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# Cerebral amyloid angiopathy–associated intracerebral hemorrhage: pathology and management

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Amyloid angiopathy–associated intracerebral hemorrhage (ICH) comprises 12%–15% of lobar ICH in the elderly. This growing population has an increasing incidence of thrombolysis-related hemorrhages, causing the management of hemorrhages associated with cerebral amyloid angiopathy (CAA) to take center stage. A concise reference assimilating the pathology and management of this clinical entity does not exist. Amyloid angiopathy–associated hemorrhages are most often solitary, but the natural history often progresses to include multifocal and recurrent hemorrhages. Compared with other causes of ICH, patients with CAA-associated hemorrhages have a lower mortality rate but an increased risk of recurrence. Unlike hypertensive arteriolar hemorrhages that occur in penetrating subcortical vessels, CAA-associated hemorrhages are superficial in location due to preferential involvement of vessels in the cerebral cortex and meninges. This feature makes CAA-associated hemorrhages easier to access surgically. In this paper, the authors discuss 3 postulates regarding the pathogenesis of amyloid hemorrhages, as well as the established clinicopathological classification of amyloid angiopathy and CAA-associated ICH. Common inheritance patterns of familial CAA with hemorrhagic strokes are discussed along with the role of genetic screening in relatives of patients with CAA. The radiological characteristics of CAA are described with specific attention to CAA-associated microhemorrhages. The detection of these microhemorrhages may have important clinical implications on the administration of anticoagulation and antiplatelet therapy in patients with probable CAA. Poor patient outcome in CAA-associated ICH is associated with dementia, increasing age, hematoma volume and location, initial Glasgow Coma Scale score, and intraventricular extension. The surgical management strategies for amyloid hemorrhages are discussed with a review of published surgical case series and their outcomes with a special attention to postoperative hemorrhage.
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**Key Words** • **diagnostic criteria** • **cerebral amyloid angiopathy** • **lobar intracerebral hemorrhage** • **Alzheimer dementia** • **neuroimaging** • **dot burden**

The deposition of a "peculiar and difficult to stain" substance in intracranial vessels was first described by Alois Alzheimer in 1907.[37] Gustav Oppenheim[83] subsequently recognized this substance as amyloid in 1909 when he discovered foci of necrosis in areas adjacent to hyalinized capillaries in patients with cognitive decline. This pathology later became popularly known as cerebral amyloid angiopathy or angiopathy dysphorique. Stefanos Pantelakis[85] made several of the pertinent pathological observations in 1954, including predilection for posterior brain regions, involvement of small arteries, and an association with increasing age.

*Abbreviations used in this paper:* ABRA = amyloid beta–related angiitis; CAA = cerebral amyloid angiopathy; GOS = Glasgow Outcome Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; PACNS = primary angiitis of the CNS; STICH = International Surgical Trial in Intracerebral Haemorrhage; tPA = tissue plasminogen activator.

In 1960, Neumann[72] reported the occurrence of symptomatic lobar as well as asymptomatic petechial hemorrhages in a 45-year-old woman. He hypothesized that CAA likely weakens the vessel wall, resulting in hemorrhage, but he was unclear as to the cause of the petechiae. Cerebral amyloid angiopathy has increasingly gained clinical importance over the past few decades due to its association with lobar hemorrhage and dementia, highlighted by an influential article in 1979 by Okazaki and colleagues.[79]

Intracerebral hemorrhage currently accounts for about 15% of acute strokes and has an incidence of 10–30 cases per 100,000.[30,47,92] Studies have shown that CAA is relatively common, especially in the elderly. In a review of 2060 autopsies of elderly patients,[7] CAA was diagnosed in 21% of those 61–70 years old, 42.2% of those 71–80 years old, 56.8% of those 81–90 years old, and 68.5% of those 91–100 years old. In the same study, CAA was pres-

ent in more than 98.5% of all patients with Alzheimer disease. The majority of cases of CAA-associated ICH are thought to be due to sporadic disease; however, the increased use of anticoagulant, antiplatelet, and thrombolytic therapies has brought attention to iatrogenic CAA-associated ICH. It has been postulated that patients with cerebral vasculopathies have an increased risk of iatrogenic ICH, particularly with the administration of thrombolytics.[57,60]

There is a strong association between CAA and dementia, and increasing age is a risk factor for both Alzheimer disease and CAA.[89,93] Up to one-third of patients with pathologically confirmed CAA had previous onset of dementia. Due to continued improvements in molecular techniques, familial forms of Alzheimer disease are being recognized with increasing frequency. However, familial forms of CAA and their potential role in ICH are frequently not addressed in neurosurgical practice. This review describes the familial forms of CAA with hemorrhages, highlighting the importance of screening family members of affected patients with inherited CAAs (Table 1).

The more common forms of familial CAA are further detailed below. Although sporadic CAA is the most common cause of nonhypertensive lobar ICH,[89,93] it is commonly found in elderly patients with or without Alzheimer disease.[93] The familial forms of CAA present with hemorrhagic strokes and occur at a much younger age.[32,108]

## Pathogenesis of CAA and Related Hemorrhages

In CAA, there is a predilection for deposition of Aβ protein in the cortical vessels compared with the brain parenchyma. Three hypotheses have been postulated to account for this selective vascular amyloid deposition. The neuronal or "drainage hypothesis" suggests that the underlying cause of amyloid deposition is due to poor drainage of amyloid protein along the perivascular spaces, eventually causing subsequent deposition along this path. This hypothesis is supported by studies on transgenic mice and is based on the derivation of amyloid precursor protein from neurons.[9,43]

The second hypothesis, the so-called "systemic hypothesis," proposes that receptor-mediated transport of systemic Aβ protein across the blood-brain barrier results in amyloid deposition. Several receptors such as the receptor for advanced glycation end-products, low-density lipoprotein receptor, and scavenger receptors have been implicated in the luminal to abluminal transport of Aβ protein. However, this concept is controversial and disputed due to preferential involvement of arteries rather than veins and the selective involvement of smaller rather than large vessels. It is intriguing that studies in transgenic mice have demonstrated, even with systemic overproduction of amyloid precursor protein, that selective deposition in intracranial vessels is a less likely occurrence when studied up to 29 months of age.[9,43] Furthermore, Aβ protein is first detected in the abluminal basement membrane, arguing against a systemic origin.[118]

The third hypothesis, or "vessel wall hypothesis," supports the notion that Aβ protein is produced by smooth muscle cells in the tunica media of cerebral arteries. Prior studies have shown that these myocytes are capable of producing Aβ.[21,89] Larger arteries have multiple layers of smooth muscle cells and should therefore contain significantly more amyloid deposits than smaller arteries. However, CAA-associated ICH preferentially involves smaller superficial arteries. This finding casts some doubt on the accuracy of the "vessel wall hypothesis."

