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## Title

Cerebral amyloid angiopathy: Clinical Presentations and Management Challenges in the Australian Context

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## Introduction

Cerebral Amyloid angiopathy (CAA) is a disease which can have a myriad of clinical manifestations including catastrophic lobar haemorrhage, to the more recently described transient focal neurological episodes (TFNE) that often mimic transient ischemic attacks. The vast majority of cases of CAA are sporadic, with a notable association between APOE $\epsilon$ 4 allele carriage (the strongest genetic risk factor for Alzheimer's disease (AD))(1). Familial cases of CAA are rare, with the commonest mutations being in the amyloid precursor protein (APP) gene(1). CAA is characterised pathologically by the deposition of amyloid- $\beta$  within the walls of small to medium sized arteries and arterioles, with relative sparing of capillaries and veins and with varying degrees of consequent vessel wall disruption. The underlying mechanism is similar to that of AD in that APP is broken down to two different peptides, A $\beta$ 42 and A $\beta$ 40, which are associated with AD and CAA respectively. Amyloid- $\beta$  deposition was traditionally demonstrated using Congo red staining on histology, with more specific immunohistochemistry techniques being used more recently. Amyloid- $\beta$  deposition in blood vessels is present in CAA, while evidence of extracellular amyloid- $\beta$  plaques is more suggestive of AD, although the two findings commonly overlap (2). In this narrative review, we examined the key literature in this field using PubMed database and summarised the diagnostic challenges and management dilemmas posed in this complex condition to broadly assist any physician managing patients with CAA.

## Diagnosis

The definitive diagnosis of CAA is based on neuropathology on post-mortem examination or brain biopsy. During life, it is particularly difficult to identify and diagnose patients with CAA as it is often asymptomatic. Several criteria have been developed to help make the diagnosis of CAA based on imaging. Gradient Echo and susceptibility-weighted imaging

(SWI) MRI sequences are particularly useful as they are sensitive to haemosiderin deposits manifesting as lobar cerebral microbleeds or superficial siderosis, both of which are suggestive of underlying CAA. The commonest diagnostic criteria used in practice are the modified Boston criteria, which have since been validated in 2010 (3), and more recently updated to the Boston 2.0 criteria (summarised in Table 1) (4). Based on these criteria, in patients aged  $\geq 50$  years with an appropriate clinical history,  $\geq 2$  strictly lobar haemorrhages, or a one haemorrhage plus the presence of white matter changes are required to make the diagnosis of probable CAA. Lobar haemorrhagic foci include any combination of intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage without another cause and in the absence of any deep haemorrhagic lesions. Haemorrhagic lesions in the cerebellum are not classified as either lobar or deep. The Boston 2.0 criteria have an improved sensitivity with the addition of novel MRI markers and a change in the requisite age from  $\geq 55$  to  $\geq 50$  years when supporting pathology or post-mortem examination are not available.(4). The Edinburgh criteria are an alternative which allows the use of Computerized Tomography (CT) and also include risk factors such as the APOE $\epsilon$ 4 allele (Table 2)(5). In light of the difficulties in diagnosis of CAA during life, new diagnostic and investigative biomarkers are now emerging, including cerebrospinal fluid (CSF) and imaging markers. A study by Verbeek et al reported decreased A $\beta$  40 and 42 and increased Tau in CSF analysis of patients with CAA, which is a pattern similar to that seen in AD(6). Further, Positron Emission Tomography (PET) imaging using <sup>11</sup>C-Pittsburgh compound B or other ligands which bind to amyloid- $\beta$  may be able to demonstrate locations at risk of haemorrhage in CAA(7). These changes are similar to those found in AD, making it difficult to distinguish between these two pathologies on these markers alone. Nonetheless, in combination with the validated imaging criteria, these new advances have the potential to help clinicians in making the diagnosis of CAA during life.

## **Manifestations**

CAA can manifest in several ways. It is likely that most patients with CAA are asymptomatic, with a recent meta-analysis showing a pooled prevalence of moderate-to-severe CAA pathology of 23% in the general population (mean age 84.9 years) and 6.4% in cognitively normal elderly people (mean age 81.8 years).(8) However, it can also present with intracranial haemorrhages (ICH), cognitive impairment, transient focal neurological episodes, and CAA related inflammation.

