Antithrombotic therapy in patients with cerebral microbleeds

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Purpose of review: Cerebral microbleeds (CMBs) are a radiological marker of cerebral small vessel disease corresponding to small haemosiderin foci identified by blood-sensitive MRI. CMBs are common in older community populations, and in individuals with ischaemic stroke (IS) or TIA, and intracerebral haemorrhage (ICH). We summarize how CMBs might contribute to assessing the future risk of IS and ICH to inform antithrombotic (antiplatelet or anticoagulant) decisions.

Recent findings: CMBs are a risk factor for future IS and ICH in all community and hospital populations studied. Following IS/TIA treated with antithrombotics, increasing CMB burden increases the risk of ICH more steeply than that of IS. In ICH populations the risk of recurrent ICH increases with CMB burden, and is highest in those with strictly lobar CMBs or other haemorrhagic findings (e.g. cortical superficial siderosis) suggesting cerebral amyloid angiopathy (CAA).

Summary: In IS or TIA patients <5 CMBs should not affect antithrombotic decisions, though with >5 CMBs the risks of future ICH and IS are finely balanced, and antithrombotics might cause net harm. In lobar ICH populations, a high burden of strictly lobar CMBs is associated with CAA and high ICH risk; antithrombotics should be avoided unless there is a compelling indication.

Key words

(200 words)

Introduction

Although cerebral microbleeds (CMBs) have been extensively investigated since their first description in 1996 (1), important questions about underlying mechanisms and clinical relevance remain unanswered. CMBs are the radiological correlate of haemosiderin-laden macrophages resulting from small, usually chronic haemorrhages (2-4). Interest has focussed on CMBs as a potential marker of a "bleeding prone" small vessel arteriopathies, with potential to predict symptomatic intracerebral haemorrhage (ICH) risk (5, 6). However, CMBs are also a risk factor for ischaemic stroke (7, 8), possibly explained by alternative "ischaemic" pathophysiological mechanisms(9-11). Antithrombotic (antiplatelet and anticoagulant) use in patients with CMBs is a highly topical clinical dilemma (12), which will become increasingly common with an aging population often investigated with MRI and exposed to antithrombotic drugs for stroke and cardiovascular prevention. This review provides up-to-date information on the clinical relevance of CMBs for antithrombotic use.

Definition, mechanisms and potential relevance of CMBs for antithrombotic decisions

CMBs are defined radiologically as small (generally <10 mm) ovoid or rounded black signal voids on paramagnetic-sensitive MRI sequences, including T2* gradient-recalled echo weighted and susceptibility-weighted imaging(13). CMBs must be differentiated from "mimics" (13), and account taken of technical imaging aspects affecting detection (14-16). Standardised rating scales or automated techniques can improve reliability of CMB rating (17-19). Studies of the pathological correlates of CMBs include only 23 patients (4, 20) mainly with ICH or dementia. Nevertheless, most observations suggest that CMBs are self-limiting regions of red cell extravasation from damaged small blood vessels. CMB location predicts the type of underlying small vessel disease: an arteriopathy associated with systemic

arterial hypertension and pathological changes in small perforating arteries of the deep grey and white matter (often termed "hypertensive arteriopathy') causes CMBs in deep (basal ganglia) as well as lobar regions. In Western (Caucasian) people with ICH, CMBs in a strictly lobar distribution are highly specific for cerebral amyloid angiopathy (CAA), which causes progressive deposition of amyloid-β in small cortical and leptomeningeal arterial walls(3), though this pattern might not be so specific in Eastern (Asian) people and in those without ICH(21, 22). Figure 1 shows the different radiological distributions of CMBs.

More recently, ischaemic mechanisms for CMBs have been identified: ischaemia-mediated iron store released by oligodendrocytes; (9) phagocytosis of red cell microemboli into the perivascular space (termed angiophagy); (10) and haemorrhagic transformation of microinfarcts (11), which might contribute to the clinical associations between CMBs and future IS risk.