Approximately 12%–15% of lobar ICH in the elderly is associated with CAA,[94] and the risk increases in carriers of the *APOE-ε2* or *APOE-ε4* allele.[117] Familial forms of Alzheimer disease are now recognized with identification of the *APOE-ε2* and *APOE-ε4* alleles in patients

**TABLE 1: Amyloid peptides related to familial CAA-associated ICHs***

| Amyloid Peptide & APP | Chromosome No. | Disease Type | Identified Mutation (codon) | AA Substitution | Clinical Features† | Index Cases |
|---|---|---|---|---|---|---|
| Aβ/APP | 21 | HCHWA-Dutch type | G to C (693) | Glu22Gln | age 50 yrs; lobar ICH, focal neurological deficits, dementia, & leukoencephalopathy | 2 Dutch families |
| | | HCHWA-Italian type | G to A (693) | Glu22Lys | lobar ICH & dementia | 3 Italian families |
| | | HCHWA-Flemish type | C to G (692) | Ala21Gly | age 45 yrs; progressive dementia, lobar ICH | 1 Dutch/British family |
| | | HCHWA-Iowa type | G to A (694) | Asp23Asn | age 50–66 yrs; memory impairment, expressive dysphasia, personality changes, myoclonic jerks, lobar ICH | 1 American & 1 Spanish family |
| | | HCHWA-Piedmont type | G to C (705) | Leu34Val | recurrent lobar ICH & cognitive decline | 1 Italian family |
| ACys/Cystatin C | 20 | HCHWA-Icelandic type | A to T (68) | Leu68Gln | recurrent lobar ICH | 9 Icelandic families |

* A = adenine; AA = amino acid; Ala = alanine; APP = amyloid precursor protein; Asn = asparagine; Asp = aspartate; C = cytosine; G = guanine; Gln = glutamine; Glu = glutamate; Gly = glycine; HCHWA = hereditary cerebral hemorrhage with amyloidosis; Leu = leucine; Lys = lysine; T = thymine; Val = valine.

† Age refers to the mean age at onset of symptoms.

with CAA.[26,57,60,74] In patients with Alzheimer dementia, the presence of the *APOE-ε4* allele appears to accelerate formation and deposition of Aβ fibrils in the blood vessel wall.[80,91] Possession of both alleles (ε2/ε4 genotype) is associated with early-onset CAA with recurrent lobar hemorrhages.[76] McCarron and colleagues[61] offered evidence that the presence of *APOE-ε2* might convey additional surgical risk. In their series, 2 of the 3 patients with postoperative hemorrhage were found to have *APOE-ε2*.

When hemorrhages occur in the setting of CAA, they are most often solitary but can also be multifocal and recurrent.[58,67] In an acute CAA-associated ICH, the area around the hematoma is typically surrounded by edema and necrosis with infiltration of inflammatory cells (Fig. 1). A secondary cascade of injury is produced by a combination of vasogenic edema from blood-brain barrier breakdown, mitochondrial dysfunction, and the products of hemoglobin breakdown. Hemostasis is eventually achieved by activation of the coagulation cascade along with mechanical tamponade.[34] In rare occasions, surgical specimens are found to have areas of both hemorrhagic and ischemic foci (Fig. 1). Extension into the subarachnoid space or the ventricles is possible, as well as secondary subdural hematomas.[87,101,115] These hemorrhages most frequently occur in the parietooccipital region with frontal hemorrhages being the next most common.[5,55,105]

## Pathological Findings in CAA-Associated Hemorrhages

Cerebral amyloid angiopathy is a vasculopathy characterized by the deposition of amyloid fibrils in the arteries and arterioles of the cerebral cortex and meninges. Hematoxylin and eosin staining of affected tissues shows hyaline thickening in vessel walls with luminal narrowing. The presence of amyloid protein can be confirmed by multiple techniques but has traditionally been diagnosed by staining with Congo red.[51] In the presence of polarized light, Congo red binds to amyloid fibrils and causes the classic finding of apple-green birefringence (Fig. 2). Alternative methods to confirm the presence of amyloid fibrils include thioflavin T/S and immunohistochemistry with anti-Aβ antibodies, the latter technique being frequently used in the diagnosis of CAA.[82]

Cerebral amyloid angiopathy can also present subacutely with progressive dementia over the course of weeks to months. Pathologically, the dementia associated with CAA is characterized by severe vascular amyloid deposition, cortical hemorrhages and/or infarctions, white matter destruction, or leukoencephalopathy. In Alzheimer disease, the deposited amyloid is primarily located in the parenchyma and leads to neuritic dystrophy and loss of synapses.[28] Despite some similarities in pathological findings,

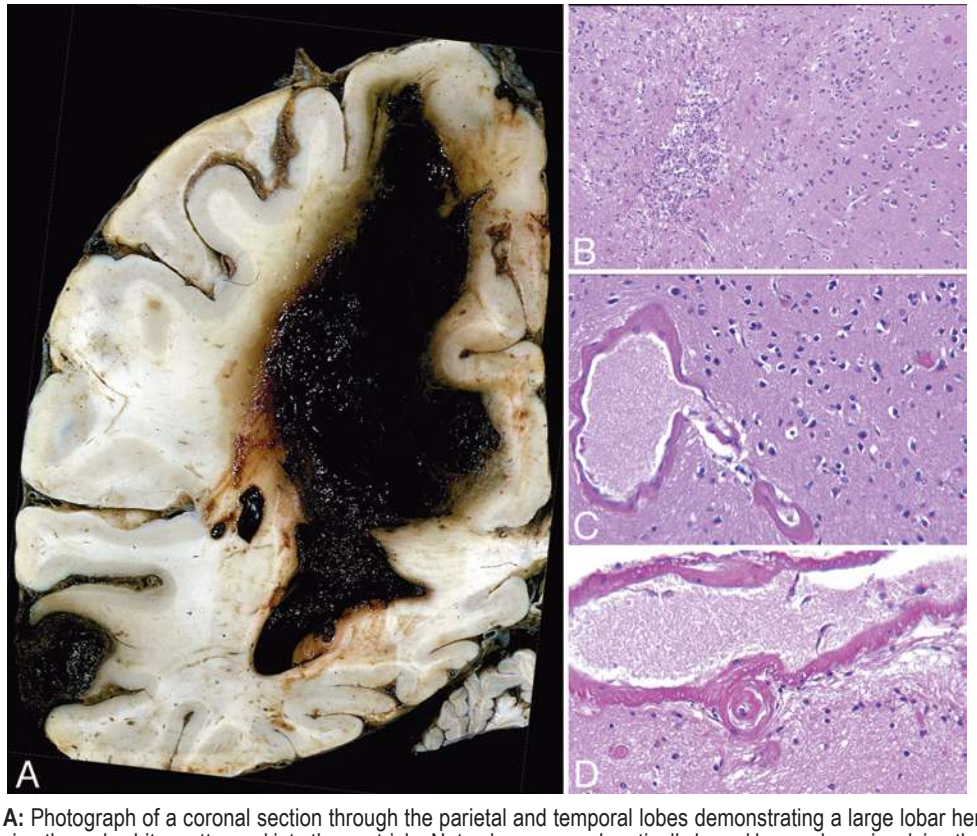


**Fig. 1. A:** Photograph of a coronal section through the parietal and temporal lobes demonstrating a large lobar hemorrhage with extension through white matter and into the ventricle. Note also a second cortically based hemorrhage involving the cerebral cortex of the middle temporal gyrus. **B:** Photomicrograph showing the organizing microinfarct within the cerebral cortex of the patient with severe amyloid angiopathy. **C and D:** Photomicrographs demonstrating amyloid-laden blood vessels showing pseudoaneurysm formation (C) and "double-barreling" (D). H & E, original magnification × 100 (B) and × 200 (C and D).

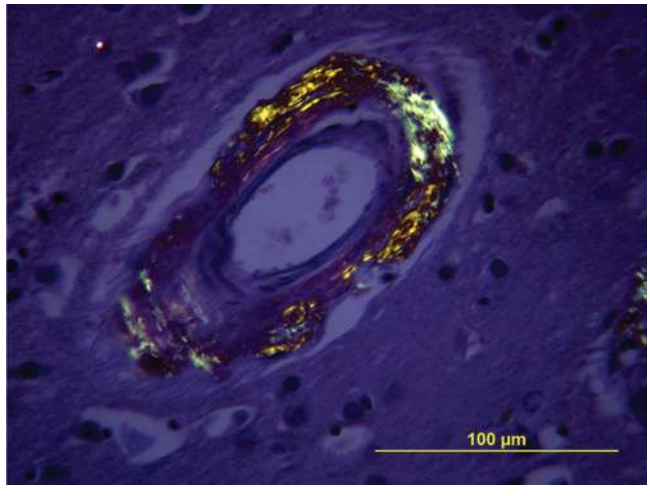


**Fig. 2.** Amyloid-laden cortical arteriole photographed with polarization microscopy, demonstrating apple-green birefringence characteristic of amyloid. Original magnification × 400.

the rapidity of symptom progression in CAA distinguishes it from Alzheimer disease.

Cerebral amyloid angiopathy is characterized by Aβ fibril deposition into the vessel wall, preferentially at vascular bifurcations and distal to these bifurcations,[44,114] causing subsequent degeneration of leptomeningeal and cortical arteries.[93] Amyloid beta protein is primarily deposited in the abluminal portion of the tunica media and adventitia of the blood vessel in close proximity of smooth muscle cells.[116] As the disease progresses, all parts of the vessel wall are affected, leading to the pathological hallmarks of obliterative intimal thickening ("onion skin" appearance), fibrinoid necrosis, hyalinoid degeneration of the media, and subsequent new media formation,[81,110] which can lead to "vessel-within-a-vessel" formation or the so-called "double-barrel" appearance. Aneurysm formation and microhemorrhages within the vessel wall have also been described and can be seen in Fig. 1.[39,53] The aforementioned *APOE-ε2* allele has been associated with fibrinoid necrosis, as well as the double-barrel appearance of blood vessels.[26,62]

These spontaneous hemorrhages are a result of vessel wall degeneration due to deposition of Aβ protein. In vitro and in vivo experiments in animal models suggest that Aβ deposition leads to degeneration of smooth muscle cells in the tunica media and creates an anticoagulative microenvironment by mimicking inhibitors of the coagulation cascade or by inducing and activating important tissue proteinases, for example, MMP-2 and MMP-9,[40,50] which may add to the fragility of affected cerebral blood vessels.

Pathological grading systems have been established to characterize CAA based on autopsy findings. Olichney and colleagues[81] classified amyloid angiopathy based on Aβ positivity in leptomeningeal and cortical blood vessels (Table 2). Vonsattel and colleagues[112] graded the severity of CAA by the degree of amyloid infiltration into the vessel wall. Both grading systems can be used in a complimentary manner; the former localizes the disease process while the latter ascertains the severity of disease.

## Clinical Presentation of CAA and CAA-Associated ICH

Clinically, patients with CAA-related ICH present with a focal neurological deficit and/or symptoms of increased intracranial pressure. Alterations in consciousness might be seen with large parenchymal hematomas. There are also reports of CAA presenting with a mass lesion[11] or transient neurological symptoms,[28,79] leukoencephalopathy,[77] and seizures.[31,89] Transient neurological symptoms are likely caused by vessel obliteration due to intimal thickening.[53,112] These symptoms may last from minutes to hours. Seizures have also been reported and are possibly caused by microhemorrhages irritating the cortex.[28]

Rosand and colleagues[98] used MRI to describe the spatial clustering in probable CAA-associated ICH. The absolute number of total hemorrhages is greatest in the frontal lobes. However, after taking into account the volume of each cerebral lobe using an atlas,[45] they found that CAA-associated ICH has a significant predilection for the temporal and occipital lobes. Recurrent hemorrhages are more likely to occur in the same lobe as prior hemorrhages; however, this scenario only occurs in 29% of recurrent hemorrhages.[98] This finding agrees with autopsy studies that have shown a predilection for the temporal and occipital lobes.[6]

**TABLE 2: Pathological grading systems for CAA**

| Grading System | Definition |
|---|---|
| Olichney et al., 1995 | |
| 0 | no Aβ-positive blood vessels |
| 1 | scattered Aβ positivity in leptomeningeal or intracortical blood vessels |
| 2 | strong, circumferential Aβ positivity in some leptomeningeal or intracortical blood vessels |
| 3 | widespread, strong, circumferential, Aβ positivity in leptomeningeal & intracortical blood vessels |
| 4 | same as Grade 3, w/ additional dysphoric changes |
| Vonsattel et al., 1991 | |
| mild | amyloid is restricted to the tunica media without significant destruction of smooth muscle cells |
| moderate | the tunica media is replaced by amyloid & is thicker than normal |
| severe | extensive amyloid deposition w/ focal wall fragmentation or even double barreling of the vessel wall, microaneurysm formation, fibrinoid necrosis, & leakage of blood through the blood vessel wall |

Originally proposed by Greenberg and colleagues,[26] the Boston Criteria guides clinical diagnosis of CAA in the setting of ICH. All of the diagnostic categories require the absence of other conditions that could cause lobar ICH, such as coagulopathy, antecedent trauma or ischemic stroke, CNS neoplasm, vascular malformation, and vasculitis. A diagnosis of definite CAA-associated hemorrhage requires a full pathological examination that demonstrates the following: lobar, cortical, or subcortical hemorrhage; severe CAA with vasculopathy; and the absence of an alternate diagnostic lesion. Probable CAA-associated hemorrhage requires an age older than 55 years and MRI or CT findings that demonstrate multiple hemorrhages restricted to lobar, cortical, subcortical, or cerebellar hemorrhage. Probable CAA-associated hemorrhage with supporting pathology requires the previous clinical data with the addition of some degree of CAA seen in pathological specimens. Possible CAA-associated hemorrhage requires age greater than 55 years with a solitary lobar, cortical, or subcortical hemorrhage.

A study by Knudsen and colleagues[46] demonstrated that the Boston Criteria can be effectively used to predict the presence of underlying CAA in lobar hemorrhages. The accuracy of the criteria was compared against pathological specimens obtained from hematoma evacuation or brain biopsy, as well as autopsy findings. All 13 patients classified as having probable CAA were pathologically diagnosed with CAA. The other 26 patients were classified as having possible CAA, and 62% of them were ultimately pathologically diagnosed with CAA. Given the apparent accuracy of this classification scheme, clinicians should strongly consider incorporating the Boston criteria into the management of CAA-associated ICH.

When patients present with lobar ICH of unknown cause, age is a good predictor of the most likely underlying cause. A study by Wakai and colleagues[113] reviewed 29 patients who presented with lobar ICH and underwent surgical biopsy. Listed by increasing mean age, the cause of ICH was cavernous malformation (27.0 years), arteriovenous malformation (45.8 years), tumor apoplexy (47.5 years), microaneurysm (59.8 years), and CAA-associated ICH (70.0 years). The difference in age was statistically significant when comparing arteriovenous malformation or microaneurysm with CAA-associated ICH, although no formal regression model was reported. These data support the use of increasing age to assist in clinical diagnosis of CAA-associated ICH.

## Thrombolysis-Related Hemorrhages in Patients With CAA

Intracranial hemorrhage is an uncommon but devastating complication after thrombolytic therapy.[64] In patients receiving thrombolysis for acute ischemic stroke, it was recognized that up to 20% of hemorrhages occur outside of the ischemic penumbra.[75] This finding provides some evidence that these patients might have an underlying vasculopathy. In a situation in which an elderly patient receives thrombolysis, it is most likely that CAA is the underlying vasculopathy.

Thrombolysis-associated ICH is seen in 0.6% of patients treated for acute myocardial infarction, 3% of patients treated for pulmonary embolism, 6% of patients receiving intravenous tPA for ischemic stroke, and 11% of patients receiving intraarterial tPA for ischemic stroke. Thrombolysis-related ICHs are usually solitary, large, and lobar in location.[23] Clinical risk factors such as age, hypertension, low body weight, and the type of thrombolytic agent appear to increase the risk for ICH after thrombolytic therapy.[42] Therefore, pathological conditions other than ischemic brain tissue, such as hypertensive vascular disease and CAA, are suspected to predispose to hemorrhage after thrombolysis.[23,101,113]

## Amyloid Beta–Related Angiitis

Amyloid beta–related angiitis (ABRA) is a unique presentation of CAA that is not commonly encountered. It is closely related to primary angiitis of the central nervous system (PACNS), and 20% of patients present with ICH. It must be noted that patients with ABRA also can present with acute changes in mental status, altered consciousness, confusion, and memory loss. Thus, PACNS and CAA are among the mimickers of ABRA. These acute symptoms are often superimposed on a subacute course of headaches, dementia, seizures, and focal neurological deficits. Approximately 20% of patients with ABRA present with ICH.[100] The distinction between these pathologies is clinically important, as the prognosis and treatments vary significantly between these entities (Table 3).[20,54,100,103] Amyloid beta–related angiitis is a frequently fatal condition that must be suspected in patients with serial focal neurological deficits of unknown origin. Brain biopsy is the gold standard for diagnosis, and some benefit has been reported with use of steroids and cyclophosphamide.[95,99]

Eng and colleagues[17] described cerebrovascular pathology in a subset of 7 patients who presented with headaches, seizures, and rapidly progressive cognitive decline over several months. Cerebral histopathology was characterized by perivascular inflammation with multinucleated giant cells. Figure 3 demonstrates these same classic pathological findings in one of our own patients diagnosed with ABRA.

## Imaging Characteristics of CAA-Associated ICH and Microhemorrhages

Currently available literature on CAA imaging defines microhemorrhages as foci of smaller than 5 mm that are hypointense on T2-weighted MR sequences.[18,27] Microhemorrhages likely result from the rupture of small blood vessels that are smaller than 200 μm in diameter. The microhemorrhages associated with CAA are best visualized on gradient echo sequences. These T2-weighted sequences are highly sensitive to the field inhomogeneity that results from hemosiderin deposition in macrophages after the breakdown of blood products.[4,96] Hemosiderin remains in macrophages for many years after hemorrhage, allowing for determination of the total microhemorrhage burden.[28] Autopsy studies have shown that microhemorrhages appear larger on MR images, which is attributed

**TABLE 3: Differences among ABRA, CAA, and PACNS***

| Parameter | ABRA | CAA | PACNS |
|---|---|---|---|
| typical age (yrs) at onset | 65–70 | 75–80 | 40–50 |
| sex predilection | none | none | none |
| clinical features | TIA, ICH, dementia | ICH, dementia | focal neurological deficits, TIA, seizures, SAH |
| type of vessel involvement | severe leptomeningeal & parenchymal amyloid angiopathy | leptomeningeal & superficial cortical vessels | small leptomeningeal & parenchymal vessels |
| pathology | angiocentric lymphocytic inflammation, perivascular multinucleated giant cells around amyloid-laden blood vessels, Aβ deposition in blood vessel walls | Aβ deposition in superficial cortical & meningeal arteries; evidence of neurofibrillary tangles & neuropil threads; occasional splitting of vessel walls w/ double-barrel appearance | segmental/circumferential involvement of blood vessels; inflammation may be lymphocytic, granulomatous, or mixed; presence of fibrinoid necrosis |
| MRI findings | focal patchy nonspecific white matter hyperintensities on T2WI | nonspecific white matter hyperintensities on T2WI; microhemorrhages on gradient echo | subcortical nonspecific white matter hyperintensities on T2WI |
| treatment | no RCTs; trial of steroids & immunosuppressive agents as described in historical case reports | withhold anti-PLT or anticoagulants if at high risk for hemorrhage; no use of steroids | no RCTs; use of steroids & steroid-sparing agents, such as cyclophosphamide, is indicated |
| complications & prognosis | poor prognosis; most patients develop ICH | unclear; dementia & ICH often result | fair prognosis w/ use of immunosuppressants |

* anti-PLT = anti-platelet therapy; RCT = randomized control trial; SAH = subarachnoid hemorrhage; T2WI = T2-weighted MRI; TIA = transient ischemic attack.

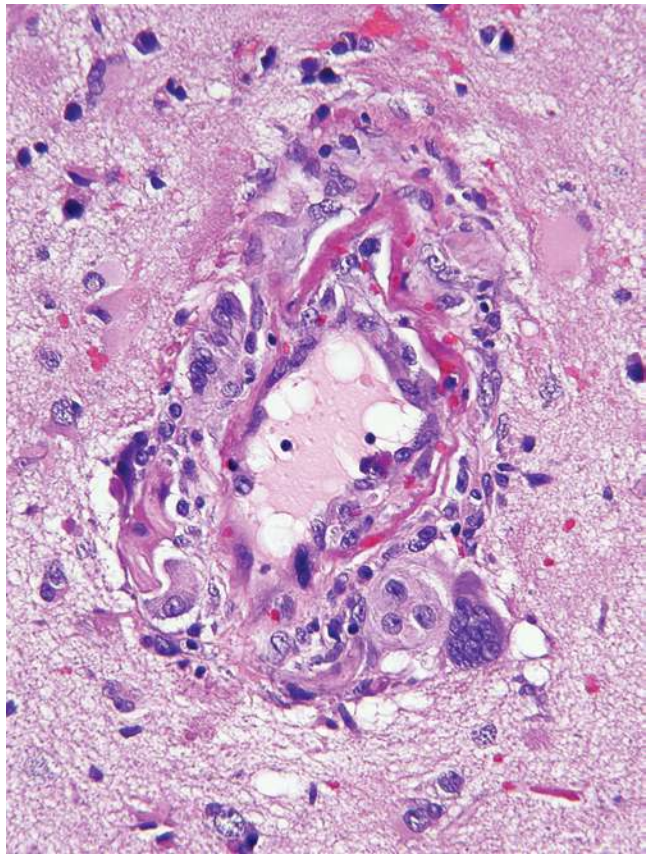

**Fig. 3.** Amyloid-laden cortical arteriole with superimposed granulomatous inflammation. H & E, original magnification × 400.

to the so-called "blooming" that is seen on susceptibility-weighted imaging. The interface between the hematoma and surrounding tissues provides susceptibility artifact that increases the apparent size of the hematoma.[2]

Asymptomatic microhemorrhages are the most common radiological findings in CAA.[18] The differential diagnosis of this appearance includes cavernous malformations, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), ABRA, and PACNS. Interestingly, imaging studies obtained in healthy volunteers also showed that asymptomatic hemorrhages occur in roughly 3%–5% of the population.[38,107] While initially considered to be incidental in nature, evidence now suggests that lobar microhemorrhages are predictive of the future lobar hemorrhages.[104] As discussed below, the presence of asymptomatic microhemorrhages also has significant implications for elderly patients requiring antiplatelet or anticoagulant therapies.

The number of microhemorrhages present at baseline is correlated with an increased risk for recurrent ICH, as well as a decline in cognitive function.[27] Figure 4 shows an example of the appearance of these microhemorrhages on MRI. This study also fortified the use of gradient echo imaging as a surrogate marker for disease severity in CAA. Nakata-Kudo and colleagues[71] demonstrated that microhemorrhages were more common in patients with Alzheimer disease and more likely to be due to CAA rather than cerebrovascular risk factors such as hypertension. The Prospective Study of Pravastatin in the Elderly at Risk (or PROSPER) study recently investigated the presence and location of microhemorrhages and their correlation with declining cognitive function. Although

the results were not statistically significant, the study did demonstrate a trend toward worsening cognitive function in patients with infratentorial microhemorrhages.[109]

## Illustrative Case

This 69-year-old man presented to the hospital with acute onset of right-sided visual field deficit. At the time of presentation, his blood pressure was 160/100 mm Hg; other vital signs were within normal limits. Neurological examination revealed the presence of a right homonymous hemianopia with no associated long tract signs. Funduscopic examination was unremarkable. The patient's medical history was significant for hypertension, dyslipidemia, and coronary artery disease. He was taking a daily aspirin but was not compliant with his antihypertensive regimen. A CT scan of the head revealed the presence of an acute left occipital ICH measuring 13.4 $cm^3$ in volume without any evidence of midline shift (see Fig. 5A). Magnetic resonance imaging and MR angiography of the brain were performed to further elucidate the cause of hemorrhage. Gradient echo and T2 sequences demonstrated the presence of microhemorrhages in the right occipital, left occipital, and left frontal lobes, suggestive of a CAA (Fig. 4). The images additionally showed diffuse hypointensities within the left occipital convexity cistern, suggestive of subarachnoid hemorrhage. The patient was started on antihypertensive medication, and his aspirin was withheld due to concern for CAA-associated ICH. Additional cranial CT scanning performed 6 months later demonstrated interval resolution of the occipital hemorrhage (Fig. 5B). The patient was readmitted to the hospital 11 months later with rehemorrhage into the region of the previous left occipital lobar ICH. He was not hypertensive at the time of his second admission. The patient was treated conservatively and discharged home. He returned again after 6 months with a third ICH, again in the right occipital lobe (Fig. 5C).

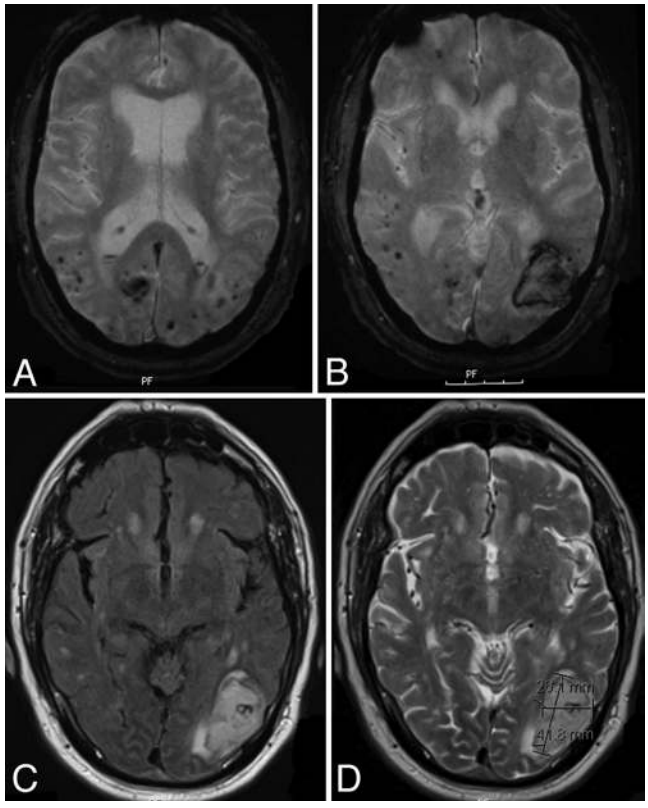


**Fig. 4.** **A:** Magnetic resonance image of the brain demonstrating dot burden on a gradient echo sequence. **B:** Gradient echo sequence demonstrating acute CAA-associated ICH in the left parietooccipital region. **C:** A FLAIR sequence showing acute CAA-associated ICH. **D:** Axial T2-weighted image showing the extent of acute CAA-associated ICH in the left parietooccipital region.

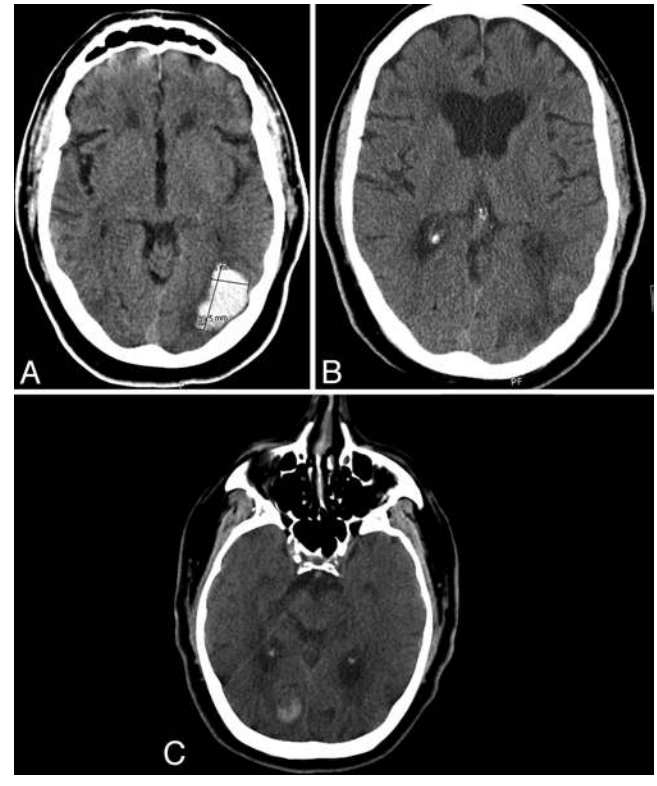


**Fig. 5.** **A:** Non–contrast administered CT scan of the head showing the patient's first diagnosed CAA-associated ICH in the left parietooccipital lobe. **B:** Interval CT of the head without contrast demonstrating resolution of the previous CAA-associated ICH at a 6-month follow-up visit. **C:** Non–contrast administered CT scan of the head in the same patient several months later, demonstrating a new ICH in the right occipital lobe. This occurred in the region of previous gradient echo changes seen in Fig. 4A.

The recurrence of lobar hemorrhages in a patient with controlled hypertension along with imaging evidence of multiple microhemorrhages are indicative of CAA-associated ICH. As seen in this case, the presence of multiple microhemorrhages is a significant risk factor for the development of recurrent hemorrhages. It should be noted that, in our illustrative case, the microhemorrhages visualized on gradient echo MRI sequences were not appreciated on the initial cranial CT (Fig. 5A).

## Medical Management of CAA-Associated ICH

The most recent update to the guidelines by the American Heart Association/American Stroke Association did not embrace amyloid-associated ICH as a separate

entity from all other causes of ICH.[70] Therefore, medical management of CAA-associated ICH does not differ from other causes of ICH. Hematoma enlargement in all-cause ICH occurs to a great extent within 3 hours of symptom onset, although it has been seen to continue up to 12 hours after onset.[13] Recent studies have focused on control of early hematoma growth by intensive antihypertensive therapy, as well as the use of procoagulants.[3,13] Similar to any ICH, emergency radiological examination with MRI or CT scanning should be pursued to differentiate it from ischemic stroke (Class IA). After diagnosis, patients with severe coagulopathy or thrombocytopenia should receive appropriate reversal (Class IC). Similarly, anticoagulant and antiplatelet therapies should be held with reversal of any iatrogenic coagulopathy (Class IC). Prevention of venous thromboembolism should be undertaken with use of elastic stockings and intermittent pneumatic compression devices (Class IB). Initial monitoring of these patients should occur in the ICU and, if available, under the guidance of staff familiar with neurological intensive care (Class IB). Blood glucose should be routinely monitored, and maintenance of normoglycemia is recommended (Class IC). Patients with clinical seizures should be started on appropriate antiepileptic drugs (Class IA). Antiepileptic therapy should also be started if a patient has a change in mental status with electroencephalographic evidence of electrographic seizures (Class IC).

The safe use of antiplatelet therapy in patients with CAA is considered controversial. Gorelick[25] demonstrated that cerebral microhemorrhages were more prevalent among patients taking antiplatelet medications (adjusted OR 1.71 [95% CI 1.21–2.41]), and these microhemorrhages were more likely to be in lobar locations among aspirin users than in nonusers (adjusted OR compared with nonusers 2.70 [95% CI 1.45–5.04]). In a similar study by Ge and colleagues,[22] patients using aspirin for longer than 5 years had a higher frequency of microhemorrhage than those taking aspirin for less than 5 years ($p < 0.0001$). Biffi and colleagues[10] showed that, after CAA-associated ICH, antiplatelet therapy significantly increased the risk of recurrent hemorrhage only if patients had MRI evidence of microhemorrhage at follow-up. In contrast to these retrospective analyses, studies by Viswanathan and colleagues[111] and Taylor and colleagues[102] demonstrated that the risk of antiplatelet agents on ICH recurrence and severity was substantially smaller than that for anticoagulation, suggesting that antiplatelet treatment may be a safer alternative to anticoagulation after ICH.

Recently, the ACTIVE A (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events–Aspirin) study[1] reported the impact of dual antiplatelet therapy versus warfarin on vascular events in patients at high risk for anticoagulation. Although previous ICH was listed as an inclusion criterion, the authors did not report the proportion of patients with previous ICH. Even though dual antiplatelet therapy reduced vascular events by 0.8% at the expense of a 0.7% increase in bleeding events, the results of this study cannot be extrapolated to those with previous ICH or microhemorrhages. The American Heart Association guidelines on management of spontaneous ICH recommend consideration of anticoagulation and antiplatelet therapy after all ICH, particularly when there are definite indications for these agents (Class IIB; Level of Evidence: B).

McCarron and colleagues[61] described 36 patients with CAA-associated hemorrhage, of whom 44% had one or more dysfunctional *APOE-ε* alleles. Those with an *ε2* allele were younger at the age of onset of their first documented hemorrhage than those without the *ε2* allele, although the difference was not statistically significant ($p = 0.088$). This study underscored the importance of using anticoagulant and antiplatelet therapy with caution as these therapies appear to further increase the risk of ICH in patients with CAA associated with the *APOE-ε2* allele.

## Surgical Management of Amyloid-Associated ICH

The commonly superficial location of CAA-associated ICH makes it an attractive surgical target for hematoma evacuation. The primary goals of hematoma evacuation are prevention of hematoma expansion, reduction of mass effect and edema, and decompression to improve local perfusion. Ultimately, halting the progression of these pathological processes is hoped to salvage the perilesional penumbra. The following discussion outlines the historical results of surgical management in CAA-associated ICH and provides prognostic data to guide operative management of CAA-associated ICH.

Concern for an increased risk of postoperative ICH after surgery in patients with amyloid angiopathy arose after Torack's description[106] of a cerebral biopsy and ventriculoperitoneal shunt placement in a patient with CAA, which resulted in a fatal postoperative ICH. Initially, 4 other authors reported difficulty with intraoperative hemostasis.[14,35,41,78] However, since those early reports, there have been numerous surgical series reporting safe performance of hematoma evacuation and cortical biopsy (Table 4).[16,19,24,29,33,49,56,97] Many of these case series specifically state that the authors experienced no problems with intraoperative hemostasis.[29,49,56,68] The establishment of surgical safety in CAA is extremely important when discussing minimally invasive techniques where hemostasis can be more cumbersome to attain.

## Literature Review of Surgical Case Series

We performed a MEDLINE search to locate all of the case series discussing surgical management of CAA-associated ICH. Seventeen relevant studies are summarized in Table 4. There is a paucity of literature regarding prospective randomized control trials that investigate surgical clot evacuation in patients with CAA-associated ICH. As summarized in Table 4, there are a number of small, retrospective studies reporting surgical outcomes. The comparison of results in medically treated patients with CAA-associated ICH is difficult, as accurate diagnosis of CAA requires a tissue diagnosis. One study demonstrated that biopsy at the time of surgical evacuation of a lobar hematoma had a 67% sensitivity (4 of 6 patients) for diagnosing CAA-associated hemorrhage.[61] This study also emphasized that, in addition to leptomeningeal vessel biopsy, cortical vessels should be biopsied whenever possible to provide the most accurate diagnosis of CAA.

**TABLE 4: Case series describing a total of 304 patients that underwent surgical intervention for CAA-associated ICH***

| Authors & Year | No. of Patients | Age (yrs) | % w/ Dementia | % on Anti-PLT Therapy | HTN | Hemorrhage Vol (ml) | % w/ IVH | % w/ POH | Mortality Rate (%) | % w/ Good Outcome† |
|---|---|---|---|---|---|---|---|---|---|---|
| Gilles et al., 1984 | 6 | 69.5 | 27 | — | 18 | — | 18 | 0 | 67 | — |
| Kalyan-Raman & Kalyan-Raman, 1984 | 10 | 70.6 | 10 | 10 | 30 | — | 10 | 0 | 70 | 20 |
| Cosgrove et al., 1985‡ | 4 | 75.2 | 46 | — | 59 | — | 24 | — | 75 | 6 |
| Roosen et al., 1985 | 1 | 59.0 | 0 | — | 0 | — | — | 0 | 0 | — |
| Filloux & Townsend, 1985 | 1 | 64.0 | 100 | — | 0 | — | — | 0 | 0 | 100 |
| Greene et al., 1990 | 9 | 72.9 | 22 | — | 33 | — | — | 0 | 33 | 44 |
| Leblanc et al., 1991 | 12 | 75.6 | 17 | — | — | — | 25 | 17 | 42 | — |
| Lange & Feiden, 1991 | 5 | 78.2 | 0 | — | — | — | — | 20 | 40 | 40 |
| Matkovic et al., 1991 | 8 | 73.0 | 25 | — | 63 | — | — | 13 | 67 | 25 |
| Wakai et al., 1992 | 6 | 70.0 | — | — | 33 | — | — | 0 | — | 50 |
| Mehdorn et al., 1992 | 15 | 65.2 | — | — | — | — | — | 20 | 40 | 27 |
| Minakawa et al., 1995 | 10 | 70.0 | — | — | — | 59 | 60 | 0 | 17 | 33 |
| McCarron & Nicoll, 1999 | 12 | 69.7 | — | — | — | — | — | 0 | 66 | 75 |
| Izumihara et al., 1999 | 37 | 75.6 | 19 | 0 | 41 | 60§ | 14 | 5 | 11 | 54 |
| Chen et al., 2004 | 5 | 76.2 | 0 | 0 | 20 | 28.5 | 80 | 0 | 0 | 40¶ |
| Petridis et al., 2008 | 99 | 75.0 | — | — | 72.7 | — | 24 | 22 | 16 | 11 |
| Hirohata et al., 2010 | 41 | 73.2 | 14.6 | 7 | 0** | — | 16 | 2.9 | 19.5 | — |
| Zhang et al., 2012 | 23 | 73.2 | 17 | 39 | 57 | 51§ | 43 | 17 | 13 | 44 |
| mean | | 72.2 | 16.4 | 10.3 | 46.0 | 55.0 | 24.9 | 11.8 | 24.4 | 33.8 |

* HTN = reported history of hypertension; POH = postoperative hemorrhage within the first 48 hours of surgery; — = not reported.
† Good outcome defined as a GOS score greater than 3.
‡ Only 4 patients underwent surgery, but demographics were available for all 17 patients with CAA-associated ICH in this series.
§ These authors provided hematoma volume by groups. The mean listed here is extrapolated from that data by assuming a uniform distribution.
¶ The GOS score was unavailable. Good outcomes here are based on a modified Rankin Scale score less than 3.
** Patients with a history of hypertension were excluded. These patients were not included when computing the mean prevalence of hypertension.

In the reviewed studies, we found that 42% of patients with CAA-associated ICH had a history of hypertension.[14,19,24,29,36,56,113,119] The prevalence of hypertension in those patients is significantly lower than that found in the general population 65–74 years old.[52] In studies reporting estimated hematoma volume, the average volume was 57 $cm^3$.[15,36,68] In more familiar terms, this result equates to a spherical hematoma that measures 4.8 cm in diameter.

In surgical case series reported in the neurosurgical literature, the indicators of poor prognosis are low preoperative functional status,[49] poor preoperative neurological examination,[60,63,88,119] age older than 75 years,[36,88] presence of IVH,[15,36,49,88] preoperative diagnosis of dementia,[24,36,119] and postoperative hemorrhage.[48,56] Additionally, there is a report of a trend toward poor outcome in CAA-associated ICH with hematoma volume greater than 60 ml,[36] which has been demonstrated as a statistically significant predictor of poor outcome in all-cause ICH.[12]

Izumihara and colleagues[36] demonstrated that the strongest predictor of poor outcome following surgery for CAA-associated ICH is the presence of IVH, with an OR of 50.5. Age older than 75 years was the second strongest predictor of poor outcome (OR 35). Patients with pathologically confirmed CAA-associated ICH have a significantly higher rate of Alzheimer disease.[110] In a study comparing CAA-associated ICH with other causes of ICH, patients with CAA-associated ICH were 9.7 years older but had a disproportionately higher rate of Alzheimer disease (68% vs 9%).[7]

The most recent case series of CAA-associated ICH was published by Zhang and colleagues[119] and demonstrated that a preoperative diagnosis of dementia is a strong predictor of poor outcome. As discussed previously, a preoperative diagnosis of dementia is a relatively common occurrence in older patients with CAA-associated ICH. However, this study showed that it is an independent predictor of poor outcome and should be considered separately from the patient's age. In their case series of 23 patients who were treated for CAA-associated ICH,[119] they reported a 13% mortality. Favorable outcome (GOS score > 3) at discharge was found in 22% of patients and at 6- to 12-month follow-up in 47% of patients. The authors noted that a history of hypertension and degree of preoperative midline shift on imaging were associated with a prolonged length of stay. Intraventricular hemorrhage was also associated with poor outcome at discharge.

Historical concerns over difficult intraoperative hemostasis have been addressed; however, postoperative hemorrhage is still a source of significant morbidity and mortality. Notably, 1 of the 4 deaths that occurred in the series by Zhang and colleagues[119] was due to a postoperative hemorrhage. Postoperative hemorrhage is not unique to CAA-associated ICH; however, it occurs much more frequently in CAA-associated ICH. As seen

in Table 1, clinically relevant postoperative hemorrhage is a relatively frequent occurrence after evacuation of CAA-associated ICH. Palmer and colleagues[84] reported only a 3.1% incidence of postoperative hemorrhage following evacuation of all-cause ICH.[86] This rate was one-fourth the historical rate we found in our meta-analysis of surgical series of CAA-associated ICH (12%) (Table 4). Palmer and colleagues[84] identified antiplatelet therapy as the most common risk factor for postoperative hemorrhage following craniotomy. Similarly, the case series of patients with CAA-associated ICH by Zhang and colleagues[119] reported that all 4 of their patients with postoperative hemorrhage were on antiplatelet therapy prior to hospitalization. We were unable to find data to support or refute any benefit of antiplatelet agent reversal in CAA-associated ICH. However, data from previous case reports suggest that these patients should therefore be monitored closely for rebleeding in the immediate postoperative setting.

When postoperative hemorrhage occurs, age appears to be the primary determinant of mortality. In a series of CAA-associated ICH surgically treated by Petridis and colleagues,[88] patients with postoperative hemorrhage who were older than 75 years had a 55% mortality rate, compared with a 30% mortality rate in patients younger than 75 years. Notably, survivors of postoperative hemorrhage all had a GOS score of 3. Repeat hematoma evacuation decreases mortality but still results in poor functional outcomes, especially in elderly patients.

As illustrated in Table 4, the two primary patient-centered outcomes of this meta-analysis are mortality and functional status. These outcomes can be compared with results from management of all-cause ICH in the STICH trial.[65] Our meta-analysis revealed that, after surgical management of CAA-associated ICH, the average mortality was 24% at 1 year, comparing favorably with the surgically treated group in STICH, which reported a 6-month mortality rate of 36%. In the reviewed studies of patients with CAA-associated ICH that was treated surgically, 33.8% attained a good outcome (GOS score > 3) at 1 year. This finding is better than the 26% of surgically treated patients in the STICH trial that had a good outcome at 6 months.

In comparison with the STICH trial, these case series are most notably limited by their retrospective nature and small patient populations.[90] Given the advanced age and increased rate of Alzheimer disease of patients with CAA-associated ICH, a concern about surgical treatment would be the reduction of mortality with worsened functional outcomes. Our findings suggest the possibility that surgical management of CAA-associated ICH may actually improve both morbidity and mortality. The results of this comparison are encouraging, especially after considering that the average age of patients in our meta-analysis was 72 years, compared with 62 years in the STICH trial. However, without prospective randomized trials of surgical management in CAA-associated ICH, it is not possible at this time to confidently state that there is a benefit from surgical intervention.

Subgroup analysis of the STICH trial suggested better functional outcomes after surgery in patients with superficial as well as lobar ICH in the absence of IVH. These outcome measures formed the basis of STICH II, aimed at randomized early evacuation of lobar ICH.[66] The results of this trial will have large implications on both the surgical management of all-cause ICH as well as the subset of these patients who have CAA-associated ICH.

## Minimally Invasive Surgical Techniques for the Treatment of CAA-Associated ICH

The use of minimally invasive surgical techniques in the treatment of hypertensive hemorrhage has produced interest in applying those techniques to CAA-associated lobar ICH. Stereotactic aspiration of ICH was originally described by Backlund and von Holst[8] in 1978, using an instrument based off of Archimedes' screw. Improvements in instrumentation and technique have expanded stereotactic aspiration to include the use of endoscopy, chemothrombolysis, and sonothrombolysis. Minakawa and colleagues[68] used stereotactic aspiration with CT guidance for aspiration of lobar ICH in 6 patients, 2 of whom had confirmed CAA-associated ICH. There were no problems with intraoperative or postoperative hemorrhage; however, no long-term functional outcomes were available for these patients.

The Minimally Invasive Surgery Plus tPA for ICH Evacuation (MISTIE) trial is currently underway, comparing the best medical management against stereotactic aspiration of all-cause ICH along with periodic injection of tPA. Preliminary results showed that this technique is safe and effective at decreasing the volume of the hematoma.[69] There is also a clinical trial currently underway for endoscopic hematoma evacuation in all-cause ICH (MISTIE-ICES). Most recently, Newell and colleagues[73] used adjuvant sonothrombolysis to attain an average of 59% hematoma reduction at 24 hours following evacuation. Results from these trials will further characterize the possible role of minimally invasive techniques in the surgical treatment of CAA-associated ICH.

## Conclusions

The increasing longevity of our patient population, advances in the medical management of cerebrovascular risk factors, and increased use of thrombolytic therapy are likely to make CAA-associated ICH a more prominent clinical problem in years to come. The Boston criteria can be used for the clinical diagnosis of CAA-associated ICH. After putative diagnosis, the clinician is faced with the difficult decision of choosing which treatment modality will provide the best outcome. From the available retrospective data, traditional open craniotomy is safe in the setting of CAA. Surgical clot evacuation in CAA-associated ICH often results in a poor outcome when the following are present: dementia, age older than 75 years, hematoma volume and location, preoperative Glasgow Coma Scale Score 8 or lower, and intraventricular extension. With the occurrence of postoperative hemorrhage after hematoma evacuation, reoperation has been

shown to be safe, with a significant decrease in mortality. However, elderly patients who undergo evacuation of postoperative hemorrhage rarely have a good functional outcome. Future prospective, randomized clinical trials of hematoma evacuation in CAA-associated ICH will be able to further characterize the role of surgery in the rather morbid natural history of CAA-associated ICH.

### Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Selman, Mehndiratta, Manjila, Cohen, Sila. Acquisition of data: all authors. Analysis and interpretation of data: Mehndiratta, Manjila, Ostergard, Eisele. Drafting the article: Mehndiratta, Manjila, Ostergard, Eisele. Critically revising the article: all authors. Reviewed submitted version of manuscript: Selman, Mehndiratta, Manjila, Ostergard, Eisele, Cohen. Approved the final version of the manuscript on behalf of all authors: Selman. Administrative/technical/material support: Selman, Mehndiratta, Manjila, Cohen, Sila. Study supervision: Selman, Manjila, Cohen, Sila.

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