## ***Imaging findings***

### ***Microhaemorrhages***

Microhaemorrhages or microbleeds are small areas of chronic haemosiderin deposition and are often an incidental imaging finding on MRI T2\* and SWI sequences (Figure 1). Lobar microbleeds are associated with CAA, while deep microbleeds tend to be associated with arteriolosclerosis (also termed sporadic non-amyloid microangiopathy) (9). The presence of microhaemorrhages is also associated with age. There are also other causes of microhaemorrhages such as cardiac bypass-associated lobar microbleeds (10). CAA related microhaemorrhages are associated with APOE $\epsilon$ 4 and correlated with areas of concentrated amyloid- $\beta$  deposition on PET imaging. In the Rotterdam study, lobar and non-lobar microhaemorrhages were found on imaging in up to 35.7% of patients over 80 years and were associated with regions of amyloid-positive vessels (11).

### ***Cortical Superficial siderosis***

CAA can present as recurrent convexity subarachnoid haemorrhages which can be clinically silent or cause transient neurological symptoms. These haemorrhages result in the deposition

of hemosiderin in the leptomeningeal space, termed cortical superficial siderosis (cSS) which can be localised or disseminated. In one study, cSS was detected in 40% of patients with probable CAA (12). Acute focal convexity subarachnoid blood is hyperintense on FLAIR MRI (and hyperdense on CT brain). Chronic siderosis is seen on T2\* and SWI sequences but, due to a predominance of oxyhemoglobin, acute subarachnoid blood may not be visible on T2\*-weighted sequences including SWI. When there are clear features of CAA on MRI, particularly in older patients, catheter angiography is not required.

### Other Imaging Findings

Other major radiological manifestations of CAA include dilated perivascular spaces, CAA white matter disease as well as occipital calcifications(13). Interestingly, CAA can manifest with cortical microinfarctions which can present acutely with diffusion restriction on MRI as well as be present chronically. These changes have the potential to be misinterpreted as embolic stroke and can cause significant challenges in management of patients including leading to inappropriate initiation or escalation of antiplatelet therapy, as well as, unnecessary cardiac work-up.

### ***Intracerebral haemorrhage***

CAA typically presents as lobar ICH, in contrast to the deep locations associated with arteriolosclerosis. There is a predilection for posterior cortical vessels, with the temporal and occipital lobes being most commonly affected. Less commonly involved areas include the cerebellar cortex and vermis. Not all CAA phenotypes have the same risk of ICH recurrence. For example, the presence of microbleeds confers a dose dependent increase in risk of ICH. In one study, the absolute increase of ICH associated with any cerebral microbleeds was 7·2 per 1000 patient-years (95% CI 2·9–14·9); 2·8 (–0·4 to 14·3) with one microbleed, and 11·8

(3·6 to 28·4) with two or more microbleeds(14). Cortical superficial siderosis is more strongly associated with risk of lobar ICH than cerebral microbleeds. A multicenter cohort study by Charidimou et al which included 118 patients with probable CAA, found in that any cSS (HR: 2.53) and disseminated cSS (HR: 3.16) were associated with increased lobar ICH risk(15). This raises challenges in starting antithrombotic therapy in patients with previous ICH or evidence of asymptomatic microhaemorrhages and cSS, which will be discussed further below. Additionally, while screening for CAA on routine MRI imaging prior to commencing antithrombotic treatment is not recommended, the risk of ICH in those with incidental CAA changes needs to be considered with caution during clinical decision making.

### ***Cognitive impairment***

Cognitive impairment in CAA can be associated with lobar ICH, microbleeds or can develop over time in association with AD. ICH itself increases the risk of new onset dementia, especially in those with CAA. The Prognosis of Intracerebral Haemorrhage (PITCH) cohort study followed 218 patients with ICH and found an incidence of 28.3% for new onset dementia at 4 years. The incidence was two times higher in patients with lobar ICH (1 year incidence of 23.4%) compared to non-lobar ICH (9.2%)(16). Further, Arvanitakis et al performed a cohort study of aging assessing 404 patients with post-mortem brain pathology(17). They found that CAA pathology often co-existed with AD pathology. However, moderate to severe CAA on autopsy, independent of AD pathology, was associated with lower perceptual speed and episodic memory function but not deficits in semantic memory or visuo-spatial skills (17). Even clinically silent manifestations of CAA, such as microhaemorrhages, can be associated with the development of cognitive impairment. One study, assessing 3979 patients without dementia undergoing cognitive testing found higher numbers of microbleeds were associated with lower Mini Mental-state Examination (MMSE)

scores, independent of other ICH(18). In particular, the presence of 5 or more microbleeds was associated with worse performance in all cognitive domains except for memory, and this was particularly prominent in those with lobar distribution of microhaemorrhages. However, this study did not adjust for biomarkers or imaging markers for AD. Thus, it is difficult to ascertain if AD contributed to the cognitive impairment either concurrently with CAA or independently.