CMBs might be relevant for ICH risk with antithrombotic exposure: first, CMBs are common in populations likely to be exposed to antithrombotic drugs, including older community-dwelling individuals and those with IS, TIA or ICH (23); and second, longitudinal studies confirm that CMBs are a dynamically develop over time after IS, TIA or ICH (24, 25) (while regression of CMBs can occur, it seems to be rare). Since antithrombotics impair haemostasis by inhibiting platelet aggregation (antiplatelets) or disrupting the coagulation pathway (anticoagulants), in the presence of a CMB-related arteriopathy, normally self-limiting red blood cell extravasation (causing a CMB) could become a symptomatic ICH (Figure 2).

Current evidence on clinical outcomes following antithrombotic use in different populations evaluated for CMBs

When CMBs are detected in a patient with a risk of future ischaemic vaso-occlusive disease, should antithrombotic drugs be recommended? Without randomised trial data, the best evidence is from prospective observational cohorts and pooled meta-analyses. We suggest considering: the population (non-stroke, IS/TIA, or ICH); the type of antithrombotic (antiplatelet or anticoagulant); the overall risk of IS and ICH; CMB presence, burden and distribution; the balance of future IS and ICH; and judgement of the likely net benefit and harm of antithrombotic treatment (Table 1).

Table 1. Summary of evidence on IS and ICH risk by CMB presence, burden and distribution

	Non-stroke (older community)	Ischaemic stroke and TIA	Intracerebral haemorrhage
Effect of CMB presence (compared to no CMBs)	**IS risk** Absolute event rate 2.6% over a mean follow up of 4.9 years HR 1.52; 95% CI 0.91 to 2.53 (23) HR 4.48; 95% CI 2.20 to 12.2 (26) **ICH risk** Absolute event rate 0.7% over a mean follow up of 4.9 years HR 5.64; 95% CI 1.66 to 19.53 (23) HR 50.2; 95% CI 16.7 to 150.9 (26)	**IS risk** Absolute event rate 9% over a median follow up of 18 months Absolute risk increase 3.4%. Pooled risk ratio 1.8 (27) **ICH risk** Absolute event rate over a median follow up of 18 months 4.3% Absolute risk increase 3.8%. Pooled risk ratio 6.3 (27)	**ICH risk** Baseline CMBs associated with recurrent ICH in lobar but not deep ICH (28)
Effect of CMB burden (all data compared to those without CMBs)	**All stroke risk** Increased risk of 'all stroke' with 2-4 CMBs and >5 CMBs (23)	**IS risk** >5CMBs Absolute event rate 10.5% over a median follow up of 18 months Absolute risk increase 5.1% Pooled risk ratio 2.7 (27) **ICH risk** >5CMBs Absolute event rate over a median follow up of 18 months 8.8% Absolute risk increase 8.2% Pooled risk ratio 14.1 (27) **Increasing CMB burden** (29) All cause mortality	**ICH risk** Baseline number of CMBs associated with recurrent ICH in lobar but not deep ICH (28) >5 CMBs HR 4.12 95% CI 1.6 to 9.3 in patients with CAA-related ICH (30) 3 year cumulative risk 51% in those with lobar ICH (5)

