Diagnosis and Management of Cerebral Amyloid Angiopathy: A Scientific Statement from the International CAA Association and the World Stroke Organization

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2 **from the International CAA Association and the World Stroke Organization**
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94   Abstract

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

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 judgement 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 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" below).

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 noninvasive CT- or MR-angiography, as indicated by local stroke guidelines, is sufficient to rule out vascular malformations or other secondary causes;	Strong

intra-arterial digital subtraction angiography is probably not needed.	
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

185 SOR: Strength of Recommendation
186
187 **Synopsis**
188
189 CAA that is sufficiently advanced to cause hemorrhagic lesions can be diagnosed in
190 life with good accuracy using criteria validated against neuropathology. For optimal
191 sensitivity of the criteria, brain MRI with hemorrhage sensitive (T2*-weighted)
192 sequences is required. However, for patients with ICH who are unable to have MRI,
193 the Edinburgh diagnostic criteria for CAA-associated lobar ICH do a reasonable job of
194 ruling in or out CAA in many patients. Most patients with CAA present with ICH, cSAH
195 (often with anatomically associated TFNE), or cognitive decline, but the clinician
196 should also be aware of less common presentations as an autosomal dominant
197 monogenic hereditary disorder, iatrogenic complication of previous neurosurgery, or
198 as CAA-related inflammation (see Diagnosis and treatment of CAA-related
199 inflammation/vasculitis" below). Emerging evidence suggests that patients with CAA
200 often have low Aβ40 in the cerebrospinal fluid and positive amyloid-PET; however,
201 more research is needed before these tests can be recommended for routine
202 diagnosis. The presence of cSS, particularly when it is disseminated, is the strongest
203 risk factor for future hemorrhagic stroke in patients with CAA.
204
205 **Recommendation-specific supportive text**
206 1. CAA can cause transient focal neurological episodes, lobar intracerebral
207 hemorrhage, and convexity subarachnoid hemorrhage and contribute to cognitive
208 decline (independent of concomitant Alzheimer's disease (AD) pathology).(2)

209

210   2. Rare causes of early-onset Aβ-CAA include autosomal dominant genetic mutations
211   in APP and presenilin-2 (and for non-Aβ-CAA transthyretin, BRI2, or cystatin-C(1)). The
212   clinician can therefore also suspect CAA in patients younger than 50, particularly
213   when there is a history of an affected first-degree relative, or when there are
214   multiple affected first-degree relatives.

215

216   3. Iatrogenic CAA is caused by seeding of the central nervous system with exogenous
217   Aβ. Cases have been linked to transplanted human dura mater, embolization of
218   lyophilized dura mater, and human cadaveric pituitary-derived growth hormone,
219   typically with a latency period of several decades. Therefore, careful questioning for
220   history of neurosurgery or other potentially relevant procedures is indicated in any
221   person with possible CAA symptoms.(8)

222

223   4. Brain MRI is more sensitive for CAA than brain CT, because it can detect prior silent
224   hemorrhagic lesions (CMB and cSS) and centrum semiovale perivascular spaces(9). The
225   MRI protocol should include a T2*-weighted sequence with high sensitivity for silent
226   hemorrhagic lesions. Sensitivity is enhanced by higher field strength (*e.g.*, 3.0 Tesla)
227   and susceptibility-weighted imaging (SWI) instead of T2*-weighted gradient-recalled
228   echo (GRE)(10).

229

230   5. The Boston Criteria 2.0 for probable CAA (Figure 3) have been validated to have
231   good accuracy for diagnosis of moderate-to-severe CAA pathology.(2) When compared
232   against autopsy, the reference standard, the criteria had 74.5% sensitivity (95% CI
233   65.4-82.7%) and 95.0% specificity (83.1.-99.4%). Diagnostic accuracy appears highest
234   for individuals presenting with ICH, lower for non-ICH presentations, and lowest for
235   individuals who do not have clinical symptoms associated with CAA.(2, 11, 12)
236   According to the criteria, probable CAA is not diagnosed when there are mixed
237   location bleeds (*i.e.*, hemorrhages or microbleeds in both lobar and non-lobar
238   locations); however, the clinician should be aware that patients with mixed bleeds
239   may still have a combination of CAA along with a non-CAA arteriopathy (*e.g.*, from
240   arteriolosclerosis). There is some evidence that patients with mixed bleeds and
241   cortical superficial siderosis or a ratio of lobar to deep microbleeds greater than 4 are
242   likely to have CAA, but more data with neuropathological correlation are needed.(13)

243

244   6. The Edinburgh diagnostic criteria for CAA-associated lobar ICH (Supplemental Table
245   1) use a combination of presence or absence of finger-like projections, subarachnoid
246   extension of hemorrhage, and APOE genotype to predict moderate or severe CAA
247   pathology in patients with lobar ICH.(3) In the derivation study, the absence of
248   subarachnoid hemorrhage and the absence of an APOE ε4 allele ruled out CAA with

249   100% sensitivity (95% CI 88-100%), while the presence of subarachnoid hemorrhage and
250   either APOE ε4 allele possession or finger-like projections ruled in CAA with a
251   specificity of 96% (95% CI 78-100%). However, a limitation of these criteria is that
252   APOE testing is not available in most regions. A simplified version of the criteria,(14)
253   omitting APOE testing, can be used to help rule in CAA based on the presence of
254   finger-like projections plus subarachnoid hemorrhage (specificity 87%, 95% CI 79–92%)
255   or to rule out CAA based on the absence of either finger-like projections or
256   subarachnoid hemorrhage (sensitivity 81% (95% CI 71–88%). Another possible limitation
257   of these criteria is their sensitivity may be reduced in low-volume ICH.(15)
258
259   7. Amyloid biomarkers have been developed from blood, cerebrospinal fluid, and
260   positron emission tomography (PET). These markers hold promise for diagnosing CAA.
261   In CAA, studies show that there is low CSF Aβ40 and Aβ42(16, 17), and mildly elevated
262   amyloid-PET signal(18) with a higher occipital to global ratio than in AD.(19) However,
263   there are limited data on sensitivity in CAA, the presence of AD pathology may
264   generate false positives for CAA, and current studies have not always produced
265   consistent results. Plasma markers of Aβ are less accurate than CSF, and so far there
266   are limited and inconsistent data on plasma markers in CAA.(20) Additional research is
267   needed to derive specific thresholds for CSF Aβ40 and Aβ42 levels and PET amyloid
268   ligand binding to make diagnoses in individual patients.
269
270   8. For patients with ICH or subarachnoid hemorrhage, clinicians should consider
271   alternative diagnoses including vascular malformation, cortical venous thrombosis, or
272   trauma.(21, 22) Published ICH guidelines recommend non-invasive angiography in
273   some scenarios, with variable levels of evidence depending on the scenario and the
274   specific guideline.(21-23) Observational data and expert consensus suggests that
275   invasive catheter angiography is probably not needed for patients with an
276   intracerebral hemorrhage or cSAH who meet criteria for probable CAA and don't have
277   evidence of a vascular malformation on non-invasive vascular imaging, such as CT-
278   angiography.
279
280   9. Several clinical and MRI features have been associated with future risk of ICH in
281   CAA; however, there are no validated multivariable prediction models to precisely
282   estimate the risk. Multiple prior ICHs and multifocal or disseminated cSS appear
283   associated with highest risk. Probable CAA with CMB only (i.e., without ICH or cSS)
284   appears to be associated with the lowest risk among CAA patients for future ICH.
285   Patients presenting with lobar ICH due to CAA have an average risk for recurrence of
286   7.4% per year (95% CI 3.2%-11.6% per year)(24) and patients presenting with cSAH
287   have an average risk for new hemorrhagic stroke of 21.4% per year (95% CI 16.7-26.9%
288   per year).(25) A meta-analysis showed that cSS is the strongest predictor of new

