Cerebral microbleeds: a new dilemma in stroke medicine

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Summary

Cerebral microbleeds (CMBs) are an increasingly common neuroimaging finding in the context of ageing, cerebrovascular disease and dementia, with potentially important clinical relevance. Perhaps the most pressing clinical question is whether CMBs are associated with a clinically important increase in the risk of intracerebral haemorrhage (ICH), the most feared complication in patients treated with thrombolytic or antithrombotic (antiplatelet and anticoagulant) drugs. This review will summarize the evidence available regarding CMBs as an indicator of future ICH risk in stroke medicine clinical practice.

Introduction

In the mid-1990s reports began to appear of small haemorrhagic lesions on magnetic resonance imaging (MRI) studies. Scharf *et al.*[1] described black dots of signal loss on T2-weighted MRI in patients with spontaneous intracerebral haemorrhage (ICH) and termed these 'haemorrhagic lacunes'. Subsequent studies using T2*-weighted gradient-echo (T2*-GRE) MRI – a technique with greater sensitivity to the signal loss from magnetic 'susceptibility' effects of blood breakdown products – detected small round black dots which have become known as 'cerebral microbleeds' (CMBs).[2] Because CMBs reflect small areas of haemorrhage, and are common in both ischaemic stroke and ICH,[3] they have caused concern regarding the risk of future ICH, especially in patients receiving antithrombotic therapy. Although randomized controlled prospective data are lacking, observational data suggest that CMBs are indeed related to an increased future stroke risk, particularly for ICH. Here, we review the available evidence with reference to common clinical scenarios including those where the optimum management may be uncertain.

Pathology, detection and definition of CMBs

Before considering their clinical significance, it is necessary to briefly discuss aspects of CMB pathology, detection and classification. CMBs are small perivascular haemosiderin-deposits (usually within macrophages) in the brain, generally associated with local vessel wall damage.[4] Histopathological analyses of the brains of patients with spontaneous ICH or Alzheimer's disease have shown that CMBs are located in proximity to vessels affected by two types of sporadic small vessel disease: (a) hypertensive arteriopathy and (b) cerebral amyloid angiopathy (CAA).[5] CMBs are found throughout the brain, including cortical grey and white matter, the basal ganglia and brainstem (Figure 1). A large number of cross-sectional studies have confirmed important risk factors and associations for CMBs,

Figure 1

(a) A T2*-weighted gradient-echo (T2*-GRE) magnetic resonance imaging (MRI) scan of a patient with cognitive decline, showing multiple strictly lobar cerebral microbleeds (CMBs) meeting the Boston criteria for probable cerebral amyloid angiopathy. Note the posterior/occipital distribution of CMBs, characteristic of amyloid angiopathy. (b) T2*-GRE MRI of a patient with a history of long-standing hypertension: CMBs are predominantly located in deep brain structures including the basal ganglia and thalami, consistent with hypertensive angiopathy (including arteriolosclerosis and fibrohyalinosis). CMBs are also visible in lobar brain regions

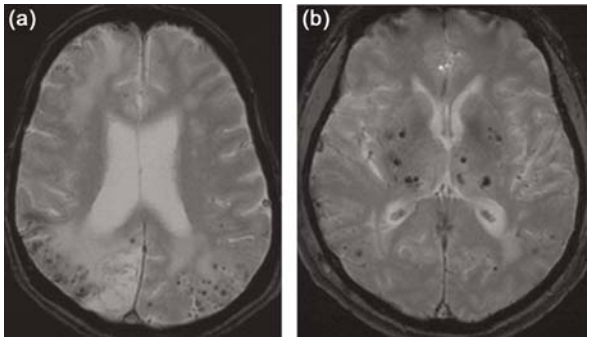


Table 1

Boston criteria for diagnosis of CAA-related haemorrhage

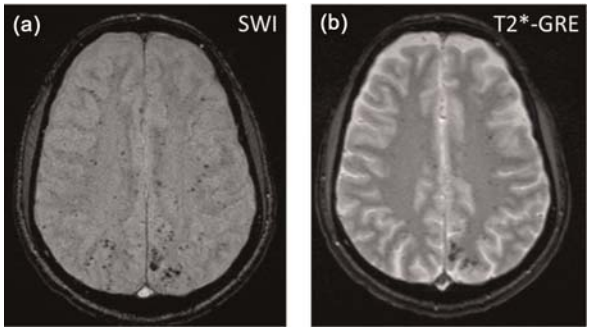
1. Definite CAA
   Full postmortem examination demonstrating:
   - Lobar, cortical or corticosubcortical haemorrhage
   - Severe CAA with vasculopathy
   - Absence of other diagnostic lesion
2. Probable CAA with supporting pathology
   Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating:
   - Lobar, cortical or corticosubcortical haemorrhage
   - Some degree of CAA in specimen
   - Absence of other diagnostic lesion
3. Probable CAA
   Clinical data and MRI or CT demonstrating:
   - Multiple haemorrhages restricted to lobar, cortical or corticosubcortical regions (cerebellar haemorrhage allowed)
   - Age ≥ 55 years
   - Absence of other cause of haemorrhage
4. Possible CAA
   Clinical data and MRI or CT demonstrating:
   - Single lobar, cortical or corticosubcortical haemorrhage
   - Age ≥ 55 years
   - Absence of other cause of haemorrhage

Criteria established by the Boston Cerebral Amyloid Angiopathy Group: Steven M Greenberg MD PhD, Daniel S Kanter MD, Carlos S Kase MD and Michael S Pessin MD. See Ref. 11
CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging; CT, computed tomography

including age, hypertension, history of stroke (both ischaemic and haemorrhagic) and neuroimaging markers of small vessel disease including white matter changes and lacunar infarcts.[6,7] There is increasing (albeit largely indirect) evidence that the distribution of CMBs reflects the underlying type of microangiopathy (Figure 1). Strictly lobar CMBs are considered likely to be due to CAA, because of their association with known risk factors for CAA including apolipoprotein E e4 genotype.[8] Furthermore, an *in vivo* positron emission tomography amyloid-β imaging study using the ligand Pittsburgh compound B, found that CMBs in patients with CAA corresponded to local regions of high amyloid-β concentration.[9] By contrast, deep CMBs are considered most likely to be due to hypertensive arteriopathy because of their associations with hypertension and other imaging manifestations of hypertensive small vessel disease.[10] In clinical practice these arteriopathies (CAA and hypertension-related) are frequently likely to coexist and interact. Diagnostic criteria for CAA have been developed (the 'Boston criteria') (Table 1) with the aim of diagnosing CAA *in vivo* without recourse to tissue biopsy. These criteria include the presence of *strictly* lobar ICH, including CMBs, and have been shown to have very high specificity.[11] However, the sensitivity of these criteria may be lower, and some patients with a mixed deep and lobar distribution of CMBs, although not fulfilling the Boston criteria, are likely to harbour some degree of CAA. New biomarkers for CAA may help improve the sensitivity of these diagnostic criteria without sacrificing their specificity.

The radiological detection of CMBs is reliant on the paramagnetic property of haemosiderin which disrupts the local magnetic field, causing

Figure 2
(a) Susceptibility-weighted imaging (SWI) is currently the most sensitive means for the detection of cerebral microbleeds (CMBs). Although SWI can detect significantly more CMBs compared with conventional T2*-weighted gradient-recalled echo (T2*-GRE) magnetic resonance imaging, whether it has 'added value' in clinical practice is still under investigation



'inhomogeneities' and focal signal loss (known as 'susceptibility effect') on appropriate MRI sequences including T2*-GRE.[12] Newer MRI techniques to detect CMBs include susceptibility-weighted imaging and its variants, which greatly increases the sensitivity of CMB detection (Figure 2) by combining both the magnitude and phase images to increase susceptibility-related tissue contrast.[13] Detection of CMB is influenced by a variety of sequence parameters including the echo time (TE), field strength and slice thickness.[14] Moreover, most current methods of defining CMBs rely on manual visual rating of scans, leading to substantial variations in agreement between observers. In an effort to improve agreement about CMB presence, number and location, two rating scales have been developed and validated for use in classifying CMB; The Microbleed Anatomical Rating Scale (MARS)[15] and the Brain Observer Microbleed Scale (BOMBS).[16] The MARS rating form (Figure 3) shows the conventional anatomical definition of deep, lobar and infratentorial regions. Lobar regions include cortical and superficial subcortical white matter regions (including subcortical U fibres). Deep regions include the basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter. Infratentorial regions include the brainstem and cerebellum. Both of these scales are validated for inter-observer agreement; the main difference is that MARS allows for the categorization of CMB distribution in different brain lobes. It is important to note that there are a number of radiological 'mimics' of CMBs including vascular flow voids, susceptibility artefacts from surrounding tissue (air, bone), cavernous malformations, haemorrhagic transformation of ischaemic areas, diffuse axonal injury and occasional haemorrhagic cerebral metastases.[4] Recent consensus criteria for the diagnosis of CMBs are summarized in Table 2.

Clinical significance of CMBs for antithrombotic drug treatments

How could CMBs affect the risk of ICH on antithrombotic drugs?

Because CMBs are a radiological marker of previous small areas of bleeding from abnormal cerebral small vessels, a key question is whether they are predictive of an increased risk of ICH in individuals treated with antithrombotic medications. It is generally assumed that most CMBs are clinically 'silent' and self-limiting because of haemostatic mechanisms and surrounding tissues. However, it is hypothesized that leakage of blood from an arteriolar rupture may on some occasions not be stemmed, resulting in potentially serious symptomatic ICH. Antithrombotic agents (antiplatelet or anticoagulant drugs) may, by impairing platelet function or the endogenous coagulation cascade, increase the likelihood of ICH resulting from a CMB. For CMBs to have clinical relevance for antithrombotic-related ICH they must first be common in the populations likely to be exposed to these drugs, and second, they must accumulate over time, to allow expansion of microbleeding into a symptomatic ICH during antithrombotic therapy.

CMBs are common in populations likely to be exposed to antithrombotic drugs

In population-based studies, CMBs have been reported in between about 5% and 25% of older people: this wide range in prevalence is likely to reflect differences in sensitivity of the MRI techniques and age of populations.[4] Evidence is emerging for a different distribution of CMBs depending on ethnicity: in Caucasians most

Figure 3
The Microbleed Anatomical Rating Scale, showing lobar, deep and infratentorial regions

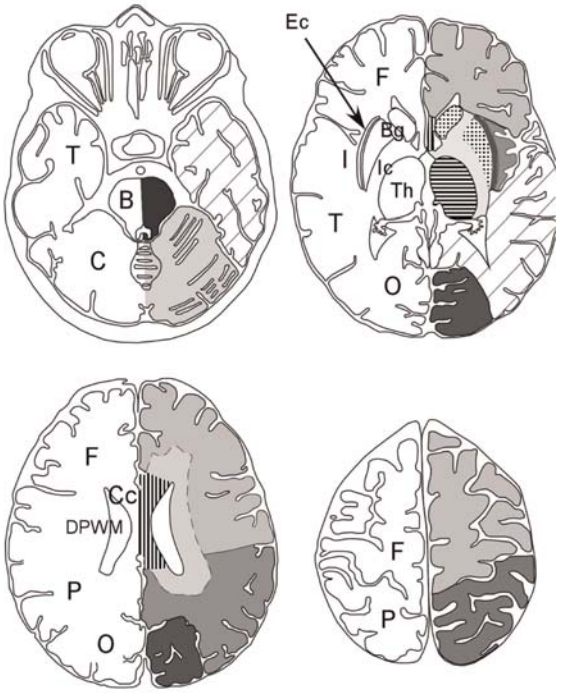
Microbleed Anatomical Rating Scale (MARS) Rating Form

Patient ID: Date of Birth _ _/_ _/_ _ _ _ Date of MRI _ _/_ _/_ _ _ _

DEFINITE MICROBLEEDS: Small, round, well-defined, hypointense on GRE T2*; 2-10 mm; not well seen on T2

MICROBLEED MIMICS
- Vessels: linear/curvilinear lesions in subarachnoid space, usually cortical or juxta-cortical (visible on T2)
- Mineralization in globi pallidi or dentate nuclei: symmetrical hypointensities (may be bright flecks on CT)
- Haemorrhages within area of infarction (look at the T2, FLAIR or DWI sequences to identify infarction)
- Air-bone interfaces: frontal/temporal lobes (check adjacent GRE T2* slices to clarify)
- Partial volume artefact at the edges of the cerebellum (check adjacent GRE T2* to clarify)
- Small haemorrhages close to a large ICH (visible on GRE T2*) or to an infarct (visible on T2, FLAIR or DWI)

		DEFINITE		POSSIBLE	
		R	L	R	L
Infratentorial TOTAL	Brainstem (B)				
	Cerebellum (C)				
Deep TOTAL	Basal ganglia (Bg)*				
	Thalamus (Th)				
	Internal capsule (Ic)				
	External capsule (Ec)				
	Corpus callosum (Cc)				
	Deep and periventricular WM (DPWM)				
Lobar** TOTAL	Frontal (F)				
	Parietal (P)				
	Temporal (T)				
	Occipital (O)				
	Insula (I)				
	TOTALS				



* (Caudate, Lentiform), **Lobar regions include cortex and subcortical white matter

CMBs are located in lobar regions,[17,18] suggesting CAA as a dominant cause. By contrast, in Asian cohorts, deep CMBs, probably indicating hypertensive arteriopathy, predominate.[19]

CMBs are also common in populations with neurological disease, including patients with cognitive impairment,[20] ischaemic stroke,[21] ICH,[22] CAA and Alzheimer's disease[23] as well as the rare genetic cause of stroke, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[24] CMBs are more common in recurrent than first-ever

stroke, suggesting that they may reflect the progression of underlying small vessel disease. In stroke cohorts, the highest prevalence for CMBs is in individuals with recurrent ICH.[25] In ischaemic stroke, the hypothesis that CMBs reflect small vessel disease is supported by preferential associations with ICH and lacunar infarction as compared with atherothrombotic or cardioembolic ischaemic stroke.[26]

Table 2
Criteria for defining cerebral microbleeds (from Ref. 4)

1 Black lesions on T2*-weighted MRI
2 Round or ovoid lesions (rather than linear)
3 Blooming effect on T2*-weighted MRI*
4 Devoid of signal hyperintensity on T1- or T2-weighted sequences
5 At least half the lesion surrounded by brain parenchyma
6 Distinct from other potential mimics such as iron or calcium deposits
7 Clinical history excluding traumatic diffuse axonal injury

MRI, magnetic resonance imaging
The blooming effect on MRI refers to the observation that CMBs as seen on T2-weighted brain imaging are larger than their actual size (or their size if they are seen on standard structural MRI [e.g. T2-weighted images]). By increasing the TE (Echo Time) on a T2* weighted GRE, the dephasing period is increased and the blooming effect is increased

CMBs develop over time

The incidence of new CMB over about three years in the Rotterdam study was 85/831 patients (about 10%).[27] In another study of a cohort of memory clinic patients, the incidence of CMB was 12% over about 2 years.[28] In a small stroke clinic population, new CMBs were noted in five of 21 patients over five years, and their development was strongly related to baseline systolic blood pressure and, as in the other studies (ref 27,28), the presence of baseline CMBs.[29] A larger study of 224 patients with stroke or TIA found that over a mean follow-up period of 27 months new CMBs developed in 10 patients (6.8%). The estimated annual rate of change of CMB numbers was 0.80 lesions per year in all patients, but the rate was more than 5% per year in patients with more than five CMBs at baseline,[30] suggesting a graded increase in risk according to CMB burden.

CMBs as a predictor of future stroke risk

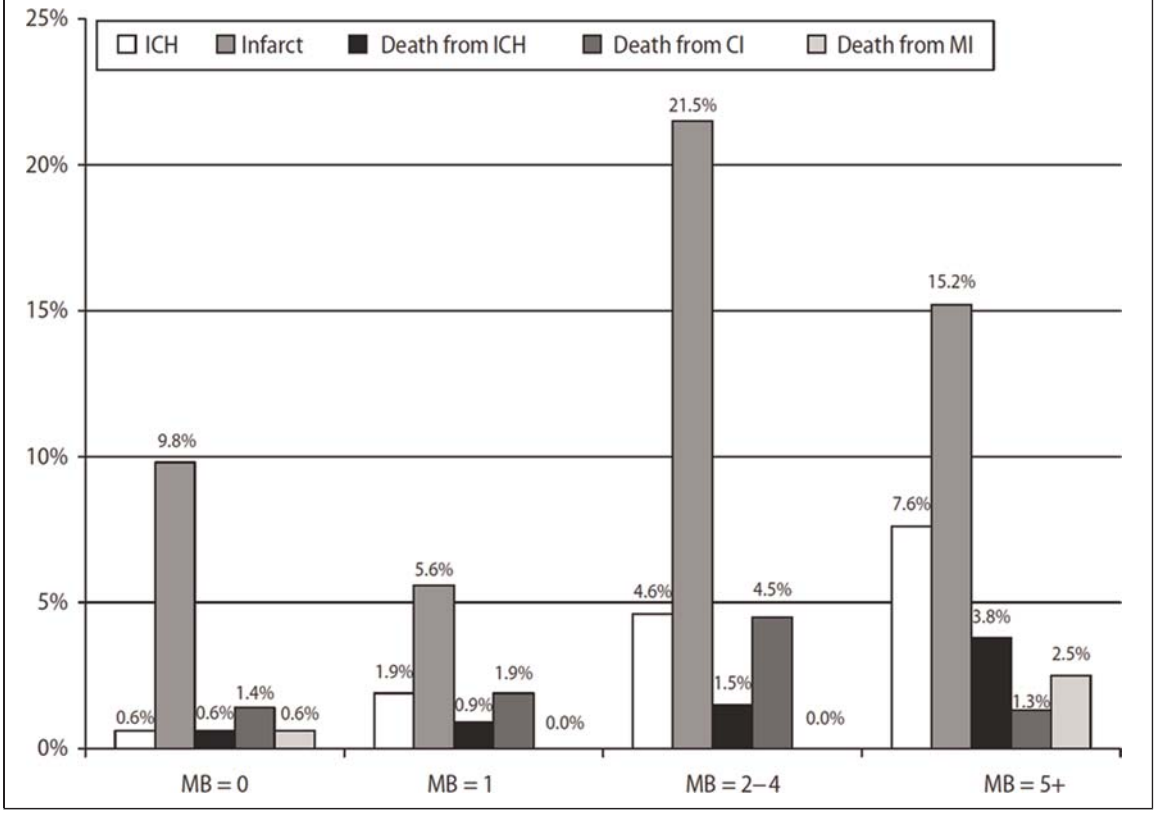
High-quality prospective data on how CMBs relate to future stroke risk are scarce. Table 3 summarizes key results of the main available prospective cohort studies. These studies, show an increased risk of recurrent stroke, mainly ICH, in patients with CMBs (with a greater risk if CMBs

Table 3
Key studies of CMBs and risk of recurrent stroke (after ischaemic stroke)

Study	*Year*	*Proportion of patients with CMB*	*Follow-up duration*	*Incidence of ischaemic stroke in individuals with CMBs*	*Incidence of ICH in individuals with CMBs*
Thijs *et al.*	2010	129/487	2.2 years	10% ($P = 0.054$)	0.8% ($P = 0.09$)
Fan *et al.*	2003	43/121	27.15 ± 11.68 months	11.6% ($P = 0.841$)	9.3% ($P = 0.053$)
Soo *et al.*	2008	252/908	26.6 ± 15.4 months	9.6% (0 CMB), 5.6% (1 CMB), 21.5% (2–4 CMB) 15.2% (≥5 CMB) ($P = 0.226$)	0.6% (no CMB), 1.9% (1 CMB), 4.6% (2–4 CMB) 7.6% (≥5 CMB) ($P < 0.001$)
Boulanger *et al.*	2006	45/236	14 months (median)	20.3% ($P = 0.039$)	3.3% ($P = 0.31$).

P values are for comparison of risk of stroke in individuals with CMBs compared with those without CMBs at baseline
CMB, cerebral microbleed

Figure 4
Risk of cerebral haemorrhage (ICH) and cerebral infarction (CI) and myocardial infarction (MI) in an Asian cohort of 908 patients with ischaemic stroke treated with an antithrombotic agent (93% of patients received aspirin)[32]. The mean follow-up period was 26 months (from Soo *et al.*, 2008, with permission)



are multiple).[31–33] By contrast, a Canadian study of ischaemic stroke or TIA found an increased risk of ischaemic stroke rather than ICH.[34] In a small prospective study of 21 surviving patients with ischaemic stroke or TIA followed up after a mean interval of 5.5 years, the investigators found only one recurrent ICH among eight patients with CMBs, compared with no ICH in 13 patients without CMBs.[29] A European cohort of 487 patients with a TIA or ischaemic stroke, also found that patients with microbleeds had a higher risk of developing new ischaemic stroke rather than ICH.[35] Interestingly, only strictly lobar CMBs (or combined with deep microbleeds) had an independent effect on the risk of recurrent stroke ($P = 0.018$) in this study, suggesting that CAA may be a risk factor for ischaemic stroke as well as ICH.

The largest prospective study of CMBs in stroke patients to date comes from an Asian population of 908 patients with ischaemic stroke or TIA[32]. The investigators prospectively evaluated patients with pre-existing CMB (27.8%) and compared the risk of developing ICH, ischaemic stroke and mortality. The found an increased risk of ICH which directly correlated with the number of pre-existing CMB (0.6% [no CMB], 1.9% [1 CMB], 4.6% [2–4 CMB] and 7.6% [≥5 CMB]), and also showed a future ischaemic stroke risk of 9.6% (0 CMB), 5.6% (1 CMB), 21.5% (2–4 CMB) and 15.2% (≥5 CMB) (Figure 4).

CMBs also influence future ICH risk after symptomatic ICH. Greenberg *et al.*[36,56] prospectively evaluated a cohort of CAA patients with lobar ICH, and found that the count of microbleeds or macrobleeds on baseline MRI predicted

an increased risk of haemorrhagic stroke (proportional to the count) in survivors. Jeon *et al*.[37] also noted an elevated risk of recurrent ICHs development associated with CMBs (but not with other clinical and laboratory data), in a prospective study of 112 survivors of ICH.

The predictive value of CMBs for the risk of occurrence of symptomatic cerebrovascular disease in the general population is largely unknown. One recent large-scale prospective study of 2102 healthy elderly individuals followed for a mean interval of 3.6 years in Japan[38] demonstrated a significant association between CMBs and subsequent ICH (hazard ratio: 50.2; 95% confidence interval [CI]: 16.7–150.9) and ischaemic stroke (hazard ratio: 4.48; 95% CI: 2.20–12.2). These findings are of interest, but it should be noted that the CIs around the risk estimates are wide, and the findings await confirmation in other longitudinal population-based studies, ideally in a range of different populations to reflect the spectrum of small vessel disease across ethnic groups.

In summary, increasing evidence suggests that CMBs are a risk factor for the risk of future stroke. Some, but not all studies, adjusted for potential confounding factors (e.g. age, hypertension). The available data suggest that overall the risk may be higher for ICH than for ischaemic stroke, but this balance may depend on the characteristics of the population studied (e.g. Asian versus non-Asian). Further studies are required to clarify this. However the critical question for clinicians is whether the risk of future ICH is increased by the presence of CMBs, and whether any increase in risk is sufficient to tip the balance away from recommending antithrombotic drug treatment.

CMBs and their implications for antithrombotic therapy

Antiplatelet drugs, CMBs and ICH risk

In ischaemic stroke from causes other than cardiac embolism (in which anticoagulation is generally preferred), antiplatelet medications are a key component of secondary prevention of future occlusive vascular events. Aspirin is the most widely studied agent, and carries only a small absolute risk of symptomatic ICH of less than 0.5%,[39] though this risk seems to be higher in Asian than in non-Asian cohorts. There has been concern that antiplatelet drugs could not only cause CMBs but also increase the risk of symptomatic ICH.

Cross-sectional studies. A number of cross-sectional studies have evaluated associations between antiplatelet exposure and the presence of CMBs, but CMB presence may be confounded by some indications for antiplatelet treatment (e.g. a history of ischaemic stroke). Nevertheless, the Rotterdam Scan study in over 1000 healthy elderly individuals found that prior antiplatelet use was associated with an increased prevalence of CMBs (odds ratio [OR]: 1.71; 95% CI: 1.21–2.41), a finding which persisted after adjusting for potential confounders including history of stroke.[40] The same study also noted that strictly lobar CMBs were more common in aspirin users than those using an alternative antiplatelet drug, carbasalate calcium (OR: 2.7; 95% CI: 1.45–5.04), suggesting that aspirin may specifically aggravate microbleeding in the context of CAA. Our small hospital-based UK case-control study[41] found that CMBs were more likely to be present in ICH patients who were on antiplatelet therapy compared with both ICH patients without antiplatelet therapy and to matched non-ICH patients on antiplatelet therapy; lobar CMBs were found in 69% of the ICH group compared with 33% of the control group of antiplatelet users without ICH ($P = 0.03$). After adjustment for leukoaraiosis, the presence of lobar (but not deep) CMBs was a significant predictor of antiplatelet-related ICH (OR: 1.42), also supporting an interaction between aspirin use and CAA. One small prospective study in CAA showed a high risk of recurrent ICH, with evidence that this risk is increased risk by aspirin treatment.[36] Thus, CAA may be an important risk factor for antiplatelet-related ICH, but because of the small sample sizes to date, further data are required to confirm this.

Three studies in eastern Asian countries have also shown a higher prevalence of CMBs in antiplatelet treated patients. Jeong *et al.*[42] evaluated 187 patients with primary ICH in order to determine associated risk factors and clinical and radiological correlates. They found the use of antiplatelets and anticoagulation to be associated with an increased risk of ICH in patients with CMBs. In a retrospective study comparing a small Asian cohort of 21 aspirin users who developed ICH

with healthy matched controls, Wong *et al.*[43] found a much higher proportion of CMBs in the ICH group (CMBs were found in 19 cases compared with only 7 of 21 matched aspirin users without any history of ICH [$P < 0.001$]). Ge *et al.*[44] retrospectively looked at 150 cases of ischaemic cerebrovascular disease patients on Aspirin and matched controls not taking Aspirin and found an increased frequency of CMB (40% versus 12%; OR: 4.899; $P < 0.0001$) and ICH (28% versus 1%; OR: 28.778; $P < 0.0001$) in Aspirin users. By contrast, in a Japanese cohort of ICH patients with underlying pre-existing white matter changes, there was an association of CMB with ICH but not with antiplatelet use.[45] A systematic review in a mixture of Asian and non-Asian cohorts including data from 1461 patients with ICH and 3817 with TIA or ischaemic stroke also found that CMBs were more common in antiplatelet users than in non-users with both ICH (OR: 1.7; 95% CI: 1.3–2.3) or ischaemic stroke (OR:1.4; 95% CI: 1.2–1.7).[46]

Prospective studies. Prospective data on CMB presence and future ICH risk on antiplatelet treatments remain scarce. The largest study published to date, as previously mentioned, is from Asia (Hong Kong), where 908 patients with ischaemic stroke treated with a single antithrombotic agent (in 93% of cases aspirin) were screened for CMBs and followed up for a mean period of 26 months.[32] CMBs were found in 28% of patients, most often in deep regions suggesting hypertensive arteriopathy as the most likely cause. The risk of ICH was higher in individuals with baseline CMBs, and increased with increasing CMB count. These data suggest that CMB presence and number of CMB are relevant for ICH risk in this Asian population. CMBs were also associated with an increased risk of ischaemic stroke, but this did not show a graded relationship with CMB count at baseline. Given that antiplatelet agents have only a modest effect in secondary ischaemic stroke prevention (absolute risk reduction approximately 1–2% per year),[47] an ICH risk of 7.6% in those with >5 CMBs may outweigh the benefit in this subgroup of patients. However, it is not known whether these data are generalizable to non-Asian populations.

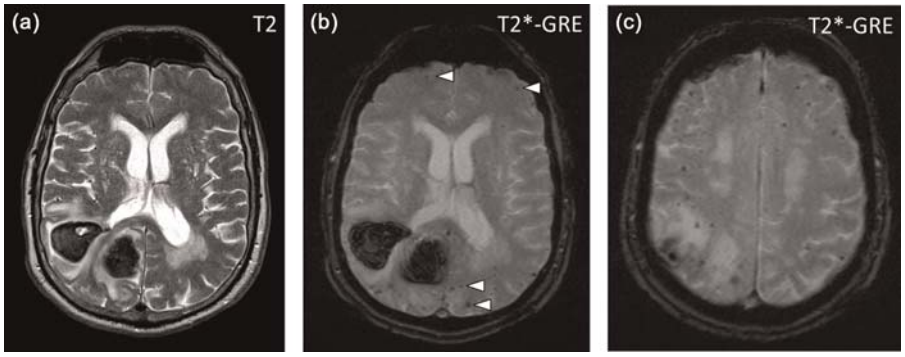
In summary, there are robust associations between antiplatelet use and the presence of CMBs, but cross-sectional studies cannot fully adjust for potential confounding factors. The largest available prospective study (in an Asian population) suggests that CMBs may also influence the future risk of ICH in ischaemic stroke patients treated with antithrombotic drugs. However, since the overall benefit of antiplatelet treatment has been established in very large randomized trials and meta-analyses, there is currently insufficient evidence to recommend withholding them in patients with CMBs. There are very few data relating to the use of multiple antiplatelet agents together, but these could pose a greater risk than single antiplatelet treatment in individuals with small vessel disease.[48] Screening for CMBs should be considered for future antiplatelet randomized trials or natural history prognosis studies after stroke.

Anticoagulant drugs, CMBs and ICH risk

Ischaemic stroke is a common consequence of atrial fibrillation, and the risk increases with the presence of other risk factors including age, hypertension, congestive heart failure and diabetes. Anticoagulation with Warfarin[49] and newer agents including Dabigatran[50] and Rivaroxaban[51] are all very effective in reducing the risk of ischaemic stroke by about 60–70%. Nevertheless all anticoagulants inevitably increase the risk of unwanted bleeding: the most feared of all complications from anticoagulation is ICH. Conventional anticoagulation in ischaemic stroke patients increases the risk of ICH up to 7–10-fold with an absolute risk of about 1% per year.[52] The risk of ICH is generally higher in inception observational cohorts in comparison to clinical trials, from which many high-risk patients are excluded.[53]

Despite the clear efficacy of anticoagulants for stroke prevention, the proportion of ICH related to the use of anticoagulant drugs has increased in recent years: about 15% are currently related to warfarin use.[54] The increasing use of anticoagulants in elderly populations is expected to result in an increasing incidence of anticoagulant-related ICH. There is thus major interest in whether new imaging or genetic biomarkers may help to predict the risk of this rare yet devastating and unpredictable complication. Because oral anticoagulant associated ICH is associated with increased age and previous stroke, and often occurs with anticoagulation intensity within the therapeutic

Figure 5
(a) Two simultaneous warfarin-related intracerebral haemorrhages in an elderly patient with atrial fibrillation. (b, c) T2*-weighted gradient-recalled echo reveals the presence of multiple strictly lobar cerebral microbleeds (some shown with arrowheads), consistent with underlying cerebral amyloid angiopathy. Note that the symptomatic haematomas are also lobar



range, it is likely that mechanisms underlying high risk relate to individual patient factors, for example an age-related disorder of small brain blood vessels. There is evidence that patients with CAA have a particularly high risk of anticoagulant-related ICH (Figure 5).[55] Patients with symptomatic lobar ICH suggestive of CAA have annual recurrent ICH risk of up to about 20%,[36,56] and anticoagulants appear to increase this risk, as well as increasing the clinical severity and mortality rate from ICH.[52]

Since MRI is the most sensitive way to image the consequences of small vessel disease,[57] some studies have investigated whether it may be useful in risk stratification. Leukoaraiosis – a confluent deep white matter abnormality seen as low attenuation on computed tomography (CT) or high signal on T2-weighted MRI, and a marker of small vessel disease – increases the risk of oral anticoagulant-related ICH.[58] CMBs provide direct evidence of leakage of blood from pathologically fragile small vessels, so might be a better predictor of oral anticoagulant-associated ICH than leukoaraiosis alone. In the current stroke risk scoring systems (CHA2DS2-VASc for thrombotic risk[59] and HAS-BLED for bleeding risk)[60] paradoxically, some of the risk factors for future ischaemic stroke risk are similar to those associated with increased bleeding risk (age, previous stroke, hypertension). Neuroimaging and genetic biomarkers that are more predictive of ICH than ischaemic stroke hold promise for refining the risk–benefit assessment in this situation.[61] Although CAA defined by symptomatic ICH is generally considered to be a contraindication to anticoagulation, it is not known whether the presence of lobar CMBs alone (without macrohaemorrhage) is a risk factor for ICH. There are few pathological validation studies to confirm whether lobar CMBs are sufficient to diagnose CAA. Below we briefly discuss the limited data relating to CMBs and anticoagulant bleeding risk.

Cross-sectional studies. There are few cross-sectional studies addressing the potential role of CMBs in anticoagulant-related ICH. One case-control study included 24 ICH patients with warfarin use compared with 48 warfarin users with no history of ICH and found a greater number of CMBs in the ICH group; prothrombin time and CMB presence were predictive of ICH.[62] A Chinese study also demonstrated an association of CMB in ICH patients previously on Warfarin.[63] By contrast, a Turkish study of anticoagulated patients did not find a significant difference in CMB prevalence between Warfarin users versus non-users.[64] In a systematic review and meta-analysis of cross-sectional data mentioned above[46] the authors found an 8 fold increase in the OR of having at least one CMB in warfarin treated ICH patients compared with ICH patients not taking warfarin.

Prospective studies. There are no reliable large-scale prospective data regarding the effect of CMBs on the risk of ICH in patients with

Table 4
Key studies of CMBs and the risk of ICH after thrombolysis

Study	*Year*	*No. of patients*	*SICH rate in CMB group*	*SICH rate in non-CMB group*
Fiehler *et al.*, BRASIL study	2007	570	5.8% (95% CI, 1.9–13.0)	2.7% (95% CI, 1.4–4.5)
Derex *et al.*[78]	2004	44	1/8 patients (12.5%) non-significant	3/36 patients (8.33%) non-significant
Kim *et al.*	2006	65	8/25 (32%) non-significant	9/40 (22.5%) non-significant
Kakuda *et al.*[79]	2005	70	0/11 (0%) non-significant	7/59 (11.9%) non-significant
Kidwell *et al.*[80]	2002	41	1/5 (20%) non-significant	4/36 (11.1%) non-significant

CMB, cerebral microbleed; ICH, intracerebral haemorrhage SICH, Symptomatic Intra Cranial Haemorrhage

previous ischaemic stroke and atrial fibrillation treated with warfarin, who in clinical practice pose perhaps the greatest dilemma for treatment. Until high-quality data about the magnitude of risk are available anticoagulation should continue to be recommended for patients with atrial fibrillation regardless of the presence of CMBs, based on the compelling results from large randomized trials and meta-analyses. The question of how CMBs may affect future ICH risk after anticoagulation in the setting of acute cardioembolic stroke is being investigated in UK-wide prospective multicentre inception cohort study, CROMIS-2 (www.ucl.ac.uk/cromis-2). Clinicians are encouraged to participate in this and other observational studies to allow a more definitive recommendation about anticoagulation in patients with CMBs to be made.[65] Although the newer anticoagulants have lower rates of ICH, the effects of small vessel disease on this risk and how the data from trials translate to day-to-day practice remain unknown.

Statins and CMBs

Some studies have found an association between low serum cholesterol and increased CMB burden,[66] although in patients with acute ischaemic stroke or transient ischaemic attack previous statin therapy was not associated with either the prevalence or the burden of CMBs.[67] A higher risk of ICH was observed in atorvastatin-treated patients in secondary prevention trials of patients with ischaemic cerebrovascular disease (SPARCL): the hazard ratio was 4.1 for those entering following ICH compared with 1.6 for those enrolled with ischaemic stroke, which suggests a possible relationship between statins and intracerebral bleeding.[68] Although a case-control study found statin use prior to ICH to be associated with reduced mortality and favourable outcome, in line with a meta-analysis,[69] others have noted an association between low LDL cholesterol levels and increased mortality.[70] These inconsistent associations do not allow a definitive recommendation to be given on statin therapy in the context of CMBs. A decision analysis suggests that CMBs in the context of CAA (e.g. multiple areas of strictly lobar cerebral haemorrhage) should lead to avoidance of statins, since they indicate a high risk of future ICH.[71] However, this decision analysis is not a substitute for observational or randomized evidence, both of which are needed to determine the true risk of statins in individuals with CMBs.

CMBs and Thrombolysis in Acute Ischaemic Stroke

The most widely used effective treatment for acute ischaemic stroke is intravenous thrombolysis. The most devastating complication is ICH,[72] which may have a devastating impact on the patient. Leukoaraiosis, a marker of cerebral small vessel disease, is associated with an increased risk of ICH.[73] CMBs, as a potential marker of bleeding-prone small vessel diseases, have long been suspected as a new risk factor for post-thrombolysis ICH. The available studies on this topic are summarized in Table 4. The largest of these studies

(BRASIL),[74] prospectively evaluated the risk of symptomatic ICH (defined as a clinical deterioration with an increase of 4 points on the NIHSS score, and a temporal association with parenchymal haematoma) found a non-significant increase in the risk of symptomatic ICH in patients with CMB (symptomatic ICH risk was 5.8% [95% CI, 1.9 to 13.0] in the CMB group as compared with 2.7% (95% CI, 1.4 to 4.5) in patients without CMBs [$P = 0.170$]). Similarly, Kim *et al.*[75] investigated 65 patients with varying numbers of CMBs (CMBs were subdvided into four grades: I – [CMB absent], II – [1–2 CMB], III – [3–10 CMB and IV – greater than 10 CMB] and did not demonstrate that the presence or burden of CMBs were independently associated with the risk symptomatic ICH after thrombolysis).

Two recently published meta-analyses suggest a trend towards increased risk of symptomatic ICH in thrombolysed ischaemic stroke patients,[76,77] but acknowledge the limitations of the available studies (e.g. non-standardized or insensitive MRI techniques, small sample sizes, varying ICH definitions). Clearly, further larger and well designed studies are urgently needed to answer this dilemma posed by CMBs.

Conclusion

CMBs are not just an incidental finding revealed by new neuroimaging technology. Current literature suggests at least two different underlying arteriopathies causing different topographic patterns of CMBs (hypertension, leading to deep CMBs, and CAA, leading to strictly lobar CMBs). In clinical practice the distribution of CMBs is mixed, suggesting that these two arteriopathies often coexist or interact. The core question that persists is whether CMBs are associated with an increased risk of ICH or ischaemic stroke or both? And if so, is this risk modified or enhanced with the concomitant administration of antiplatelets and anticoagulation therapy. Current data, both prospective and cross-sectional, suggest an increased stroke risk in the presence of CMBs. The risk of ICH may be higher than the risk of ischaemic stroke, but population ethnicity (Asian versus non-Asian) may play a role in this balance of risk. There is consistent evidence of an association between antithrombotic use (mainly relating to antiplatelet drugs) and CMBs in cross-sectional studies, and limited prospective data suggesting an increased hazard for antiplatelet drugs if CMBs are present. Few data are available on whether CMBs influence the risk of ICH during anticoagulation after ischaemic stroke. Since cross-sectional data are unable to prove causation there remains an urgent need for larger prospective studies, in a range of populations, to specifically investigate the risks of ICH associated with CMBs. Until clear and consistent data are available to show an increased hazard of CMBs, clinicians should continue to recommend antithrombotic therapy after ischaemic stroke or TIA based on the results of large randomized trial and meta-analyses. In patients with previous symptomatic ICH and evidence of CAA, antithrombotics should be used with particular caution, and only when clear treatment indications, that are judged to outweigh the very high ICH risk, are present.

Summary points

- CMBs are an important neuroimaging finding on a T2* GRE MRI scan and are indicative of underlying small vessel damage; they correspond to perivascular haemosiderin deposits, which are presumed to be due to small areas of bleeding from small vessels;
- The distribution of CMBs reflects the underlying type of microangiopathy – hypertensive arteriopathy (deep CMBs) or CAA (strictly lobar CMBs);
- People with pre-existing CMBs are likely to develop more CMBs over time;
- In stroke patients (both ischaemic stroke and ICH), CMBs are associated with an increased risk of future ICH and ischaemic stroke, independent of potential confounding factors;
- The presence of CMBs in patients with ischaemic stroke (including those treated with antiplatelet agents) is associated with an increased risk of future stroke (ICH risk>ischaemic stroke risk). CAA may be a particular risk factor for ICH on anticoagulant or antiplatelet drugs. However, current data are insufficient to recommend with holding antiplatelet drugs in patients with CMBs. Although CMBs are associated with anticoagulant related ICH in

cross-sectional studies, there are no large-scale prospective studies of CMBs and ICH risk after anticoagulation;
- The role of CMBs in predicting thrombolysis-related ICH risk in ischaemic stroke is currently uncertain; there is a non-statistically significant trend towards increased ICH risk if CMBs are present prior to thrombolysis, but the clinical relevance is not yet established and requires further study.

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