		HR 1.99; 95% CI 1.03 to 3.85 IS mortality HR 3.39; 95% CI 1.39 to 8.28.	
Effect of CMB distribution **(compared to no CMBs)**	**Strictly lobar (probable CAA)** IS risk Absolute event rate 1.4% over a mean follow up of 4.9 years HR 0.84; 95% CI 0.41 to 1.74 (23) ICH risk Absolute event rate 0.6% over a mean follow up of 4.9 years HR 5.27; 95% CI 1.38 to 20.23 (23) 5 cases/100 patient years (31) (median 10 CMBs in these patients)	**Strictly lobar (probable CAA)** IS risk Absolute event rate over a median follow up of 18 months 9.3% Absolute risk increase 3.9%. Pooled risk ratio 2.0 (27) ICH risk Absolute event rate over a median follow up of 18 months 3.6% Absolute risk increase 3.2 % Pooled risk ratio 10.5 (27) ICH mortality HR 5.91; 95% CI 1.58 to 22.11(29)	**Probable CAA patients** ICH risk 3 year cumulative ICH rates (5) 17% 2 strictly lobar CMBs, 37% 3-5 strictly lobar CMBs, 51% strictly lobar CMBs 8.9 events/ 100 patient years (31) 2-4 CMBs (30) HR 2.9; 95% CI 1.3 to 4.0; >5 CMBs (30) HR 4.12; 95% CI 1.6-9.3
	Not strictly lobar (i.e. not probable CAA) (23) IS risk Absolute events rate 1.4% over a mean follow up of 4.9 years HR 3.05; 95% CI 1.65 to 5.63 ICH risk Absolute event rate 0.6% over a mean follow up of 4.9	**Mixed CMBs** IS risk Absolute event rate over a median follow up of 18 months 10.7% Absolute risk increase 5.3% Pooled risk ratio 2.6 (27) ICH risk Absolute event rate over a median follow up of 18 months 6.1%	

	years HR 5.27; 95% CI 1.07 to 32.86	Absolute risk increase 5.7% Pooled risk ratio 11.1 (27)	
Antithrombotic-CMB interactions	Antiplatelets did not significantly change IS or ICH risk according to CMB presence, burden or distribution(23)	Risks outlined above (excluding ICH mortality) are for patients largely on antiplatelets. No data on interaction available. ICH mortality was from patients on anticoagulants.	**ICH risk in CAA** Aspirin HR 3.95; 95% CI 1.6 to 8.3(30)
Conclusions and recommendations	CMBs increase the risk of both ICH and IS. Those in a strictly lobar distribution have a higher risk of ICH. **However, currently neither presence, burden or distribution should routinely affect antithrombotic decisions**	CMBs increase the risk of both IS and ICH. An increasing burden increased the risk of ICH more dramatically than the risk of IS, but absolute rates of IS remain higher at all CMB counts. Although CMBs should generally not affect antithrombotic decisions, **in IS or TIA patients with a large number of CMBs (e.g.>5) the risks of future ICH and IS are finely balanced, and antithrombotics might cause net harm.** Further studies are needed in patients on anticoagulants.	CMBs presence and increasing burden increase the risk of ICH. **Patients with lobar ICH with a high burden of strictly lobar CMBs or other haemorrhagic markers (e.g. cortical superficial siderosis), should if possible avoid antithrombotics.** NOACs are preferable to VKA. LAAO is an option in ICH patients with AF.

Non-stroke (older community) populations

The diagnostic accuracy of a strictly lobar CMB pattern for CAA seems limited in non-ICH (community) cohorts: in a recent study strictly lobar CMBs had a positive predictive value for pathology-proven CAA of only 25% (32), though participants had very few CMBs (33).

Longitudinal studies of outcome related to CMBs in community cohorts are shown in Table 1. In the Rotterdam study (23) of 4759 participants aged ≥45 years with mean follow-up of 4.9 years, CMBs were associated with an increased risk of all stroke (HR 1.93; 95% CI 1.25 to 2.99); this was lower (and not statistically significant) for IS (HR 1.52; 95%CI 0.91 to 2.53) than for ICH (HR 5.64; 95% CI 1.66 to 19.53). Non-strictly lobar CMBs (i.e. non-CAA pattern), were associated with an increased the risk of both IS and ICH while strictly lobar CMBs (indicating probable CAA) were associated only with ICH risk. Six participants with multiple CMBs developed a first-ever ICH during follow-up; 3 had used antithrombotic agents (either platelet inhibitors or oral anticoagulants). However, the overall stroke risk associated with CMBs was not affected by the use of antithrombotics. Pre-existing CMBs were associated with lacunar infarction whilst incident lobar CMBs are associated with progression of white matter lesions, suggesting shared ischaemic mechanisms.