289 hemorrhagic stroke in patients with CAA, including patients who presented with or
290 without ICH. In that study, the presence of disseminated cSS (meaning that four or
291 more sulci are involved) increased risk of future ICH by 4.28 fold (95% CI 2.91-6.30)
292 while the presence of focal cSS (three or fewer sulci involved) increased risk by 2.11-
293 fold (95% CI 1.31-2.41).(26) Another meta-analysis confined to patients presenting
294 with CAA-related ICH had similar findings: disseminated cSS predicted ICH recurrence
295 (HR 3.59, 95% CI 1.96-6.57) but the risk in patients with focal cortical superficial
296 siderosis, while elevated, was not statistically significant (HR 1.41, 95% CI 0.68-
297 2.95).(27)
298
299 In statistical models that don't control for cSS, other factors have been associated
300 with risk for recurrent ICH including APOE genotype, history of prior symptomatic
301 hemorrhage, and number of microbleeds. Models that control for cSS (potentially
302 limited by insufficient sample size) have not confirmed these additional factors as
303 independent predictors of risk.
304
305 10. The APOE ε4 and ε2 alleles are associated with higher prevalence and severity of
306 CAA. APOE genotype testing increases the accuracy of the Edinburgh criteria(3) and is
307 also recommended to stratify risk of ARIA in patients being evaluated for treatment
308 with anti-Aβ immunotherapy.

309 **Management of CAA**

310

311 Antithrombotic Agents and Vascular Interventions
312

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" above). Similarly, risk of major ischemic vascular events should be estimated based on patient characteristics, and if available,	Strong

on validated scores (e.g. CHA$_2$DS$_2$-VASc in patients with atrial fibrillation).	
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$_2$DS$_2$-VASc ≥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$_2$DS$_2$-VASc ≥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.	Weak Weak

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.	
9. Multiple other conditions exist for which long term anticoagulation is indicated, e.g. 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

313 SOR: Strength of Recommendation

314

315 **Synopsis**

316 For patients with CAA, the decision of whether to initiate or resume antithrombotic

317 treatment or consider alternatives is influenced by the relatively high risk of

318 hemorrhagic complication in comparison with patients without CAA. This decision

319 requires balancing the established benefit of antiplatelet or anticoagulant treatments

320 in preventing future ischemic vascular events against their potential to increase the

321 risk of major bleeding events (including ICH), the required duration of the

322 antithrombotic treatment and the availability of alternatives.

323

324 **Recommendation-specific supportive text**

325 1. The complexity of balancing relative risks and benefits of treatment options

326 dictates an individualized, situation-specific approach rather than a one-size-fits-all

327 blanket recommendation.

328

329 2. The recommendation is based on data from studies of aspirin for primary

330 prevention in people without prior symptomatic vascular disease. In these people,

331 aspirin is of uncertain net value as the reduction in occlusive events is offset by

332 increased major bleeds.(28)

333

334 3. The recommendation is based on the results of a pooled analysis of individual

335 patient data from cohort studies in 20 322 adults from 38 cohorts (over 35 225

336 patient-years of follow-up; median 1·34 years [IQR 0·19-2·44]) adults with recent

337 ischemic stroke or transient ischemic attack.(29) Irrespective of cerebral microbleeds

338 anatomical distribution or burden (available in 12,669 patients, of whom <4% fulfilled

339 the criteria for probable CAA; personal communication D. Werring), the rate of

340   ischemic stroke exceeded that of intracranial hemorrhage. The recommendation
341   recognizes that the outcome of intracranial hemorrhage may be worse than for
342   ischemic stroke, partially offsetting the higher frequency of the latter relative to the
343   former.
344
345   In an MRI sub-study of a randomized controlled trial assessing apixaban versus aspirin
346   in patients with atrial fibrillation (AF) and at least one other risk factor for stroke,
347   there was no increase in the percentage of patients who developed new microbleeds
348   1 year after treatment (HR 0.9, 95% CI 0.5-1.6).(30) Whether these findings apply to
349   patients with CAA, particularly those with disseminated superficial siderosis, is
350   unknown.
351
352   4. In patients with ICH who had previously taken antithrombotic therapy, restarting
353   antiplatelet therapy had no significant effect on recurrent ICH or all major vascular
354   events in a pilot-phase trial.(31) In explanatory subgroup analysis there was no
355   significant heterogeneity in treatment effect for patients with lobar versus those with
356   non-lobar location of the ICH,(32) presence of focal/disseminated superficial
357   siderosis, or probable CAA according to the modified Boston or Edinburgh criteria for
358   CAA.(33) These findings provide some reassurance about the use of antiplatelet
359   therapy after ICH if indicated for secondary prevention of major ischemic vascular
360   events, including patients with lobar ICH due to CAA, with the caveat that the
361   confidence intervals in these exploratory CAA subgroups were wide.
362
363   5. Risk of non-fatal stroke or vascular death in AF patients following anticoagulation-
364   related ICH is high, both when treated with a DOAC and when anticoagulation is
365   avoided.(34, 35) As patients with ICH were excluded from the pivotal DOAC non-
366   valvular AF trials,(36-40) it is uncertain whether their reported safety and efficacy
367   relative to VKA(37-40) and aspirin(36) generalizes to ICH survivors, including CAA-
368   related ICH.
369   There are five completed randomized trials (one unpublished).(34, 35, 41, 42) Four of
370   these were included in a recent individual patient data meta-analysis of a total of 412
371   participants (310 [75%] aged 75 years or older and 163 [40%] with CHA2DS2-VASc score
372   >4).(43) The intervention was a DOAC in 209 (99%) of 212 participants who were
373   assigned to start oral anticoagulation, and the comparator was antiplatelet
374   monotherapy in 67 (33%) of 200 participants assigned to avoid oral anticoagulation. All
375   trials sought and recorded major adverse cardiovascular events between 2–6 years of
376   maximum follow-up. The primary outcome of any stroke or cardiovascular death
377   occurred in 29 (14%) of 212 participants who were assigned to start oral
378   anticoagulation versus 43 (22%) of 200 who were assigned to avoid oral
379   anticoagulation (pooled HR 0·68 [95% CI 0·42–1·10]; I²=0%). Oral anticoagulation

380 reduced the risk of ischemic major adverse cardiovascular events (nine [4%] of 212 vs
381 38 [19%] of 200; pooled HR 0·27 [95% CI 0·13–0·56]; I²=0%). Hemorrhagic major
382 adverse cardiovascular events occurred in 15 (7%) of 212 participants assigned to start
383 oral anticoagulation vs nine (5%) of 200 assigned to avoid oral anticoagulation (pooled
384 HR 1·80 [95% CI 0·77–4·21]; I²=0%). Death from any cause occurred in 38 (18%) of 212
385 participants assigned to start oral anticoagulation vs 29 (15%) of 200 of 212
386 participants assigned to avoid oral anticoagulation (1·29 [0·78–2·11]; I²=50%). Death
387 or dependence after 1 year occurred in 78 (53%) of 147 participants assigned to start
388 oral anticoagulation with available data vs 74 (51%) of 145 participants assigned to
389 avoid oral anticoagulation with available data (pooled odds ratio 1·12 [95% CI 0·70–
390 1·79]; I²=0%). There was no significant interaction between ICH location and the
391 primary outcome (p-interaction = 0.98), although power to detect an interaction was
392 limited. Recently, the results of PRESTIGE-AF(41) (n=319), further supported the
393 protective effect of DOACs on the occurrence of ischemic stroke (1/158 participants
394 assigned to DOAC, 20/161 participants assigned to avoiding anticoagulant; HR 0.05,
395 95% CI 0.01–0.36), but at the cost of an increased risk of ICH (11/158 in DOAC group,
396 1/161 in no anticoagulant group; HR 10.89, 95% CI 1.95–60.72). The HR for recurrent
397 ICH did not reach the pre-specified HR "non-inferiority" margin of 1.735. Completion
398 of ongoing trials and further individual patient data meta-analysis should enable
399 subgroup analyses, including in patients with ICH due to CAA.
400
401 In one of the ongoing trials, ENRICH-AF, the Data Safety Monitoring Board
402 recommended in 2023 that participants with lobar ICH or convexity SAH should have
403 the study drug terminated as soon as possible and that no further patients with lobar
404 ICH or acute convexity SAH should be enrolled.(44) This recommendation was based
405 on observation of an unacceptably high risk of recurrent hemorrhagic stroke among
406 those assigned to edoxaban in those with lobar ICH (n=174, 25%) or convexity SAH
407 (n=34, 5%) as their qualifying event, among a total of 699 partipcipants included at
408 that time. Other trials continue to include these patients and subgroup analyses of
409 participants with CAA are awaited.
410
411 If anticoagulation were to be considered following CAA-related ICH, it is reasonable to
412 begin within weeks after the ICH, but there is no evidence from randomized
413 controlled trials to inform the precise timing.
414
415 6. Left atrial appendage closure has not been reported in randomized controlled trials
416 in patients with ICH in general, patients with CAA-related ICH, or CAA without ICH.
417 Accordingly, it is unknown whether the relative safety and efficacy of left atrial
418 appendage closure compared to anticoagulation generalizes to patients with CAA or
419 CAA-related ICH, who have high risks of recurrent ICH and major ischemic events. The

420 procedural risk of left atrial appendage closure has decreased since its introduction,
421 and the antithrombotic regime after the procedure is increasingly moderated towards
422 less intense regimes.(45, 46) The immediate risk of the procedure and the risk of
423 subsequent short term dual antiplatelet regime (or DOAC) followed by longer single
424 antiplatelet treatment should be weighed against the estimated benefit and risk of
425 life-long anticoagulation or other antithrombotic regimens.
426
427 7. Risk for cardioembolic stroke associated with mechanical heart valves appears
428 increased by additional factors such as age and prior ischemic stroke.(47). When
429 resuming VKAs following CAA-related ICH, it is reasonable to begin within weeks after
430 ICH, but there is no evidence from randomized trials to inform precise timing. The
431 alternative of surgically exchanging the mechanical valve with a bioprosthetic valve is
432 unattractive because of the high risk of such operation and should be considered only
433 in exceptional circumstances, e.g., individuals with recurrent CAA-related ICH and
434 acceptable surgical risk.

435 8. There is currently no evidence to exclude patients from endovascular
436 thrombectomy based on the presence of CMBs.(48) Expert opinion is divided on
437 whether to avoid intravenous thrombolysis altogether in patients with prior CAA-
438 related ICH versus deciding on a case-by-case basis. Patients with intracranial
439 hemorrhage (including ICH) were excluded from the randomized controlled trials
440 assessing intravenous thrombolysis. Currently, ICH (irrespective of its cause) >3
441 months previously is not considered an absolute contraindication in many practices. In
442 patients with a known history of CAA who present with symptoms of acute stroke, the
443 possibility of TFNE should be considered and their neuroimaging carefully examined
444 for cSAH. Patients with CMBs appear to have an increased risk of ICH after intravenous
445 thrombolysis,(49, 50) and a higher risk of poor functional outcome relative to those
446 without CMBs.(49) The risk of ICH increases with the number of CMBs.(49) However,
447 there is no evidence that intravenous thrombolysis should be withheld from otherwise
448 eligible patients solely because of CMBs, including patients with strictly lobar CMBs
449 indicative of CAA.(50)
450
451 9. There are less data to guide anticoagulation for the range of indications outside of
452 AF and thus greater need for an individualized approach. A guiding principle is that
453 shorter duration and lower intensity of anticoagulation help to mitigate ICH risk.
454
455
456 <u>Vascular Risk Factors and Concomitant Medications</u>
457

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 mmHg 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

458   SOR: Strength of Recommendation

459

460   **Synopsis**

461   The prevalence of vascular risk factors among patients with CAA is high,[51] and

462   patients with CAA are at risk for both (recurrent) ICH, ischemic stroke, and cognitive

463   decline. Uncontrolled hypertension is a major risk factor for hemorrhagic and

464   ischemic stroke.[52] It is, therefore, important to closely monitor BP and aggressively

465   treat hypertension. Observational non-randomized data and meta-analyses have

466   linked statins,[53-56] SSRIs[57, 58] and NSAIDs[59, 60] to increased risk of hemorrhage

467   occurrence/recurrence. More research is needed to confirm and refine these potential

468 risks. Avoidance of smoking and excessive alcohol consumption have overall health
469 benefits.
470
471 **Recommendation-specific supportive text**
472 1. Long-term BP control is inadequate in ICH patients, including those with CAA,(61)
473   and is associated with higher risk for ICH recurrence.(62, 63) In a prospective
474   cohort study of ICH patients, <50% of patients achieved consistent BP control
475   based on AHA/ASA guidelines during a median follow-up of 36.8 months, and the
476   hazard ratio (HR) for a recurrent lobar ICH was 3.53 (95% CI, 1.65– 7.54).(63) In the
477   Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, BP
478   lowering with perindopril plus indapamide significantly reduced the overall stroke
479   risk during a mean follow-up of 3.9 years. BP lowering was beneficial across all
480   stroke types, particularly ICH. The adjusted HR of first ICH was 0.44 (95% CI, 0.28-
481   0.69).(64) This reduction appeared to apply to lobar and deep ICH and mainly
482   concerned patients whose qualifying events was an ICH; the HR for ICH recurrence
483   among subjects with prior ICH relative to a first ICH in subjects with prior ischemic
484   stroke was 6.60 (95% CI, 4.50-9.68).(65) In a secondary analysis, active treatment
485   reduced the risk of probable CAA-related ICH (defined by Boston criteria using CT
486   imaging) by 77% (95% CI, 19-93%), that of hypertension-related ICH by 46% (95%CI,
487   4-69%) and unclassified ICH by 43% (95%, -5%-69%).(66) The recommendation for a
488   target BP of ≤130/80 mmHg is based on data from the Prevention Regimen for
489   Effectively Avoiding Second Strokes (PRoFESS)(67) and Secondary Prevention of
490   Small Subcortical Strokes (SPS3)(68) trials and the AHA/ASA ICH management
491   guidelines.(21)
492
493   Home BP monitoring may be helpful to empower patients, improve compliance,
494   and allow more frequent and accurate BP measurements to avoid BP variability.
495   Screening for and treatment of obstructive sleep apnea(69) and lifestyle
496   modifications should be considered as adjunctive to pharmacotherapy for BP
497   management.
498
499 2. Aggregate randomized data do not show significant increase in ICH risk with statins
500   in patients without a history of stroke, but there are limited data on statins or
501   other lipid-lowering drugs in patients with CAA or history of ICH.(70, 71) For
502   example, trials of PCSK-9 inhibitors excluded patients with history of ICH. Some
503   studies reported an association between statin use and the prevalence of lobar
504   CMB or the occurrence of lobar ICH, particularly in patients carrying APOE-ε4 and
505   APOE-ε2 genotypes.(55, 72, 73) Results from observational non-randomized studies
506   examining the association between statin therapy, lipid-lowering, and ICH
507   risk have been inconsistent.(53-56, 74, 75) Other single-center, observational,

508 non-randomized, studies have suggested that pre-ICH use of statins is associated
509 with improved recovery and that statin discontinuation during hospitalization is
510 associated with increased in-hospital mortality.(76, 77) However, selection bias
511 and confounding-by-indication limit the interpretation of these studies.
512 Randomized trials addressing this uncertainty are ongoing. At present, the decision
513 to use statins in CAA patients must consider the risk of ischemic events versus the
514 potential risk of ICH.
515
516 3. CAA patients are at high risk of depressive symptoms. SSRIs are effective in
517 treating depression and anxiety, however, there are inconsistent data regarding
518 their association with ICH risk.(57, 58, 78) A switch to another class of
519 antidepressants could be considered, balancing the possibility of increased ICH risk
520 against the important quality of life considerations in adequately treating
521 depression.
522
523 4. Observational studies and meta-analyses reported increased risk of ICH with
524 NSAIDs-use.(59, 60) Randomized data from ICH patients are lacking. If safer
525 alternatives are available, frequent/daily use of NSAIDs is not recommended.
526
527 5. Excessive alcohol use (≥2 drinks per day) has been linked to elevated BP and
528 increased ICH risk.[29-30] Healthy lifestyle, including reduction in alcohol
529 consumption, smoking cessation, healthy diet, and physical activity, has multiple
530 positive effects and can lead to reduced BP and risk of stroke and cardiovascular
531 disease.
532
533
534 Treatment of CAA Manifestations
535

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	Weak

	blood pressure of 130-140 mm Hg), anticoagulation reversal, and avoiding antithrombotic (antiplatelet and anticoagulant) medications for 24-48 hours before reassessment.	
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, 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.	Strong
	When hematoma evacuation is performed, a tissue sample should be obtained for histopathological analysis	Strong

536   SOR: Strength of Recommendation

537

538   **Synopsis**

539   The treatment of CAA manifestations requires a tailored approach with specific

540   considerations based on clinical presentation. For CAA-TFNEs, maintaining a high

541   index of suspicion and differentiating them from transient ischemic attacks (TIAs)

542 through clinical judgment and appropriate neuroimaging is essential. Early recognition
543 and management are particularly crucial in patients presenting with acute cSAH.
544 While TFNEs are often self-limited, symptomatic management may be considered in
545 select cases. CAA-related cognitive impairment represents another key clinical entity,
546 frequently in accompaniment with neurodegenerative pathologies such as AD.
547 Although no disease-modifying treatments exist for CAA, symptomatic therapies, such
548 as cholinesterase inhibitors, may offer modest benefit.(79) A major emerging concern
549 is the interaction between CAA and anti-Aβ immunotherapies in patients with
550 concomitant AD and CAA, given the increased risk of amyloid-related imaging
551 abnormalities (ARIA). Current evidence suggests that AD patients with a significant
552 CAA burden are at heightened risk for ARIA, necessitating careful eligibility
553 assessment before initiating these treatments. Until further evidence is available,
554 anti-Aβ monoclonal antibodies should not be used as a treatment for CAA outside of
555 research settings. Lastly, acute management of CAA-ICH should align with established
556 stroke guidelines. Notably, CAA should not be considered a contraindication for
557 hematoma evacuation in eligible patients. When hematoma evacuation is performed,
558 obtaining tissue for histopathological analysis can provide valuable diagnostic insights
559 to support a CAA diagnosis.
560

561 **Recommendation-specific supportive text**
562 **A.**
563   1. CAA-related TFNEs are brief, transient, and often stereotyped focal
564   neurological episodes that occur in patients with CAA.(80-82) They typically
565   present with motor, somatosensory, or visual disturbances and can be mistaken
566   for TIAs or focal seizures. However, unlike TIAs, TFNEs frequently exhibit a
567   spreading progression of symptoms across contiguous cortical territories over
568   minutes, often lasting less than 30 minutes, with a high recurrence rate.(83)
569   Recognizing these episodes as CAA-related is crucial, as misdiagnosis can lead
570   to inappropriate initiation of antithrombotic therapy. CAA-related TFNEs
571   definition and diagnostic criteria have been suggested, in order to avoid both
572   misdiagnosis and overdiagnosis.(80)
573

574   2. TFNEs are closely associated with acute cSAH, and patients experiencing these
575   episodes have a substantially increased risk of subsequent ICH.(81) In a meta-
576   analysis, 24.5% of patients with TFNEs developed symptomatic ICH within eight
577   weeks,(25) highlighting the urgency of appropriate acute management. Blood
578   pressure management is reasonable, as acute cSAH may progress to ICH, with
579   observational data suggesting that early expansion of cSAH to parenchymal
580   hemorrhage can occur within 24 hours. While no randomized trials have
581   directly evaluated blood pressure targets in TFNEs, the general consensus is to

582   apply ICH guidelines, lowering systolic blood pressure to below 140 mmHg
583   within the first 6 hours if tolerated, with a long-term systolic blood pressure
584   target of 130mmHg.

586 3. Although TFNEs are not epileptic in nature, their symptoms overlap with
587   spreading cortical depolarization phenomena observed in migraine and
588   epilepsy.(6) Clinical experience suggests that antiseizure medications or
589   migraine-preventive agents like topiramate, lamotrigine or levetiracetam may
590   reduce the frequency and severity of recurrent TFNEs.(6) However, no
591   randomized trials have evaluated antiseizure therapy for TFNEs, and treatment
592   should be individualized based on symptom burden.

594 4. The presence of TFNEs in conjunction with cSS or cSAH, is a strong predictor of
595   future ICH, with an estimated annual hemorrhage risk of about 19% in patients
596   fulfilling the Boston Criteria for probable CAA.(84) Given the high risk of
597   hemorrhagic complications, these patients should be managed similarly to
598   those with spontaneous ICH, with aggressive blood pressure control and
599   avoidance of antithrombotic agents unless outweighed by the clinical
600   benefits.(6)

602 **B.**

603 5. Anti-Aβ monoclonal antibodies, such as lecanemab and donanemab, have been
604   approved by the US Food and Drug Administration (and the European Medicines
605   Agency for lecanemab) for the treatment of early AD. However, these therapies
606   carry a significant risk for ARIA.(85, 86) The pathophysiological mechanisms of
607   ARIA are not fully understood, but may in part be due to antibodies binding to
608   Aβ in the cerebral vessels, particularly small vessels affected by pre-existing
609   CAA.(87, 88) Given potentially devastating complications associated with
610   severe ARIA and the lack of evidence supporting disease-modifying effects in
611   CAA, the use of anti-Aβ immunotherapy for CAA itself is not recommended
612   outside the context of a clinical trial.(89)

614 6. In patients with early AD who are eligible for passive immunotherapy with
615   monoclonal antibodies targeting Aβ (e.g., lecanemab, donanemab), the
616   presence of concomitant CAA appears to be a strong risk factor for ARIA. In line
617   with appropriate use recommendations,(90, 91) patients with early AD and
618   evidence of ICH, more than four CMBs or foci cSS (trials of lecanemab excluded
619   all individuals with cSS, trials of donanemab permitted one focus of cSS) should
620   be excluded from treatment. Patients with early AD and concomitant probable
621   CAA based on Boston criteria v2.0 based on the presence of 2 or more

622   hemorrhagic markers might also be at high risk for ARIA,(92) and a careful risk
623   and benefit assessment should be performed before administering anti-Aβ
624   monoclonal antibody infusions. Of note, anti-amyloid trials in AD have not
625   systematically evaluated the proportion of participants meeting the Boston
626   criteria v2.0 for probable CAA and risk for ARIA.
627
628   C.
629   7. The management ICH in patients with CAA-related lobar ICH should follow the
630   established guidelines from the American Heart Association (AHA),(21)
631   European Stroke Organisation (ESO),(22) and the Heart and Stroke Foundation
632   of Canada/Canadian Hemorrhagic Stroke Trials Initiative (CoHESIVE).(93) These
633   recommendations cover BP control, reversal of anticoagulation, avoidance of
634   early antithrombotic therapy, supportive care, and rehabilitation strategies.
635
636   8. Surgery, including hematoma evacuation and minimal invasive endoscopic
637   removal of hemorrhage(94) is generally safe in CAA-related ICH when
638   indicated.(95) When a lobar hematoma evacuation is performed, obtaining and
639   sending a tissue sample for histopathological analysis is strongly recommended,
640   as this provides a high degree of certainty in confirming or excluding CAA.(2,
641   96) The diagnostic yield of histopathology is maximized when the sample
642   includes brain parenchyma and/or leptomeninges in addition to clot material,
643   as vascular amyloid deposition is often best visualized in cortical and
644   leptomeningeal vessels.(96)
645
646

647 **Diagnosis and Treatment of CAA-ri and Vasculitis**
648

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	Strong

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.	
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 1g/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

649 SOR: Strength of Recommendation

650

651 **Synopsis**

652 The term CAA-related inflammation (CAA-ri) refers to an inflammatory and

653 autoimmune response to sporadic CAA.(97) Initial reports from the 1970s

654 onwards(98) described a true obliterative and destructive vasculitis, sometimes

655 with a granulomatous component in association with Aβ–CAA. Subsequent

656 papers described perivascular inflammation around amyloid-beta laden vessels,

657 and then radiological findings including confluent and asymmetrical white

658 matter hyperintensities. CAA-ri is now increasingly recognized as a distinct

659 clinical, radiological, and neuropathological entity. The typical syndrome of

660 CAA-ri includes cognitive symptoms (ranging from an acute encephalopathy to a

661 slower decline in cognition), seizures, and frequent headaches, characterised

662 radiologically by MRI hemorrhagic biomarkers of CAA, asymmetrical confluent

663 fluid-attenuated inversion recovery (FLAIR) MRI hyperintensities due to edema

664 or inflammation and frequently with improvement associated with

665 immunosuppression with corticosteroids.(99-102) The CAA-ri radiological

666 syndrome has expanded to include features such as leptomeningeal

667 enhancement only (i.e. without parenchymal hyperintensities) and sulcal

668 hyperintensities on FLAIR MRI, and rarely symptomatic ICH.(103, 104) While

669 amyloid PET can detect both parenchymal and vascular Aβ distinguishing

670 patients with CAA from normal controls with moderate-to-good diagnostic

671 accuracy(105) - its role in the diagnosis of CAA-ri is currently limited because it

672 does not detect inflammation. However, it may be useful in diagnostically
673 challenging cases where the presence of CAA is uncertain, brain biopsy is not
674 possible, or both. The underlying triggers for inflammation remain uncertain,
675 but a natural history study of CAA-ri suggested that radiological CAA severity
676 may be important for determining onset while prognosis may be related to the
677 autoimmune and focal inflammatory response.(102) In published case series
678 most patients with CAA-ri (from 80% to 88%) make a favourable short-term
679 functional recovery, although relapses can occur (rate 38%-40% over 3 years
680 (99) (102)), with recurrence more likely if IV high-dose corticosteroid pulse
681 therapy is suddenly stopped compared to slow oral tapering off (hazard ratio
682 4.68, 95% CI 1.57-13.93; p=0.006) (102). Long term follow-up data for a full
683 range of important outcomes in patients with CAA-ri remain limited, justifying
684 further study.
685
686 CAA-ri has parallels with Amyloid-related Imaging Abnormalities due to edema
687 (ARIA-E) in the anti-Aß monoclonal antibody trials in AD.(106) However, ARIA-E
688 seems to be mostly asymptomatic in AD trials, possibly related to the routine
689 use of surveillance trial scan protocols. Other similarities between CAA-ri and
690 ARIA-E include a high frequency of the APOE $\varepsilon 4/\varepsilon 4$ genotype, the CAA burden
691 at baseline, and the dose of monoclonal antibodies administered,(107)
692 suggesting that ARIA-E might be an 'iatrogenic' form of CAA-ri.
693
694 **Recommendation-specific supportive text**
695 1. Evidence to date suggests that CAA-ri represents a spectrum of clinical,
696   radiological and pathological severity. The term ABRA can be reserved as an
697   additional descriptor where a true angio-destructive vasculitis (rather than
698   perivascular inflammation) is pathologically demonstrated.(108) The term
699   "inflammatory CAA" does not seem to be a useful addition. It is likely there
700   is a spectrum of inflammatory responses to vascular amyloid ranging from a
701   perivascular infiltrate to ABRA; whether the pathological severity affects
702   the clinical and radiological phenotype remains uncertain.
703
704 2. In 2016, diagnostic criteria were suggested for CAA-ri based on a study
705   including 17 individuals with pathologically confirmed CAA-ri and 37 control
706   individuals with pathologically confirmed 'non-inflammatory' CAA.(109) The
707   proposed criteria for probable CAA-ri, requiring asymmetric (sub)acute
708   FLAIR hyperintensity abnormalities (not attributable to ICH) extending to

709 the subcortical white matter, yielded a sensitivity and specificity of 82% and
710 97%, respectively, for the probable criteria. A recent systematic review of
711 CAA-ri reported a mean age at diagnosis of 66 years.(110) The probable
712 criteria appear useful for clinical practice but might not have sufficient
713 diagnostic accuracy to reliably identify patients with the condition, since
714 the main differential diagnoses for CAA-ri include CNS vasculitis, PRES and
715 autoimmune or infectious encephalitides.
716
717 3. These imaging sequences are needed to detect white matter
718 hyperintensities and hemorrhagic manifestations of CAA. Gadolinium
719 enhancement has been reported in over 50% of cases of CAA-ri in some
720 studies.(110)
721
722 4. Current clinical-radiological diagnostic criteria(109) are useful to guide
723 initial investigation and treatment, but do not have sufficient diagnostic
724 accuracy to be used alone and cannot replace the need for more detailed
725 investigation, including CSF testing and, depending on the specific clinical
726 situation, consideration of brain biopsy, body PET imaging, or other
727 specialised tests to rule out alternative diagnoses (e.g., infectious or
728 autoimmune encephalitis, cerebral vasculitis or malignant diseases). The
729 potential need for additional testing is implicitly acknowledged in the
730 published criteria themselves, which require exclusion of neoplastic,
731 infectious or other cause. Often investigations will require discussion with
732 infectious diseases and neuroimmunology colleagues in cases of particular
733 differentials where more specialized tests are needed, e.g. CSF
734 autoantibodies, next generation sequencing for viral studies.
735
736 The detection of CSF anti-Aβ antibodies in CAA-ri is an important research
737 topic, but testing is not validated for routine clinical diagnostic use. Anti-Aβ
738 antibodies in CSF were described in 2013, titres of which correlated with
739 the clinical and radiological improvement and to the response to
740 immunosuppression, supporting the hypothesis of an immune-mediated
741 phenomenon for CAA-ri.(111) Other case reports and cohort studies have
742 subsequently also reported these antibodies,(112-116) but further research
743 including external validation in other cohorts and laboratories, is needed
744 before they can be applied in clinical practice.(117, 118) The clinical utility
745 of additional biomarker testing (e.g., CSF Aβ and tau species, neurofilament

746 light chain, amyloid PET), are not established in CAA-ri and require further
747 research.
748

