a strong risk factor for ARIA. In line with appropriate use recommendations,[90,91] patients with early AD and evidence of ICH, more than four CMBs or foci cSS (trials of lecanemab excluded all individuals with cSS, trials of donanemab permitted one focus of cSS) should be excluded from treatment. Patients with early AD and concomitant probable CAA based on Boston criteria v2.0 based on the presence of two or more hemorrhagic markers might also be at high risk for ARIA,[88] and a careful risk and benefit assessment should be performed before administering anti-Aβ monoclonal antibody infusions. Of note, anti-amyloid trials in AD have not systematically evaluated the proportion of participants meeting the Boston criteria v2.0 for probable CAA and risk for ARIA.

C.

7. The management ICH in patients with CAA-related lobar ICH should follow the established guidelines from the American Heart Association (AHA),[22] European Stroke Organization (ESO),[23] and the Heart and Stroke Foundation of Canada/Canadian Hemorrhagic Stroke Trials Initiative (CoHESIVE).[92] These recommendations cover BP control, reversal of anticoagulation, avoidance of early antithrombotic therapy, supportive care, and rehabilitation strategies.
8. Surgery, including hematoma evacuation and minimal invasive endoscopic removal of hemorrhage[93] is generally safe in CAA-related ICH when indicated.[94] When a lobar hematoma evacuation is performed, obtaining and sending a tissue sample for histopathological analysis is strongly recommended, as this provides a high degree of certainty in confirming or excluding CAA.[2,95] The diagnostic yield of histopathology is maximized when the sample includes brain parenchyma and/or leptomeninges in addition to clot material, as vascular amyloid deposition is often best visualized in cortical and leptomeningeal vessels.[95]

Diagnosis and treatment of CAA-ri and vasculitis

Diagnosis and treatment of CAA-ri and vasculitis	
Recommendations	SOR
1. The term CAA-related inflammation (CAA-ri) is preferred for all cases, with the terms amyloid-beta related angiitis (ABRA) or CAA-related vasculitis reserved (as an additional descriptor) only where there is clear pathological evidence of an angio-destructive vasculitis.	Weak
2. CAA-ri should be suspected in patients (usually over the age of 50 years) with: an appropriate clinical syndrome (including headache, subacute encephalopathy, seizures, focal neurological symptoms and signs, but also less severe symptoms or an acute and rapidly progressive cognitive syndrome); and appropriate radiological findings (including asymmetric cortico-subcortical confluent hyperintensities or sulcal hyperintensities/effusions on fluid-attenuated inversion recovery (FLAIR) MRI, lobar CMB (with or without cSS or ICH), or leptomeningeal enhancement) not otherwise attributable to acute ICH.	Strong
3. Patients suspected of CAA-ri should have MRI including FLAIR, T2*-weighted imaging (e.g. susceptibility sensitive SWI sequences), diffusion-weighted imaging, and contrast-enhanced T1-weighted or FLAIR MR imaging.	Strong
4. In suspected CAA-ri, CSF testing should be performed to seek evidence of alternative diagnoses including other autoimmune or infectious diseases.	Strong
5. If there is diagnostic doubt regarding CAA-ri after detailed non-invasive tests, or a lack of response to first-line immunotherapy, then a brain biopsy should be considered after evaluating the risks and benefits.	Weak
6. Early immunosuppression (as soon as possible after diagnosis) with corticosteroids is recommended (e.g. intravenous or oral methylprednisolone 1 g/day for 5 days, followed by an oral steroid taper, typically over 3–6 months.	Strong
7. Response to treatment of CAA-ri should be monitored with clinical assessments (neurological and cognitive examination), repeat MRI, and blood test monitoring as needed.	Strong
8. If there is a limited response, poor tolerability, or relapse with corticosteroids, and the diagnosis is secure, then alternative second-line longer-term immunosuppression should be considered; reasonable options include cyclophosphamide, azathioprine, or mycophenolate. Where these agents are used, local protocols should guide preventive treatments to reduce the incidence of known side-effects or complications.	Weak
9. The efficacy of monoclonal antibodies (e.g. rituximab), plasma exchange and intravenous immunoglobulin in CAA-ri are unknown; further research is required.	Weak

SOR: Strength of Recommendation.

Synopsis

The term CAA-related inflammation (CAA-ri) refers to an inflammatory and autoimmune response to sporadic CAA.[96] Initial reports from the 1970s onwards[97] described a true obliterative and destructive vasculitis, sometimes with a granulomatous component in association with Aβ−CAA. Subsequent papers described perivascular inflammation around amyloid-beta laden vessels, and then radiological findings including confluent and asymmetrical white matter hyperintensities. CAA-ri is now increasingly recognized as a distinct clinical, radiological, and neuropathological entity. The typical syndrome of CAA-ri includes cognitive symptoms (ranging from an acute encephalopathy to a slower decline in cognition), seizures, and frequent headaches, characterized radiologically by MRI hemorrhagic biomarkers of CAA, asymmetrical confluent fluid-attenuated inversion recovery (FLAIR) MRI hyperintensities due to edema or inflammation and frequently with improvement associated with immunosuppression with corticosteroids.[98–101] The CAA-ri radiological syndrome has expanded to include features such as leptomeningeal enhancement only (i.e. without parenchymal hyperintensities) and sulcal hyperintensities on FLAIR MRI, and rarely symptomatic ICH.[7,102] While amyloid-PET can detect both parenchymal and vascular Aβ distinguishing patients with CAA from normal controls with moderate-to-good diagnostic accuracy[103]—its role in the diagnosis of CAA-ri is currently limited because it does not detect inflammation. However, it may be useful in diagnostically challenging cases where the presence of CAA is uncertain, brain biopsy is not possible, or both. The underlying triggers for inflammation remain uncertain, but a natural history study of CAA-ri suggested that radiological CAA severity may be important for determining onset while prognosis may be related to the autoimmune and focal inflammatory response.[101] In published case series most patients with CAA-ri (from 80% to 88%) make a favorable short-term functional recovery, although relapses can occur (rate 38%-40% over 3 years (99)),[101] with recurrence more likely if IV high-dose corticosteroid pulse therapy is suddenly stopped compared to slow oral tapering off (hazard ratio 4.68, 95% CI 1.57–13.93; $p = 0.006$).[101] Long-term follow-up data for a full range of important outcomes in patients with CAA-ri remain limited, justifying further study.

CAA-ri has parallels with Amyloid-related Imaging Abnormalities due to edema (ARIA-E) in the anti-Aβ monoclonal antibody trials in AD.[104] However, ARIA-E seems to be mostly asymptomatic in AD trials, possibly related to the routine use of surveillance trial scan protocols. Other similarities between CAA-ri and ARIA-E include a high frequency of the APOE ε4/ε4 genotype, the CAA burden at baseline, and the dose of monoclonal antibodies administered,[105] suggesting that ARIA-E might be an "iatrogenic" form of CAA-ri.

Recommendation-specific supportive text

1. Evidence to date suggests that CAA-ri represents a spectrum of clinical, radiological and pathological severity. The term ABRA can be reserved as an additional descriptor where a true angio-destructive vasculitis (rather than perivascular inflammation) is pathologically demonstrated.[106] The term "inflammatory CAA" does not seem to be a useful addition. It is likely there is a spectrum of inflammatory responses to vascular amyloid ranging from a perivascular infiltrate to ABRA; whether the pathological severity affects the clinical and radiological phenotype remains uncertain.
2. In 2016, diagnostic criteria were suggested for CAA-ri based on a study including 17 individuals with pathologically confirmed CAA-ri and 37 control individuals with pathologically confirmed "non-inflammatory" CAA.[107] The proposed criteria for probable CAA-ri, requiring asymmetric (sub)acute FLAIR hyperintensity abnormalities (not attributable to ICH) extending to the subcortical white matter, yielded a sensitivity and specificity of 82% and 97%, respectively, for the probable criteria. A recent systematic review of CAA-ri reported a mean age at diagnosis of 66 years.[108] The probable criteria appear useful for clinical practice but might not have sufficient diagnostic accuracy to reliably identify patients with the condition, since the main differential diagnoses for CAA-ri include CNS vasculitis, PRES and autoimmune or infectious encephalitides.
3. These imaging sequences are needed to detect white matter hyperintensities and hemorrhagic manifestations of CAA. Gadolinium enhancement has been reported in over 50% of cases of CAA-ri in some studies.[108]
4. Current clinical-radiological diagnostic criteria[107] are useful to guide initial investigation and treatment, but do not have sufficient diagnostic accuracy to be used alone and cannot replace the need for more detailed investigation, including CSF testing and, depending on the specific clinical situation, consideration of brain biopsy, body PET imaging, or other specialized tests to rule out alternative diagnoses (e.g. infectious or autoimmune encephalitis, cerebral vasculitis, or malignant diseases). The potential need for additional testing is implicitly acknowledged in the published criteria themselves, which require exclusion of neoplastic, infectious or other cause. Often investigations will require discussion with infectious diseases and neuroimmunology colleagues in cases of particular differentials where more specialized tests are needed, for example, CSF autoantibodies, next generation sequencing for viral studies.

The detection of CSF anti-Aβ antibodies in CAA-ri is an important research topic, but testing is not validated for routine clinical diagnostic use. Anti-Aβ antibodies in CSF were described in 2013, titres of which correlated with the clinical and radiological improvement and to the response to immunosuppression, supporting the hypothesis of an immune-mediated phenomenon for CAA-ri.[109] Other case reports and cohort studies have subsequently also reported these antibodies,[110–114] but further research including external validation in other cohorts and laboratories, is needed before they can be applied in clinical practice.[115,116] The clinical utility of additional biomarker testing (e.g. CSF Aβ and tau species, neurofilament light chain, amyloid-PET), are not established in CAA-ri and require further research:

5. This recommendation is based on the limitations of current criteria such as the absence of other encephalitides from the control group in the validation study.[107] Where indicated a brain biopsy should be discussed, if possible, within a multidisciplinary meeting. The biopsy should include full thickness of the cortex and leptomeninges and have fresh and fixed sample processing to allow appropriate virology testing. The diagnostic yield of a biopsy may reduce after initiation of immunotherapy for CAA-ri.
6. Observational data indicate that early immunosuppressive treatment (e.g. with five daily infusions of high-dose corticosteroids) is associated with better outcome (i.e. clinical and radiological improvement) and that subsequent longer-term immunosuppression is associated with reduced risk of recurrence.[100,101] For subsequent oral steroid tapering, one suggested regimen would be 1 mg per kg (up to a maximum of 60 mg [or 40 mg for patients older than 70 years]) reducing by 5 mg every 1–2 weeks until a dose of 10 mg is reached. At this point, a repeat MRI scan can be performed prior to a final slower taper, for example, 1 mg per month. Standard prevention measures to reduce steroid-related complications are required in all cases (e.g. blood pressure monitoring, measures to reduce infection, gastrointestinal and bone protection, investigation of potential hypoadrenalism and osteoporosis) according to local protocols and procedures. The dose of steroids given acutely may be adjusted on a case-by-case basis; for example, lower total doses could be considered in patients with comorbidities that may increase the risks of steroid-related side-effects.
7. Follow-up patient monitoring is recommended based on clinical experience of the guideline group. There are few data to guide the timing of monitoring, but first follow-up assessment approximately 2–6 weeks after commencing steroid treatment is common practice. Radiological improvement may lag clinical improvement.

8. Evidence is limited, but immunosuppressive treatments other than steroids, for example, cyclophosphamide, methotrexate, and mycophenolate mofetil, have also been used with clinical improvement in case reports[99,117] and in the authors' practice.
9. These impressions are based on the lack of evidence for these forms of immunosuppression in CAA-ri.

Concluding comments

The authors emphasize that these guidelines should be used as reference and are not intended to substitute for judgment of treating clinicians in the care of their patients. Updated versions of these guidelines will be made available at caaforum.org. The authors acknowledge with gratitude the participation of their patients in research studies that have formed the basis for these guidelines.

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Supplemental material

Supplemental material for this article is available online.

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