A large Japanese population-based study showed that CMB presence was associated with both IS (hazard ratio 4.48; 95 % CI 2.20 to 12.2) and ICH (hazard ratio 50.2; 95 % CI 16.7 to 150.9)(26), but did not explore CMB burden, topography, or associations with antithrombotics. A hospital-based study in patients with incidental lobar CMBs without stroke reported ICH rates comparable to CAA-associated ICH (31) and that warfarin was an independent risk factor for ICH (p=0.02). However, this population had a median of 10 lobar CMBs, suggesting severe CAA, so these findings cannot be generalised to other stroke-free populations with incidentally found CMBs.

In summary, in community-dwelling populations, there is no clear evidence that the benefits of IS prevention by the use of antithrombotic drugs outweigh the risk of ICH in people with CMBs. Further interventional controlled clinical trials, including stratification according to CMB presence, burden and distribution, will be needed to definitively answer this question.

Ischaemic stroke and TIA populations

The clinical relevance of CMBs is perhaps most uncertain in the IS and TIA population, because standard care includes antithrombotics for stroke secondary prevention. Does any increased risk of ICH in patients with CMBs outweigh the benefit in reduced future IS risk associated with antithrombotic therapy? Although risk instruments can be used to assess overall future IS risk in AF (e.g. CHA_2DS_2VASC) or after TIA (ABCD2), as well as overall bleeding risk in AF (e.g. HAS-BLED), there are currently very limited data on how CMBs and other brain imaging findings might help personalise antithrombotic therapy to maximise benefit and minimise risk.

In recent studies, antiplatelets (34-36) and anticoagulants (36, 37) are associated with the presence of CMBs and the development of new CMBs over time. However, establishing the clinical relevance of CMBs requires key clinical outcomes, including recurrent stroke. A recent aggregate data meta-analysis from 15 studies of patients with IS or TIA including 5068 patients over a median of 18 months follow-up showed that baseline CMBs are associated with an increased risk of both IS (pooled RR 1.8; 95% CI 1.4 to 2.5) and ICH (pooled RR 6.3; 95% CI 3.5 to 11.4) (27) . The risk ratio for both IS and ICH increased with CMB burden, but more steeply for ICH than IS: in individuals with >5 CMBs the RR of IS was 2.7, while that of ICH was 14.1 (Figure 3). At all CMB counts, the absolute risk of IS exceeded that of ICH, though in those with >5 CMBs, the absolute risk of ICH (8.8%) approached that of IS (10.5%). In randomised trials, antiplatelet agents only modestly reduce the absolute risk of ischemic stroke (0.5 to 2.5%) (38), while the recent meta-analysis showed that ≥5 CMB are associated with an absolute risk increase of 8.2% for ICH and 5.1% for IS. Since ICH is generally more severe than IS, it is possible that in individuals with >5 CMBs, antithrombotic

treatment may be associated with net harm. The prevalence of patients with ≥5 CMBs ranged from 12 to 51%, suggesting this dilemma will be encountered often in clinical practice. However, since most individuals in this meta-analysis were treated with antithrombotic drugs (79% with antiplatelets, 15% with anticoagulants), it cannot be concluded that CMBs should be avoided in patients with >5 CMBs. The benefit of antithrombotics in IS/TIA patients with many (e.g. >5) CMBs will only be determined by randomised controlled trials. Nevertheless, these data do provide reassurance that in individuals with IS or TIA and <5 CMBs, there is no suggestion that antithrombotics are hazardous, so should be used according to current care guidelines.