749 5. This recommendation is based on the limitations of current criteria such as
750 the absence of other encephalitides from the control group in the validation
751 study.(109) Where indicated a brain biopsy should be discussed, if possible,
752 within a multidisciplinary meeting. The biopsy should include full thickness
753 of the cortex and leptomeninges and have fresh and fixed sample processing
754 to allow appropriate virology testing. The diagnostic yield of a biopsy may
755 reduce after initiation of immunotherapy for CAA-ri.
756

757 6. Observational data indicate that early immunosuppressive treatment (e.g.
758 with 5 daily infusions of high dose corticosteroids) is associated with better
759 outcome (i.e., clinical and radiological improvement) and that subsequent
760 longer-term immunosuppression is associated with reduced risk of
761 recurrence.(101, 102) For subsequent oral steroid tapering, one suggested
762 regimen would be 1mg per kg (up to a maximum of 60mg [or 40mg for
763 patients older than 70 years]) reducing by 5mg every 1-2 weeks until a dose
764 of 10mg is reached. At this point, a repeat MRI scan can be performed prior
765 to a final slower taper, e.g., 1mg per month. Standard prevention measures
766 to reduce steroid-related complications are required in all cases (e.g., blood
767 pressure monitoring, measures to reduce infection, gastrointestinal and
768 bone protection, investigation of potential hypoadrenalism and
769 osteoporosis) according to local protocols and procedures. The dose of
770 steroids given acutely may be adjusted on a case-by-case basis; for
771 example, lower total doses could be considered in patients with
772 comorbidities that may increase the risks of steroid-related side effects.
773

774 7. Follow-up patient monitoring is recommended based on clinical experience
775 of the guideline group. There are few data to guide the timing of
776 monitoring, but first follow-up assessment approximately 2-6 weeks after
777 commencing steroid treatment is common practice. Radiological
778 improvement may lag clinical improvement.
779

780 8. Evidence is limited, but immunosuppressive treatments other than steroids,
781 e.g., cyclophosphamide, methotrexate, and mycophenolate mofetil, have

782   also been used with clinical improvement in case reports(100, 119) and in
783   the authors' practice.
784
785   9. These impressions are based on the lack of evidence for these forms of
786   immunosuppression in CAA-ri.
787
788
789   **Concluding Comments**
790   The authors emphasize that these guidelines should be used as reference and are not
791   intended to substitute for judgement of treating clinicians in the care of their
792   patients. Updated versions of these guidelines will be made available at
793   caaforum.org. The authors acknowledge with gratitude the participation of their
794   patients in research studies that have formed the basis for these guidelines.
795
796

797 **Figures**
798
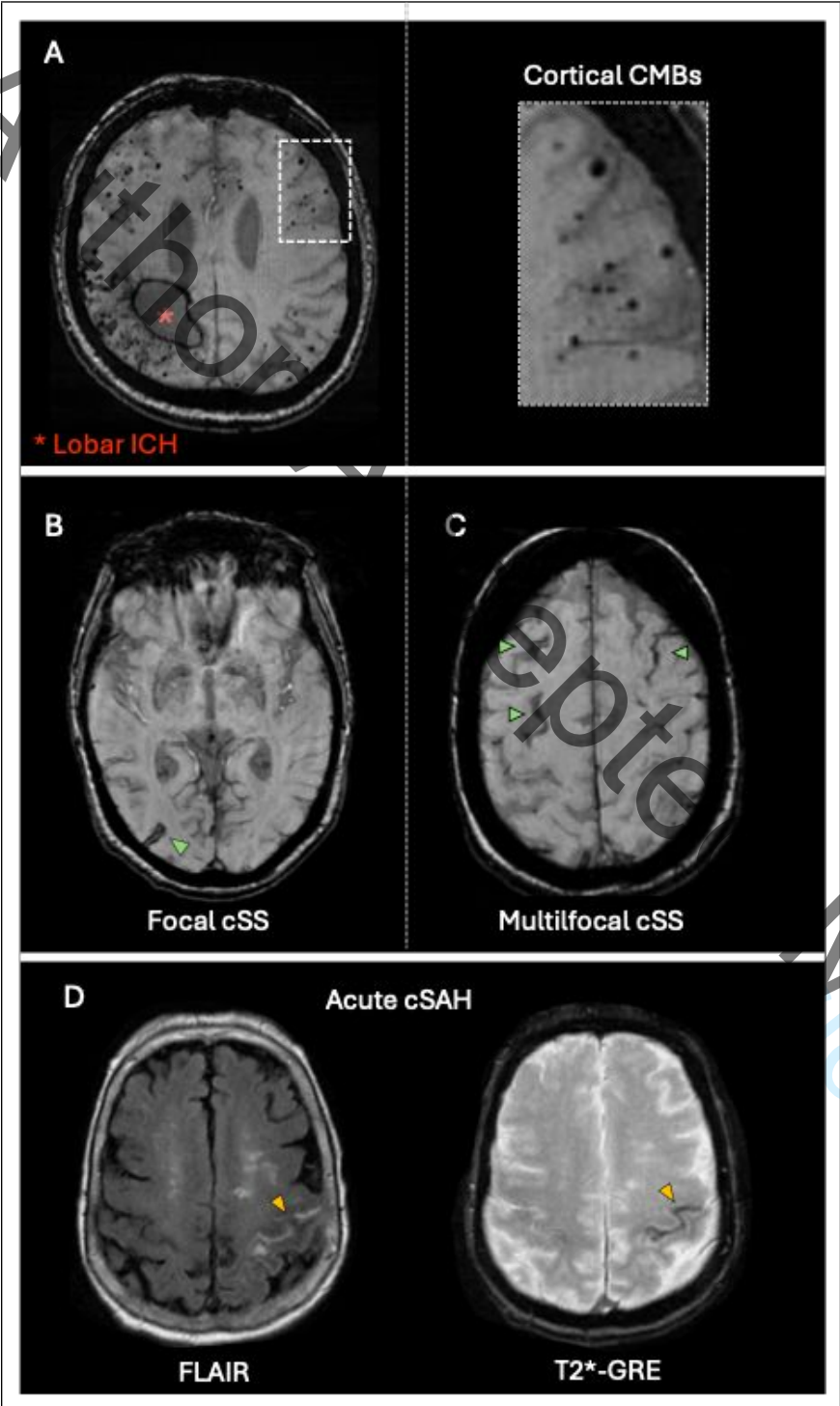
799 **Figure 1.** Representative example of hemorrhagic MRI markers of cerebral
800 amyloid angiopathy. (A) Axial SWI demonstrating a subacute lobar hemorrhage
801 (red asterisk) with multiple strictly lobar, mostly cortical, cerebral microbleeds

802   (CMBs) (magnified in the inset). (B-C) Axial SWI examples of cSS in patients with

803   cerebral amyloid angiopathy: a single sulcus with cSS (arrowhead, B), and 3

804   affected sulci (arrowheads, C). (D) Acute convexity subarachnoid hemorrhage

805   (linear hypertense signal) on axial FLAIR with corresponding T2*-GRE curvilinear

806   hyposignal along the left central sulcus, in a patient presenting with cerebral

807   amyloid angiopathy-reated transient focal neurological episodes. Of note, within

808   the Boston criteria v2.0, acute convexity subarachnoid hemorrhage is treated

809   and rated as a hemorrhagic equivalent of cSS (the chronic form of the same

810   lesion). Images modified from Int J Stroke. 2019 Dec;14(9):956-971.

811
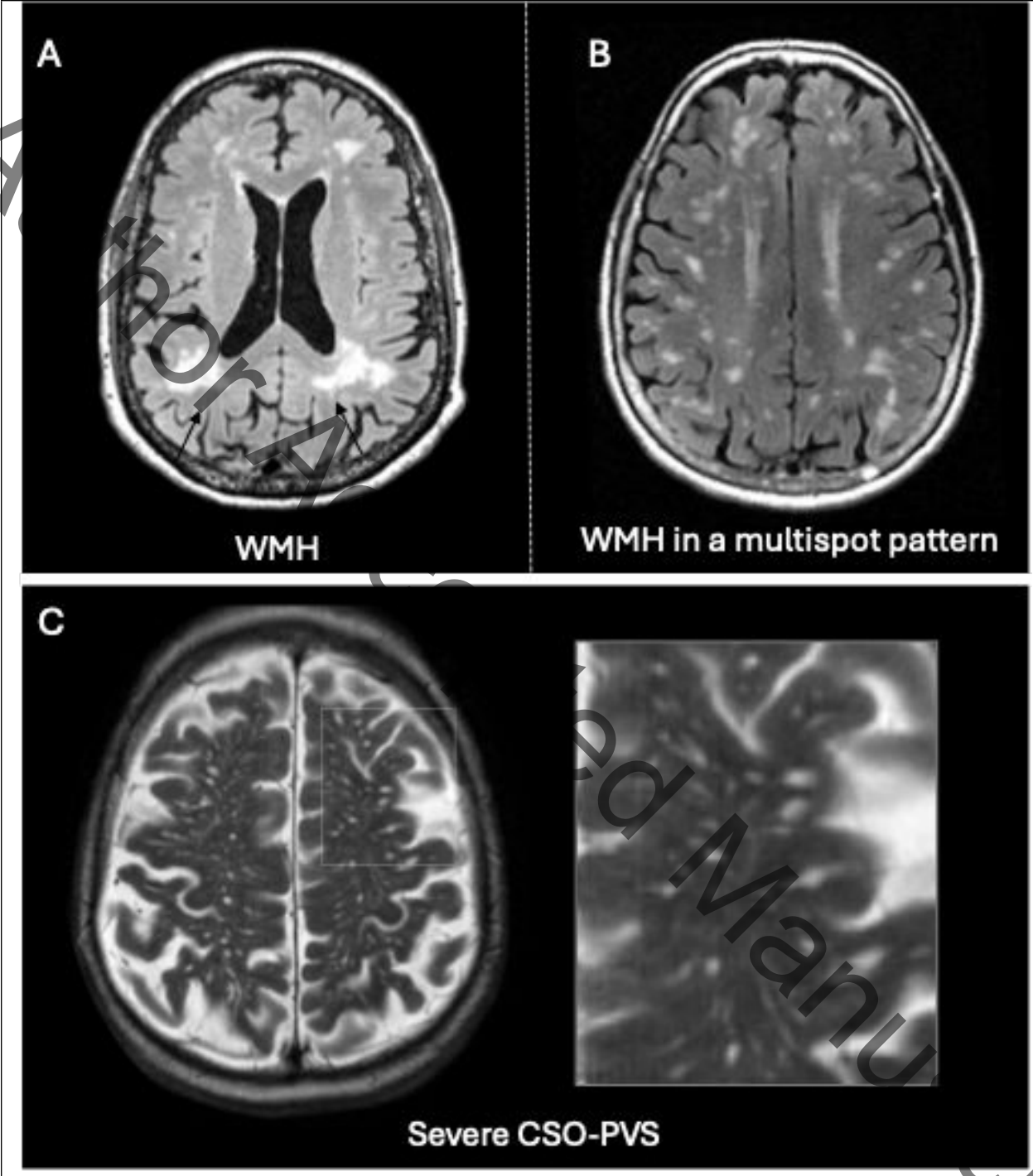
Figure 2. Non-hemorrhagic white matter markers included in the Boston criteria v2.0 (B and C). (A) Axial FLAIR sequence showing white matter hyperintensities of presumed vascular origin, with posterior (occipital) predominance (B) White matter hyperintensities in a multispot pattern, corresponding to more than 10 small (circular or ovoid) spots of hyperintensities in the subcortical white matter.

817   (C) Axial section of a T2-weighted sequence at the level of centrum semiovale,

818   magnified in the inset, showing innumerable MRI-visible perivascular spaces

819   (CSF-like contrast, dots or lines in shape, following the path of small calibre

820   penetrating arteries). Images modified from Int J Stroke. 2019 Dec;14(9):956-

821   971.

822

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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Figure 3. Framework of the Boston criteria v2.0 for possible and probable sporadic cerebral amyloid angiopathy. (Boston criteria v.2.0 framework© 2025 by Andreas Charidimou is licensed under CC BY-NC-ND 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by-nc-nd/4.0/)

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Supplemental Table 1. Edinburgh Diagnostic Criteria for CAA-Related Lobar Intracerebral Hemorrhage (modified from refs(3, 120))

1. CT scan showing subarachnoid hemorrhage associated with the intracerebral hemorrhage
2. CT scan showing finger-like projections of the intracerebral hemorrhage
3. Possession of ≥1 APOE ε4 alleles

2 of 3 present meet criteria for high-probability ("rule-in") diagnosis
0 of 3 present meet criteria for low-probability ("rule-out") diagnosis

Simplified Edinburgh criteria omit APOE genotype, otherwise identical to above.