### ***Cerebral Amyloid Angiopathy-Related Transient Focal Neurologic Episodes (TFNE)***

Amyloid angiopathy can also manifest as recurrent Transient Focal Neurological Episodes, often referred to as ‘amyloid spells’, typically lasting a few minutes. These are stereotypic positive or negative neurological symptoms, that often spread over contiguous body parts, and can mimic other presentations such as transient ischemic attacks (TIA), focal seizures or migraine aura. The majority of acute clusters of CAA-associated TFNE are associated with convexity subarachnoid haemorrhage or cortical superficial siderosis (cSS), often in the central or adjacent sulci, hypothesised to be triggering cortical spreading depression or depolarisation of adjacent grey matter (19). Analogous to migraine with aura, there is often a gradual progression or march of symptoms, and it is possible that the underlying electrical cortical process of migraine aura (cortical spreading depolarisation) could be the cause of both phenomena, triggered in the case of CAA by microinfarction, microhaemorrhage or convexity subarachnoid haemorrhage. Charidimou et al, in a multicenter retrospective cohort study, found 25 out of a total 172 (14%) patients with CAA had transient focal neurological episodes (20). They found that approximately 50% of patients with these transient episodes had associated cortical superficial siderosis (cSS) compared to only 19% in those without transient neurological episodes. Further, these episodes were associated with high early risk of symptomatic ICH: 50% of patients with a median 14-month follow-up. The latter is

presumably related to the risk associated with cSS rather than TFNE themselves. Given these episodes are often misdiagnosed as TIAs and are associated with higher risk of rebleeding in the future, there are major management implications, particularly regarding the risk of inappropriate administration of antithrombotic medications. The management of recurrent transient neurological symptoms in CAA is challenging, with no clinical trial evidence to guide treatment selection.

### ***CAA and Inflammation***

CAA related inflammation (CAA-ri) most commonly presents with subacute and progressive cognitive impairment (48% of patients), seizures in 32%, headaches in 32%, and focal neurological deficits in 27%(21). Diagnosis is based on neuroimaging, brain biopsy, and CSF analysis. The mechanism of CAA related inflammation is thought to be due to an immune reaction to vascular amyloid- $\beta$  (22). A similar entity has also been described called amyloid- $\beta$ -related angiitis (ABRA). Clinically, ABRA and CAA-ri have similar presentations(23). CSF analysis may be normal, but there is often a mild pleocytosis or elevated protein. In terms of imaging, while multiple microhaemorrhages and T2 white matter hyperintensities are well established aspects of CAA-ri, MRI gadolinium enhancing lesions, pseudotumor and vasculitic changes on angiography are more common in ABRA. Pathologically, ABRA is characterized by A $\beta$  deposition in blood vessels triggering autoimmunity, leukocytic infiltration, and vasculitic destruction of affected blood vessels. In comparison, CAA-ri demonstrates more perivascular non-vasculitic inflammation with multinucleated giant cells associated with amyloid- $\beta$  laden vessels. The diagnosis of CAA related inflammation is further corroborated by clinical and radiological response to immunosuppression. While CAA-ri may respond to short courses of immunosuppression, prolonged immunosuppression is often preferred in the treatment of ABRA(23). It is important to remember that evidence

for these treatment approaches is based on small case series, rather than clinical trials and further evidence is required to guide the most appropriate management.

### **Controversies in CAA Related ICH management and anticoagulation**

Controversies in management of patients with CAA relate to management of concurrent age associated co-morbidities including cerebrovascular disease, cardiovascular disease, and AF. There are major implications for patients starting or continuing anticoagulation in the setting of CAA associated ICH risk. Our recommendations based on current literature are summarized in Table 3.

#### ***Anticoagulation***

Anticoagulation in patients with CAA can pose major management challenges, especially in the setting of Atrial Fibrillation (AF) and primary or secondary stroke prevention.

#### ***Anticoagulation in microhaemorrhages***

In one multicentre observational cohort study of patients with atrial fibrillation anticoagulated after recent ischaemic stroke or TIA, a higher risk of ICH was seen with anticoagulation in the presence of microhaemorrhages (especially if there were more than 2 microhaemorrhages, where the risk of ICH was three times higher), and in the presence of cortical superficial siderosis(14). While 1% of this cohort had a prior ICH, of the patients with symptomatic ICH on follow up, none had a prior ICH. Notably, the absolute rate of recurrent ischaemic strokes (24.1 per 1000 patient-years) in those with microbleeds was higher than the rate of ICH (9.8 per 1000 patient-years), although microbleeds were not associated with recurrent ischaemic strokes in univariate or multivariable analyses. Further, in the population anticoagulated for AF with prior ischaemic stroke/TIA, microbleeds were

independently associated with increased risk of symptomatic ICH but not ischaemic stroke. This is supported by the Microbleeds International Collaboration Network (MICON) which further reviewed the comparative risk of ICH and subsequent ischaemic stroke in patients with presence of microbleeds versus those without. This cohort study demonstrated an increased hazard ratio for subsequent ICH post initial ischaemic stroke or TIA; however, this was still outweighed by the overall risk of subsequent ischaemic stroke(24).

### *Risk Assessment*

It is thought that in the setting of symptomatic ICH, the risk of ICH recurrence in the presence of CAA generally outweighs the risk of thromboembolic events. Further, the utility of the CHA<sub>2</sub>DS-VASc and HAS-BLED scores is not well validated in this subgroup, which may underestimate the bleeding risk (25). To provide a risk tool, the MICON cohort from 38 centres has been utilised to create the MICON-ICH risk stratification tool to determine 5-year risk of ICH with antithrombotic therapy post ischaemic stroke or TIA(26). Of note, this risk profile is for all antithrombotic treatments, and does not discriminate between oral anticoagulants and antiplatelets. The MICON-ICH score considers number of microbleeds, age and background of patient, presence of previous ischaemic stroke/TIA, previous ICH, and presence of anticoagulation with a c-index of 0.73, demonstrating a good concordance between the risk predicted by the algorithm and actual risk observed over a 5 year period(26).

### *Anticoagulation with prior ICH*

A meta-analysis of ICH survivors from 3 large multicentre studies, stratified by lobar compared to non-lobar haemorrhages assessed restarting anticoagulation for AF, and had opposing results(27). They found that starting anticoagulation after lobar ICH was associated with decreased mortality and favourable functional outcome without an increase in recurrent

ICH, even in CAA patients. However, this data is derived from predominantly retrospective and observational studies, which would be prone to selection bias, whereby physicians may be more likely to restart anticoagulation in patients who they deem to be lower clinical risk of further ICH and who are healthier. The European Society of Cardiology guidelines suggest that anticoagulation for stroke prevention in AF should be avoided in patients with symptomatic lobar ICH and probable or confirmed CAA (in the absence of alternative explanation) (28). Further, individual risk-benefit analysis should be undertaken for patients with two or more microhaemorrhages and a plan for anticoagulation made on a case-by-case basis. Results from trials such as ExoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation (ENRICH-AF, clinicaltrials.gov NCT03950076) are also keenly awaited and will provide empiric evidence to guide clinicians in these decisions(29).

#### *Choice of anticoagulation*

If anticoagulation is used, consideration should be given to the different available anticoagulants and their different risk profiles. In general, direct oral anticoagulants (DOACs) are the preferred agent due to a lower ICH risk. However, most of the trials of these agents excluded patients with previous ICH. A meta-analysis of 20,500 AF patients with previous stroke or TIA found a lower risk of ICH with DOACs compared to warfarin (relative risk reduction: 46.1%, absolute risk reduction: 0.88%) over 1.8–2.8 years(30). The use of DOACs in this setting would also need to be considered in terms of the locally available reversal agents. There are several new Phase 2 Randomised controlled trials (RCT) underway for anticoagulation for AF after ICH, including those with CAA. The recently published APACHE-AF trial was a phase 2 randomised trial which compared apixaban to anticoagulation avoidance in patients with anticoagulation-related ICH and underlying AF. After a median follow up of 1.9 years, similar rates of non-fatal stroke or vascular death were

seen in those treated with apixaban compared to those avoiding anticoagulation, 26% and 24% respectively (adjusted hazard ratio 1.05,  $p=0.90$ ), suggesting that rates of subsequent vascular events in this group of patients are high whether using apixaban or avoiding anticoagulation (31). It is notable that only 9 of the 101 patients in the trial were reported as fulfilling the Edinburgh CT criteria for CAA, and only 28 patients had ICH in lobar locations. Larger randomised controlled clinical trials are required to determine the groups which may specifically benefit or be harmed from restarting anticoagulation.

#### *Left atrial appendage closure (LAAC)*

Left atrial appendage closure (LAAC) devices are an alternative option for patients with AF, high CHADSVasc score, and contraindications to long-term anticoagulation (initial antithrombotic use is still required post-implantation). The PREVAIL and PROTECT AF trials found LAAC had an 80% reduction in haemorrhagic stroke and was non-inferior to warfarin in prevention of ischemic strokes(32). Overall, at 5 years follow up for both studies, both the LAAC and warfarin groups had a similar frequency of stroke, systemic embolism and cardiovascular/unexplained death. While there was no difference in overall major bleeding, when excluding peri-procedural bleeding, there was a statistically lower bleeding observed in the LAAC group (HR: 0.48;  $p = 0.0003$ )(32). However, while both studies included mostly patients who were high risk for stroke in the setting of AF (CHADSVASC 1 or more), only a very small minority of patients actually had a previous stroke or TIA. Further, there is no readily available data on previous ICH, which may reduce the generalizability of these studies to those with prior ICH or CAA. Similarly, the Prague 17 trial, a randomised non-inferiority trial in high-risk patients with AF, demonstrated equivalence in all-stroke/TIA, ICH and cardiovascular death in patients treated with LAAC compared to DOAC. However, patients with prior ICH may also be functionally impaired to

the point that LAAC may not be deemed appropriate. Nonetheless, we would suggest that LAAC is a suitable option for selected patients with CAA and AF(33).

### ***Antiplatelet agents***

The use of antiplatelet agents, such as aspirin, in CAA is contentious because their use is associated with increased risk of microhaemorrhages and ICH. A cross-sectional analysis as part of the Rotterdam scan study by Vernooji et al with 1000 patients over the age of 60, undergoing MRI for microbleeds, found a higher prevalence of microbleeds (OR 1.71), particularly with a lobar distribution (OR 2.70) in patients using antiplatelet agents (34). The number of microhaemorrhages was associated with the risk of antiplatelet-related ICH (adjusted OR 1.33 per additional microhaemorrhage). Interestingly, the RESTART trial suggested that antiplatelet agents may reduce the risk of recurrent ICH compared to antiplatelet avoidance showing a non-statistically significant hazard ratio of 0.51 over a 2-year period. In the subgroup analysis of this trial for patients with microbleeds, there was no statistically significant difference in risk of recurrent ICH based on the presence or number of microbleeds, and the location of microbleeds (lobar versus other locations). As this is a single trial and using an analysis of small subgroups who were noted to have microbleeds (but no diagnosis of probable CAA), more information is required before a definitive recommendation can be made regarding use of antiplatelet agents in the setting of CAA (35), although we would generally advise that in patients with clear indications for antiplatelet therapy, the benefits are likely to outweigh the risks. Nonetheless, caution needs to be taken in the use of antiplatelets in those at highest risk (eg. cSS) as the benefits may not necessarily outweigh risks in this subgroup.

### ***Thrombolysis***

CAA may be associated with increased risk of thrombolysis related ICH but the available data are retrospective and observational. Previous MRI is often not available to exclude imaging features of CAA prior to making thrombolysis decisions and given the strong association between time to treatment and thrombolysis efficacy, we do not recommend delaying thrombolysis to obtain an MRI in the Australian context. In cases where a previous MRI is available, the issues of safety of thrombolysis in the setting of known microbleeds may arise. Two individual patient meta-analyses have been completed to answer the question of risk of symptomatic ICH post thrombolysis. Charidimou et al found that increasing CAA-related microbleed burden was most strongly associated with the risk of parenchymal haemorrhages remote from the ischaemic area (OR 3.26), with marginal increased risk of parenchymal haemorrhage within the ischaemic area (OR 1.78). The presence of microbleeds was not associated with an increased risk of symptomatic ICH in this study (OR 1.14), but the presence of >5 and >10 microbleeds was associated with increasing risk of poor functional outcome (mRS >2 at 3-6 months) post ischaemic stroke (OR 1.28 and 3.99 respectively)(36). Tsivgoulis et al demonstrated the presence of microbleeds was independently associated with increased risk of symptomatic ICH (OR 3.28). The presence of >10 microbleeds was associated with an adjusted odds ratio of 18.17 for symptomatic ICH, but this only comprised 8 patients in the study cohort(37). While the presence of cerebral microbleeds is not an absolute contraindication for thrombolysis, a large number of known microbleeds should warrant careful assessment of risk and benefit. In Australia, this issue rarely arises given CT and CT perfusion rather than MRI scanning is generally performed prior to thrombolysis. However, as MRI for dementia becomes increasingly common, review of readily available MRI imaging should be considered when a patient with dementia presents with stroke potentially for thrombolysis. Of note, in a study which modelled thrombolysis outcomes of patients with >10 versus  $\leq$ 10 microbleeds, it was noted that while

>10 microbleeds was associated with higher mortality, the pre-test probability of >10 microbleeds was low (0.6%-2.7%) and other factors such as age, stroke severity and treatment delays were also important contributors to the risk of poor outcome. The authors recommended that pre-treatment MRI to quantify microbleed burden would only be justified if it delayed thrombolysis by <10 minutes (38).

### **Other measures**

Hypertensive vasculopathy can contribute to lobar haemorrhages as well as deep brain haemorrhages and can increase the risk of intracerebral haemorrhage. In a secondary analysis of the PROGRESS Trial, patients randomized to perindopril + indapamide demonstrated a 77 percent relative risk reduction of probable CAA-related ICH compared to placebo, with an absolute risk reduction of 0.33 percent(39). This highlights the importance of careful management of hypertension in the setting of CAA.

Statin use in ICH is controversial as there are insufficient data, and the existing data are conflicting. Some studies suggest that there is an inverse relationship between total and low-density lipoprotein cholesterol and risk of ICH, while others suggest that statins do not increase risk of primary ICH or impact prognosis (40). A post hoc analysis of the SPARCL trial demonstrated increased haemorrhagic stroke with statin therapy versus placebo(41), which was further supported a systemic review and meta-analysis by Ziff et al (2019) demonstrating an increase in ICH risk in patients irrespective of stroke sub-type, but it should be noted that this was outweighed by the benefit of reduced ischaemic stroke risk (42). Further, the TST trial demonstrated that more aggressive LDL targets appeared to increase ICH risk, with associated predictors such as uncontrolled hypertension and anticoagulant use (43). Thus, the current data suggest there is no indication to start a statin in patients who

present with ICH, with evidence for potential harm. However, in those already taking statins for established atherosclerotic disease with a strong indication such as previous ischaemic stroke, the benefit of statins is generally thought to outweigh the risk.

## **Conclusions**

The multi-faceted presentations of CAA pose important diagnostic and management challenges. Although pathological diagnosis remains the reference standard, MRI abnormalities can be diagnostic in the relevant clinical context. As most patients are diagnosed only after an ICH, primary prevention opportunities are rare in current practice. Older patients at high risk of ischaemic cardiovascular and cerebrovascular events, many of whom use antiplatelet agents or anticoagulants for primary or secondary prevention of cardiovascular disease, pose a particular management challenge when a diagnosis of probable or possible CAA is made. There are limited studies to guide clinicians in balancing the risk of ICH versus ischemic events and there is a critical need for randomised trials in this setting. Beyond intracerebral haemorrhage, improved recognition of TFNE and CAA-related cortical microinfarction by clinicians is important to reduce complications of unwarranted antithrombotic treatment for misdiagnosed transient ischemic attack and embolic stroke, as well as identifying novel treatment options for these events. Improved understanding of the pathophysiology underpinning CAA related inflammation and the ARIA phenomenon may lead to further therapeutics in this domain, and improve our understanding not only of CAA but also other amyloid- $\beta$  deposition diseases such as AD.

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**Abstract**

Cerebral Amyloid angiopathy (CAA) is a disease with several clinical manifestations. It is characterized by amyloid beta deposition in cerebral blood vessels, making them prone to bleeding. The incidence of CAA increases with age and may be associated or co-exist with intraparenchymal neurodegenerative proteinopathies, which makes it an increasingly relevant condition for adult physicians in all areas of medical practice. The vast majority of cases of CAA are sporadic with a small minority of familial cases. CAA is asymptomatic in many older adults but increases the risk of fatal intracerebral or subarachnoid haemorrhage. We reviewed the existing literature on CAA and summarized the key findings. We specifically explore clinical challenges relevant to CAA, particularly in diagnosis, management of intracranial haemorrhage and management of concurrent medical conditions.

**Key words**

Cerebral Amyloid angiopathy

Beta Amyloid

Superficial cortical siderosis

Microhaemorrhages

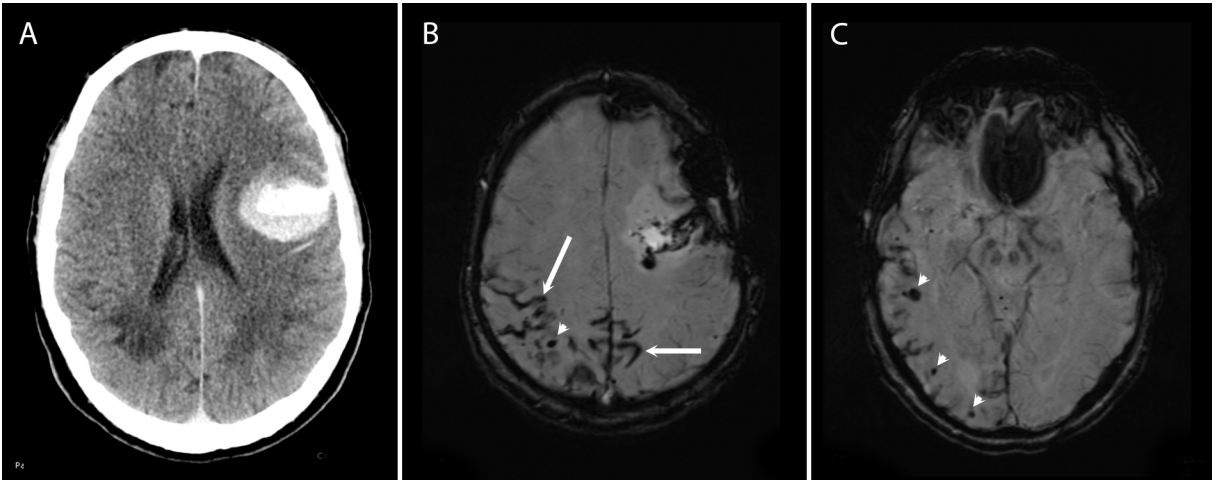
Anticoagulation

**List of Abbreviations**

Cerebral amyloid angiopathy (CAA), Alzheimer's disease (AD), Amyloid precursor protein (APP), Susceptibility-weighted imaging (SWI), Magnetic Resonance Imaging (MRI), Cerebrospinal fluid (CSF), Computerized Tomography (CT), Intracranial haemorrhage (ICH) Positron Emission Tomography (PET), Cortical superficial siderosis (cSS), Mini-mental state examination (MMSE), Transient Ischaemic Attack (TIA), Central Nervous System (CNS),

Amyloid Related Imaging Abnormalities (ARIA), Atrial Fibrillation (AF), non-vitamin K oral anticoagulants (NOACs), left atrial appendage closure (LAAC)

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**Table 1:** Summary of the Boston 2.0 Criteria (4).

	<i>Autopsy</i>	<i>Pathology</i>	<i>Radiology</i>	<i>Presentation</i>
<b>Definite CAA</b>	Severe CAA with vasculopathy, with absence of another diagnostic lesion.	x	x	Clinical presentation consistent with CAA: <i>Spontaneous intracerebral haemorrhage, transient focal neurological episodes, convexity subarachnoid haemorrhage, or cognitive impairment or dementia</i>
<b>Probable CAA with supporting pathology</b>	x	Tissue evidence from cortical biopsy or evacuated hematoma showing some degree of CAA in specimen, in the absence of another diagnostic lesion.	x	Clinical presentation consistent with CAA
<b>Probable CAA</b>	x	x	At least two strictly lobar haemorrhagic lesions on T2-weighted MRI in any combination*  OR  One lobar haemorrhagic lesion on T2-weighted MRI* AND one white matter feature**	Age $\geq 50$  Clinical presentation consistent with CAA
<b>Possible CAA</b>	x	x	One strictly lobar haemorrhagic lesion on T2-weighted MRI in any combination*  OR  One white matter feature**	Age $\geq 50$  Clinical presentation consistent with CAA

\* Including intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage without another cause and in the absence of any deep haemorrhagic lesions.

\*\* White matter features include severe perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern

**Table 2:** Edinburgh criteria 2018. (5)

	<b><i>CT imaging</i></b>
<b>High Probability CAA</b>	Lobar ICH showing SAH on CT + <ul style="list-style-type: none"><li>- Finger like projection from the ICH OR</li><li>- At least one APOE e4 allele</li></ul>
<b>Intermediate Probability CAA</b>	Lobar ICH showing either <ul style="list-style-type: none"><li>- SAH on CT OR</li><li>- At least one APOE e4 allele</li></ul>
<b>Low Probability CAA</b>	Lobar ICH + neither SAH nor APOE e4 allele

**Table 3:** Clinical practice points: general recommendations based on literature review and stroke guidelines.

<b>Overall general recommendation for patients with probable or confirmed CAA</b>		<b>Literature</b>
<b>Anticoagulation for stroke prevention in AF</b>	Randomised data pending. Reasonable to consider alternatives (LAAO) in patients with symptomatic lobar ICH and probable or confirmed CAA, however still contentious. Timing for recommencement is uncertain however, Recommended avoidance for minimum 4 weeks in non-mechanical valve patients.	Wilson 2018 (14) European Society of Cardiology 2016 (28) Hemphill 2015 (44)
<b>Warfarin</b>	Should be avoided but conflicting data, especially if warfarin-associated ICH	Biffi 2017 (27) Hemphill 2015 (44)
<b>DOACs</b>	Can be considered on a case by case basis in light of the local availability of reversal agents, particularly if strong prior indication.	Ntaios 2017 (30) Hemphill 2015 (44)
<b>LAAO</b>	Can be considered when long-term anticoagulation is absolutely contraindicated	Reddy 2017 (32) Stroke Foundation 2021 (45) Osmancik 2020 (33)
<b>Thrombolysis</b>	Previous ICH is a contraindication. A known high microbleed burden (greater than 10) may increase risk of ICH post thrombolysis and can be weighed in risk benefit considerations.	Chacon-Portillo 2018 (46)
<b>Antiplatelet agents</b>	Antiplatelets can be considered in some patients with clear indications. Restarting antiplatelet therapy for pre-existing indication can be considered after the acute phase following ICH. However, conflicting evidence as to harm versus benefit in this patient group.	Vernooij 2009 (34) Al-Shahi Salman 2019 (35) Stroke Foundation 2021 (45)
<b>Blood Pressure control</b>	Lowering BP is the key modifiable risk factor with no lower threshold for benefit identified. Standard blood pressure target of systolic <140mmHg with potential benefit of 120-130mmHg target.	Arima 2010 (39) Hemphill 2015 (44) Stroke Foundation 2021 (45)
<b>Statins</b>	No indication to commence statin for ICH. However, patients with established atherosclerotic disease with a strong indication can continue statin.	Wang 2013 (40) Amarenco 2006 (41) Stroke Foundation 2021 (45)

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<b>Probable CAA</b>	x	x	At least two strictly lobar haemorrhagic lesions on T2-weighted MRI in any combination*  OR  One lobar haemorrhagic lesion on T2-weighted MRI* AND one white matter feature**	Age ≥50  Clinical presentation consistent with CAA
<b>Possible CAA</b>	x	x	One strictly lobar haemorrhagic lesion on T2-weighted MRI in any combination*  OR  One white matter feature**	Age ≥50  Clinical presentation consistent with CAA

\* Including intracerebral haemorrhage, cerebral microbleeds, or foci of cortical superficial siderosis or convexity subarachnoid haemorrhage without another cause and in the absence of any deep haemorrhagic lesions.

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<b>Intermediate Probability CAA</b>	Lobar ICH showing either <ul style="list-style-type: none"> <li>- SAH on CT OR</li> <li>- At least one APOE e4 allele</li> </ul>
<b>Low Probability CAA</b>	Lobar ICH + neither SAH nor APOE e4 allele

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**Table 3:** Clinical practice points: general recommendations based on literature review and stroke guidelines.

Overall general recommendation for patients with probable or confirmed CAA		Literature
<b>Anticoagulation for stroke prevention in AF</b>	Randomised data pending. Reasonable to consider alternatives (LAAO) in patients with symptomatic lobar ICH and probable or confirmed CAA, however still contentious. Timing for recommencement is uncertain however, Recommended avoidance for minimum 4 weeks in non-mechanical valve patients.	Wilson 2018 (14) European Society of Cardiology 2016 (28) Hemphill 2015 (44)
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## Title

Cerebral amyloid angiopathy: Clinical Presentations and Management Challenges in the Australian Context

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None