Data on the association between CMBs and stroke risk on patients with IS or TIA treated with anticoagulants are extremely limited. A small study in 134 patients with TIA or IS associated with AF (65% treated with anticoagulants) over a median follow-up of 2.4 years (39), found that CMBs were associated with an increased unadjusted risk of all stroke (21% vs 9%, p = 0.06) but there was only 1 ICH. A study from Korea in 504 patients with IS or TIA (97% discharged on anticoagulation) (29) found that strictly lobar CMBs were associated with ICH mortality (HR 5.91; 95% CI 1.58 to 22.11) whilst increasing CMB burden was associated with all cause (HR 1.99; 95% CI 1.03 to 3.85) and IS mortality (HR 3.39; 95% CI 1.39 to 8.28) but did not report on non-fatal IS or ICH. A retrospective study from the same Korean group including 550 ischaemic stroke patients with AF (83% discharged on anticoagulation) found that higher CHADS2 and CHA(2)DS(2)VASC scores were associated with the presence and number of CMBs. Recurrent ICH was associated with CMB presence (HR 3.79; 95 % CI 1.09 to 13.15) but not CHADS2 or CHA(2)DS(2)VASC scores; recurrent IS risk was not reported (40). A small prospective single centre study from Japan followed 119 patients with AF (86% anticoagulated) for a median of 17 months (41);

There is thus an urgent need for more large-scale data on how CMBs might affect the balance of IS and ICH in IS/TIA patients treated with oral anticoagulants. Two large large multicentre inception cohort studies will help to address this gap: Clinical Relevance of Microbleeds in Stroke (CROMIS 2; see https://www.ucl.ac.uk/cromis-2, https://clinicaltrials.gov/ct2/show/NCT02513316)(42) and Intracerebral Hemorrhage Due to Oral Anticogulants: Prediction of the Risk by Magnetic Resonance (HERO; see http://heropub.pic.es, https://clinicaltrials.gov/ct2/show/NCT02238470).

ICH populations

The most feared, often lethal, complication of antithrombotic therapy is ICH. Recurrent ICH risk varies according to the location of the initial ICH: the annual ICH recurrence risk after deep (non-lobar, in the basal ganglia or brainstem) ICH is between 1.3 to 10.6% compared with 2.5 to 28.2% after lobar ICH. (43) While deep ICH is attributed to hypertensive arteriopathy, lobar ICH may be due to either hypertensive arteriopathy or CAA. Cohort studies in CAA-related ICH or CMBs, diagnosed according to the Boston criteria indicate a high recurrence rate of ~10% per year (31). The presence, burden and distribution of CMBs might increase the risk of recurrent ICH, and help to judge difficult antithrombotic decisions (Table 1). In a study of 207 survivors of ICH followed for a median of 20 months there were 39 recurrences of ICH(28). CMB number was associated with recurrent ICH in patients with lobar but not deep ICH, while antiplatelet use did not affect the risk of recurrent ICH in either lobar (HR 0.8; 95% CI 0.3 to 2.3, $p = 0.73$) or deep location (HR 1.2; 95% CI 0.1 to 14.3, $p = 0.88$). By contrast, a small single centre study in CAA-related ICH reported that aspirin was an independent risk factor for recurrent ICH (HR 3.95; 95% CI 1.6 to 8.3, $p = 0.021$) (30).

Three other studies found that increasing CMB burden is associated with increasing ICH risk (5, 6, 30), but none reported on IS risk. Two of these studies included only patients with lobar ICH, whilst the third included both deep and lobar ICH. The risk of ICH was particularly high with >5CMBs (HR 4.12 95% CI 1.6 to 9.3 vs. no CMBs $p = 0.001$ (30) with a 51% 3 year cumulative risk for >5 CMBs vs. 14% 3 year cumulative risk for 1 CMB p = 0.003(5).

The use of anticoagulants following ICH thus presents a major clinical dilemma. The risk of ischaemic stroke without antithrombotic treatment must be weighed carefully against the possible increase in ICH risk associated with antithrombotic therapy. A decision analysis which modelled warfarin for AF in an ICH survivor suggested that in lobar ICH avoiding warfarin increased quality-adjusted life (QOL) years by 1.9, compared with 0.3 for deep ICH; the authors concluded that anticoagulation for AF should not be offered to patients with lobar ICH and only to survivors of deep ICH if the risk of ischaemic events was high (>7% per year)(44). However, CMBs were not considered in this analysis. By contrast, recent real-world studies in large datasets from ICH survivors with AF suggest that anticoagulation reduces mortality and ischaemic complications, without an increase in ICH (45, 46), and also reduced hospitalization costs (47). However, none of the real world studies stratified ICH by location, nor by CMB burden or distribution. Further studies in ICH cohorts phenotyped according to CAA diagnostic criteria, with assessment of interactions of CMB pattern and burden with antithrombotic use may help clarify this enduring clinical dilemma. Two ongoing randomised trials of antithrombotic use after ICH will also help guide clinicians in these decisions in future: APACHE-af (http://apache-af.nl –aspirin vs. apixaban vs. noantithrombotics for the treatment of AF in patients after ICH) and RESTART

(www.restarttrial.org –antiplatlets vs, no antiplatelets in patients with ICH with an indication for antiplatelets*).*

Other imaging markers

Other imaging markers of small vessel disease include cortical superficial siderosis (cSS), leukoaraiosis and enlarged perivascular spaces. cSS seems to be strongly associated with probable CAA(48, 49) and with increased recurrent ICH risk(49-51), especially if disseminated (49).

Conclusion

Cerebral microbleeds are a risk factor for both future IS and ICH in all populations studied, including healthy older people people, and those with IS, TIA or ICH. Following IS or TIA treated with antithrombotics, increasing CMB burden increases the risk of ICH more steeply than that of IS; in patients with a large number of CMBs (e.g.>5) the risks of future ICH and IS are finely balanced, and antithrombotics might cause net harm. However, most of the evidence in IS and TIA cohorts is from patients treated with antiplatelet agents rather than anticoagulants. Large global collaborative networks will be needed to obtain the necessary data to assess any potential hazard of CMBs, especially associated with the use of in anticoagulants; the Microbleeds International Collaborative Network(52) will undertake a systematic review and individual patient data meta-analysis of the clinical relevance of CMBs in patients with TIA and ischaemic stroke treated with antithrombotics (the prospectively registered protocol is published at: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036602).

ICH patients with probable CAA (i.e. those with lobar ICH and either strictly lobar CMBs or disseminated cortical superficial siderosis) have a high baseline annual risk of ICH (>5% per year), which is likely to be increased substantially with the use of anticoagulants. We suggest that these patients should usually avoid anticoagulation; if essential to prevent further ischaemic events (e.g. in the presence of high risk atrial fibrillation), non-vitamin K antagonists are preferable because of a lower risk of ICH(53). Alternatives to anticoagulation for patients with AF include left atrial appendage occlusion (54), which is as effective as oral anticoagulants but likely to have lower future ICH risk than long-term oral anticoagulation in ICH survivors. Figure 4 is a treatment algorithm suggested by the authors based on current evidence.

Key points

- CMBs can be due to both haemorrhagic and ischaemic mechanisms, and are associated with an increased risk of both IS and ICH in all populations studied, including community-dwelling older adults, IS or TIA, and ICH

- CMBs should not currently influence antithrombotic decisions in non-stroke (community-dwelling) populations

- In IS or TIA populations, a small number of CMBs (<5) is associated with a higher risk of recurrent IS than ICH, so should not routinely influence antithrombotic decisions

- In patients with IS or TIA treated with antithrombotics, an increasing burden (number) of CMBs is associated with a steep increase in ICH risk: individuals with a high CMB burden (>5) have similar absolute risks of ICH and recurrent IS, so that antithrombotic use might cause net harm

- CMBs and other haemorrhagic imaging markers (e.g. cortical superficial siderosis) are associated with a substantial risk of recurrent CAA-related ICH, and current limited evidence suggests that avoiding antithrombotics is probably appropriate in individuals with this high risk profile

Important papers

**Akoudad S, Portegies ML, Koudstaal PJ, Hofman A, van der Lugt A, Ikram MA, et al. Cerebral Microbleeds Are Associated With an Increased Risk of Stroke: The Rotterdam Study. Circulation. 2015;132(6):509-16.
Important paper which examines the associaiton of CMBs with both IS and ICH risk in a healthy population cohort. The paper explores both the distribution and burden of CMBs as well as their interaction with antithrombotics.

*Martinez-Ramirez S, Romero JR, Shoamanesh A, McKee AC, Van Etten E, Pontes-Neto O, et al. Diagnostic value of lobar microbleeds in individuals without intracerebral hemorrhage. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015

This radiological-pathology study examins the diagnostic value of CMBs between a hospital cohort and healthy patients in the community. They show lobar a strictly lobar CMB pattern has a low positive predictive value for CAA in community patients.

**Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: A meta-analysis.Wilson D, Charidimou A, Ambler G, Fox ZV, Gregoire S, Rayson P, Imaizumi T, Fluri F, Naka H, Horstmann S, Veltkamp R, Rothwell PM, Kwa VI, Thijs V, Lee YS, Kim YD, Huang Y, Wong KS, Jäger HR, Werring DJ. Neurology. 2016. A large up-to-date meta-analysis comparing ICH and IS risk with regrard to CMB presence, burden and distribution in patients presenting with IS or TIA

*Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA : the journal of the American Medical Association. 2015;313(8):824-36.

*Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study. Circulation. 2015;132(6):517-25.
Both tof hese large observational registry studies show that restarting anticoagulation in patients with ICH and AF is associated with decreased mortlaity and ischaemic complications without an increase in ICH.

**van Veluw SJ, Biessels GJ, Klijn CJ, Rozemuller AJ. Heterogeneous histopathology of cortical microbleeds in cerebral amyloid angiopathy. Neurology. 2016;86(9):867-71
Recent histopathological correlation study which reveals CMBs have a heterogeneous histopathological substrate suggesting multiple different mechanisms

*Janaway BM, Simpson JE, Hoggard N, Highley JR, Forster G, Drew D, et al. Brain haemosiderin in older people: pathological evidence for an ischaemic origin of MRI microbleeds. Neuropathology and applied neurobiology. 2013.

*Grutzendler J, Murikinati S, Hiner B, Ji L, Lam CK, Yoo T, et al. Angiophagy prevents early embolus washout but recanalizes microvessels through embolus extravasation. Science translational medicine. 2014;6(226):226ra31.
Both of the above papers give mechanistic insights into the possible ischaemic mechanisms which may lead the formation fo CMBs.

*Microbleeds International Collaborative Network. Worldwide collaboration in the Microbleeds International Collaborative Network. Lancet neurology. 2016 Volume 15, Issue 11, October 2016, Pages 1113–1114
A global collaborative effort which will help answer key questions about CMBs and stroke risk. Only large international efforts will have statistical power to address prediction of rare outcomes, including antithrombotic-related ICH.

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Figure titles

Figure 1: Distribution of microbleeds.
  A. Mixed distribution of microbleeds in both deep (thalamic and basal ganglia) and lobar regions; this pattern is hypothesised to be due to either severe hypertensive arteriopathy, or mixed hypertensive arteriopathy and cerebral amyloid angiopathy
  B. Strictly lobar distribution of microbleeds, suggesting a diagnosis of probable cerebral amyloid angiopathy (CAA)

Figure 2: Hypothetical possible mechanisms of CMBs and intracerebral haemorrhage.

Figure 3: Risk ratio of both ischaemic stroke and intracerebral haemorrhage depending on CMB burden in patients with ischaemic stroke or TIA
Legend: CMB –cerebral microbleeds; TIA-transient ischaemic attack; IS –ischaemic stroke; ICH – intracerebral haemorrhage

Figure 4: Suggested decision making algorithm for antithrombotic use in patients with CMBs based upon the authors recommendations
Legend: TIA –transient ischaemic attack; ICH –intracerebral haemorrhage; CMB –cerebral microbleed; AF –atrial fibrillation; LAA –left atrial appendage; CAA –cerebral amyloid angiopathy; RESTART - REstart or STop Antithrombotics Randomised Trial; APACHE-AF - Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation.