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Anticoagulation for Atrial Fibrillation in Patients with Cerebral Microbleeds

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Abstract Intracranial haemorrhage (ICH) is the most feared and devastating complication of oral anticoagulation, with high mortality and disability in survivors. Oral anticoagulant-related ICH is increasing in incidence, most likely in part due to the increased use of anticoagulation for atrial fibrillation in the elderly populations with a high prevalence of bleeding-prone cerebral small vessel diseases. Risk scores have been developed to predict bleeding, including ICH, as well as the risk of ischaemic stroke. Recently, attention has turned to brain imaging, in particular, MRI detection of potential prognostic biomarkers, which may help better predict outcomes and individualize anticoagulant decisions. Cerebral microbleeds (CMBs)—small, round areas of signal loss on blood-sensitive MR sequences—have been hypothesized to be a marker for bleeding-prone small vessel pathology, and thus, future symptomatic ICH risk. In this review, we outline the prevalence and prognostic value of CMBs in populations affected by AF for whom anticoagulation decisions are relevant, including healthy older individuals and survivors of ischaemic stroke or ICH. We consider the limitations of currently available evidence, and discuss future research directions in relation to both prognostic markers and treatment options for atrial fibrillation.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a lifetime risk of 1 in 4 for those over 40 years [1]. AF is strongly associated with increasing age, and thus, it is becoming more common as life expectancy increases and populations become older [2]. AF is a strong risk factor for ischaemic strokes, which tend to be more severe than strokes due to other mechanisms [3]. Oral anticoagulation effectively reduces the incidence of ischaemic stroke in patients with AF by about two thirds [4], but carries a small risk of a devastating but unpredictable complication: intracranial haemorrhage. The risk of intracranial haemorrhage during oral anticoagulation in randomized controlled trials is generally reported to be less than 1 % [5], but these may underestimate the real-world incidence, which is up to 2.5 % in some observational inception cohort studies [6]. Intracranial haemorrhage accounts for the vast majority (over 90 %) of bleeding-related deaths on warfarin [7], making it a clinical research priority.

The most common form of intracranial bleeding during oral anticoagulation is intracerebral haemorrhage (ICH)—bleeding into the brain parenchyma—which causes death or disability in 76 % of patients [7, 8]. Although the incidence of ICH has reduced in young populations (a trend generally attributed to better control of hypertension), in older populations, ICH incidence is increasing [9, 10]. In one population-based study, a fivefold increase in the incidence of ICH was associated with a fourfold increase in oral anticoagulant use over a similar time period [11], a link most likely due to increased rates of anticoagulation-related ICH [11]. The most plausible explanation for this trend is an interaction between

the effect of more widespread use of oral anticoagulants and increasingly common age-related bleeding-prone small vessel diseases, probably including cerebral amyloid angiopathy (CAA) [10, 12].

Risk scores to predict ischaemic stroke and bleeding risk have been developed to help guide clinicians in deciding whether to use or avoid anticoagulation in patients with AF [13, 14], summarised in recent consensus guidelines [15]. However, these bleeding risk scores were not specifically developed to predict ICH risk. A key recent development is the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), with rates of ICH consistently around 50 % lower than for vitamin K antagonists [16–18]. However, this lower ICH risk may paradoxically lead to a higher incidence of anticoagulation-related ICH, as the use of these more convenient agents becomes more widespread and patients previously excluded from anticoagulant therapy are offered NOACs. Thus, improving the understanding and prediction of anticoagulant-related ICH risk has become a recent research focus [19]. Interest has increased in the use of brain imaging, and the question of whether markers of small vessel disease, particularly cerebral microbleeds (CMBs)—small, round areas of signal loss on blood-sensitive MR sequences—better predict ICH and ischaemic stroke risk to personalise decisions on anticoagulation in AF [19–21].

This paper will focus on CMB history, pathophysiology, prevalence and potential significance for risk prediction and treatment in different populations likely to be considered for oral anticoagulation (including healthy older populations, those with ICH and ischaemic stroke). Other markers of small vessel disease seen on MRI (including cortical superficial siderosis, a marker of bleeding from superficial cerebral small vessels) will also be briefly reviewed, as well as future research directions.

Search Strategies

Cerebral Microbleeds

1) "Cerebral Microbleed*" OR CMB OR "cerebral microh?emorr*" OR "brain microbleed*" OR "Brain microh?emorr*"
2) "Atrial fibrillation" OR AF
3) Anticoagul* OR "Vitamin K antagonists" OR "novel adj3 anticoag*" OR NOAC OR "non adj2 vitamin k" OR Rivaroxaban OR Warfarin OR Apixaban OR Dabigatran
4) 1 AND 2
5) 1 AND 3

Cortical Superficial Siderosis

1) "Cortical adj2 siderosis" OR "convexity adj2 siderosis" OR "convexity adj h?emo*" OR "cortical adj2 h?emo*"

LAA Occlusion Device

1) "Left atrial appendage adj2 device" OR "LAA adj2 device" OR Watchman
2) ICH OR "intrac* adj2 h?emorrh*"
3) "Atrial fibrillation" or AF
4) 1 AND 2
5) 1 AND 3
6) 2 AND 3

In addition to the above strategies, we also searched the reference lists of the retrieved studies and review articles, as well as manual searches of our own files.

Cerebral Microbleeds (CMBs)

In 1996, Offenbacher and colleagues hypothesised that asymptomatic small cerebral haemorrhages seen in ICH cases at autopsy may be visible on MRI. Using T2* gradient-recalled echo, they found regions of ovoid-shaped signal drop-out (caused by paramagnetic haemosiderin), which they inferred corresponded to small haemorrhages, and named these "microbleeds" [22]. A subsequent histopathological-MRI correlation study confirmed that small clusters of haemosiderin-laden macrophages were the pathological correlate of the majority of microbleeds seen on MRI [23]. Further histopathological correlation studies showed that vessels in close proximity to CMBs are affected by pathological changes of cerebral small vessel disease [23–27]. Thus, it is inferred that most CMBs represented direct extravasations of blood from bleeding-prone vessels affected by small vessel diseases. Support for the concept of microbleeding in direct response to impaired integrity of the blood brain barrier is also provided by recent studies of high altitude cerebral oedema, where CMBs, especially in the corpus callosum, were consistently observed and correlated with the clinical severity of the syndrome [28]. It should be noted, however, that mechanisms of CMBs development other than direct red cell extravasation have since been postulated, for example ischaemia-mediated iron store released by oligodendrocytes [29] and phagocytosis of red cell microemboli into the perivascular space (termed angiophagy) [30]. A recent pathological analysis of the "oldest old" (over 85 years) found that areas of haemorrhage (including microscopic bleeding) were frequently associated with microinfarcts [31], suggesting a "secondary" mechanism, perhaps related to haemorrhagic transformation of ischemic infarcts. Indeed, a recent editorial suggests a possible framework for the classification for CMBs: primary (artery/arteriole rupture or blood brain barrier dysfunction), secondary (haemorrhagic infarction or microinfarction) and "pseudo" CMBs (angiophagy and ischaemia-related iron store release) [32].

The anatomical location of CMBs correlates with different risk factor profiles and microvascular pathology. Deep CMBs (brainstem, thalamus and basal ganglia; Fig. 1a) are often accompanied by a clinical history of hypertension and moderate to severe fibrohyalinosis [23], whilst strictly lobar CMBs (Fig. 1b) are specifically associated with pathological evidence of CAA [25]. These findings, and other indirect evidence from population and hospital-based imaging studies [33, 34], suggest that there are broadly two small vessel arteriopathies which cause CMBs: CAA (associated with strictly lobar CMBs) and "hypertensive arteriopathy" (a term often used to describe multiple pathologies affecting mainly the deep arterial perforators including arteriolosclerosis, lipohyalinosis and fibrinoid necrosis), associated with deep CMBs [35]. Recent evidence from a cohort of patients with cognitive impairment suggests that lobar CMBs are also associated with ischemic subcortical small vessel disease markers as well as amyloid burden [36]. Thus, a "mixed" pattern of deep and lobar CMBs could represent severe hypertensive arteriopathy or mixed CAA and hypertensive arteriopathy, but evidence to support this hypothesis remains limited [37, 38]; confirmation will require further pathological correlation studies.

CMBs are common in many settings including: healthy elderly populations [39], memory impairment or dementia cohorts [40, 41] and stroke cohorts (both ischaemic stroke and intracerebral haemorrhage) [42, 43], thus widening their potential clinical implications. The importance of standardized

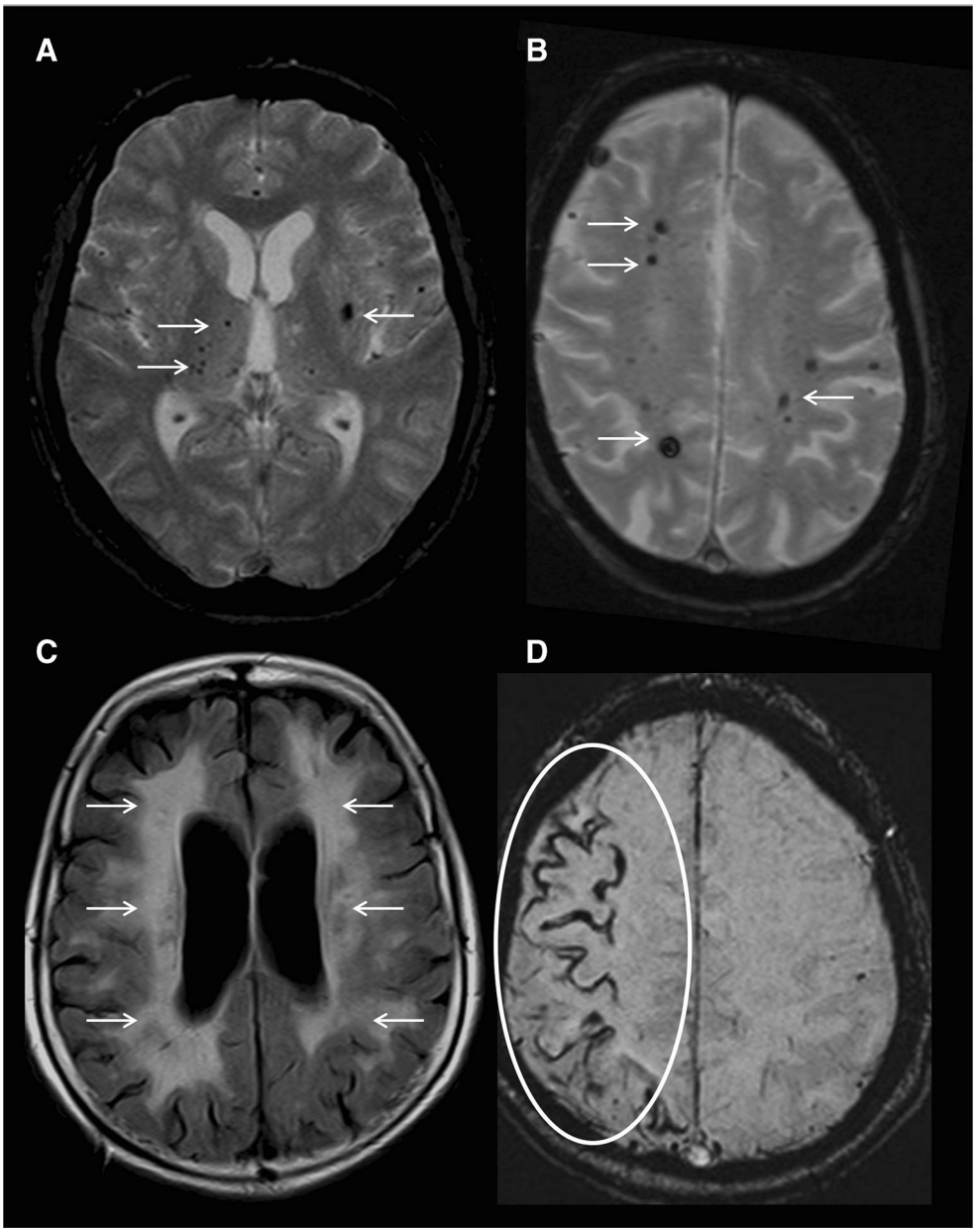

Fig. 1 **a** T2* GRE showing deep cerebral microbleeds in the right thalamus and left basal ganglia (lentiform nucleus); *white arrows*. **b** T2* GRE showing cerebral microbleeds in both frontal lobes (*white arrows*). **c** FLAIR image showing extensive diffuse confluent white matter hyperintensities of presumed vascular origin (*white arrows*). **d** T2* GRE showing diseminated cortical superficial siderosis of the right frontal and parietal sulci (*white oval*)

definitions for CMBs has been recognized [44, 45] as well as the critical role of technical aspects of imaging acquisition: higher field strength [46], choice of echo time [47] and optimised T2* GRE sequences [48] all increase sensitivity to CMBs. In addition, there is now evidence that SWI is superior to T2*GRE in detecting microhaemorrhages in a number of different patient cohorts, including patients with memory impairment [49], dementia [50] and CAA [48].

Consensus guidelines suggest that the term CMB is used to describe the radiological finding of small (<10 mm) ovoid or rounded regions which appear black on T2* gradient-recalled echo weighted or susceptibility-weighted imaging [45]. Although their radiological definition is established, given the complexity of possible mechanisms underlying CMBs, they may not be associated with the same risks of haemorrhage or ischaemia in all populations.

How Could CMBs be Associated with Bleeding Risk During Oral Anticoagulation?

It has been observed that in many cases, CMBs are direct extravasations of RBC through damaged vessel walls [27]. It is postulated that these usually self-limiting and asymptomatic leaks could evolve into a symptomatic macrohaemorrhage when haemostasis is impaired, such as during anticoagulation [19, 51]. For CMBs to be relevant for anticoagulation-related ICH, they must also be common in the populations likely to be exposed to these agents and must dynamically accumulate over time to allow the expansion of a new CMB into a symptomatic "macrobleed". There is now clear evidence that CMBs do indeed evolve dynamically over time in various populations including healthy community-dwelling older people [52], patients cared for at a memory clinic [53], ischaemic stroke patients [54, 55] (including specifically lacunar stroke) [56], ICH [57] and hypertensive patients [58]. The annual rate of accumulation of new CMBs per annum varies between about 2 % for healthy population-based studies [52], to 9 % in lacunar stroke [56] and nearly 40 % individuals with probable CAA [57].

CMBs in Healthy and Non-Stroke AF Populations

Prevalence, Dynamics and Associations

CMBs are common in healthy older populations, including those with AF but no stroke (Table 1). In four population-based studies, the prevalence of CMBs ranged from 4.7 % in the Framingham study [59] to 23.5 % in the Rotterdam study [60]—the high prevalence in the latter study likely reflecting the use of optimized imaging parameters. Studies in AF populations without symptomatic stroke show a CMB prevalence of 10–20 % [33, 44]. Age is consistently a strong risk factor for CMBs: in the Rotterdam study, prevalence was 17.8 % in persons aged 60–69 years, increasing to 38.3 % in those over 80 years. Cardiovascular risk factors, presence of lacunar infarcts and white matter lesions were associated with CMBs in a deep or infratentorial region, whereas APOE ε4 and diastolic blood pressure were related to CMBs in a strictly lobar location, supporting different aetiologies of CMBs depending on their distribution [33]. In a subset of the Rotterdam study, those with baseline CMBs were more likely to develop more CMBs (OR 5.83; 95 % CI 3.34 to 8.67), suggesting that baseline CMBs might identify those at risk of future intracerebral bleeding events. However, other predictors of new CMBs seem to differ according to location: incident deep CMBs are associated with cardiovascular risk factors, large white matter lesion volume and lacunar infarcts, whilst lobar CMBS were associated with Apo E ε4/ε4 genotype or large

Table 1 Prevalence of MRI markers of small vessel disease in different populations affected by AF

	Healthy populations	AF populations (without stroke)	Ischaemic stroke (with and without AF)	ICH (with and without AF)
CMBs	4.7–23.5 %* [59, 60]	10–20 % [33, 44]	29 % (7–32 % in AF related ischaemic stroke) [61, 62]	47–80 % [63, 64]
Moderate–severe white matter hyperintensities of presumed vascular origin	0.004–33 % [65, 66]**	Unknown	13–42 % [62, 67]	32 % in Lobar ICH [67]
cSS	0.7 % (all had lobar CMBs) [68]	Unknown, likely very rare	Unknown, likely very rare	Approximately 40–60 % in CAA related ICH 14.9 % in lobar or mixed ICH not meeting CAA criteria 4.6 % in Deep ICH [69, 70]

*Prevalence related to imaging techniques used

** Strongly age-dependent

CMBs cerebral microbleeds, *cSS* cortical/convexity superficial sidersosis

white matter lesion volumes [52]. These findings suggest that genetic or neuroimaging biomarkers could also have potential to predict ICH risk.

Other studies also show that CMBs are associated with incident stroke, including ICH, in healthy populations [71]. A Japanese study of 2,102 healthy volunteers (mean age 62.1) found CMBs were associated with both subsequent ICH (hazard ratio 50.2; 95 % CI 16.7 to 150.9) and ischaemic stroke (hazard ratio 4.48; 95 % CI 2.20 to 12.2). All ICH occurred in deep regions of the brain probably reflecting the high prevalence of hypertensive arteriopathy in Japanese populations. Another study observed that CMBs are associated with progression of ischaemic lesions in healthy populations [72]. Pre-existing CMBs in any location were associated with the development of lacunar strokes (OR 4.67; 95 % CI 1.84 to 11.85) whilst incident strictly lobar CMBs were associated with a progression of white matter disease (mean difference in WML volume (milliliters) increase: 0.41; 95 % CI 0.21 to 0.62), providing further evidence that CMBs are not solely a risk factor for ICH.

In the Rotterdam study, deep and infratentorial CMBs were associated with all-cause mortality (HR 1.90; 95 % CI 1.20 to 3.00), stroke mortality (HR 5.02 95 % CI 1.33 to 18.91) and cardiovascular mortality (HR 4.08; 95 % CI 1.78 to 9.39), whereas strictly lobar CMBs had no association with mortality. Similarly, more than 5 CMBs was associated with all-cause mortality (HR 2.76; 95 % CI 1.65–4.62) and stroke mortality (HR 6.87; 95 % CI 1.62 to 29.07) [73]. The association of deep CMBs and cardiovascular mortality likely reflects the risk factors "hypertensive arteriopathy" shares with systemic vascular disease (e.g. hypertension). Strictly lobar CMBs, on the other hand, are highly suggestive of CAA, a condition confined to the brain [74], so it is perhaps not surprising that they are not linked to cardiovascular mortality. The low number of stroke-related deaths (n=11) particularly ICH-related death (n=2) did not provide statistical power to assess any association between strictly lobar CMBs and stroke-related mortality in this population.

Relationship of CMBs to Anticoagulation

In a cross-sectional analysis of nearly 5,000 participants in the Rotterdam scan study, after adjusting for confounders, previous vitamin K antagonist (VKA) use was associated with deep or infratentorial CMBs only (OR 1.57; 95 % CI 1.10 to 2.25) [75]. A higher maximum anticoagulation intensity (measured by the INR) was also associated with deep or infratentorial CMBs. There was no association with strictly lobar CMBs and VKA use. In just over 3,000 patients who had follow-up MRI, there was a trend toward the development of any incident CMBs in those who had VKA exposure vs. those that did not (OR 1.67; 95 % CI 0.96–2.89). Recently, in a single centre hospital-based study of patients mainly with cognitive complaints (but not symptomatic stroke or dementia), those with strictly lobar CMBs without ICH had a similar high risk of subsequent ICH to patients with index CAA-associated ICH (5 cases vs 8.9 cases per 100 patient years, respectively); furthermore, warfarin use and increasing age were independent predictors of future ICH, although the number of ICH events was very small [76••]. Although this population came to the attention of neurologists for a variety of different reasons (and cannot therefore be considered a healthy population sample), the data may nonetheless be relevant to the use of anticoagulants in healthy older populations or those attending stroke or cognitive outpatient clinics.

In summary, CMBs are highly prevalent in healthy populations, and are strongly associated with age and cardiovascular risk factors. Deep CMBs appear to be more prevalent among VKA users. Those with strictly lobar CMBs have a high risk of subsequent ICH, which may be aggravated by anticoagulation. However, there is currently no convincing evidence to suggest that presence, number or location of CMBs should influence anticoagulation decisions in this population. Further larger prospective studies with longer follow-up after exposure to oral anticoagulants are required.

CMBs in Ischaemic Stroke and TIA Populations

Prevalence, Dynamics and Associations

About 1 in 5 ischaemic strokes is attributed to AF [77], making this a common setting for anticoagulation decisions. The prevalence of CMBs in a meta-analysis of published prospective ischaemic stroke or transient ischaemic attack (TIA) cohorts was 29 % [78••], with individual study prevalence estimates ranging from 7 to 32 % [61, 79]. Furthermore, CMB prevalence varies according to stroke subtype: a systematic review reported a CMBs prevalence in lacunar infarction of 53.5 % compared with 19.4 % in patients with cardioembolic infarction, and 36 % in patients with atherothrombotic infarction [44]. The same review found CMBs were more prevalent among recurrent strokes (44 %) than first-ever strokes (23 %) [44]. Another study suggested that CMBs are rare in TIAs in comparison to ischaemic stroke [80]. CMBs are associated with increasing age, hypertension, severe white matter disease and previous history of stroke in this population [78••]. The presence of baseline CMBs is a consistent risk factor for the development of further CMBs [44, 47, 75], suggesting, as in healthy older populations, that baseline CMBs may predict future ICH risk.

The most robust evidence to examine the risks CMBs contribute to the risk of ICH and ischaemic stroke in stroke cohorts is from prospective studies. A meta-analysis of 10 such studies found that the risk of any subsequent stroke was 2.2 times higher for those with CMBs (OR 2.25; 95 % CI 1.70 to

2.98). The risk was higher for ICH (OR 8.52; 95 % CI 4.23–17.18) than for ischaemic stroke (OR 1.55; 95 % CI 1.12–2.13) [78••]. When stratified by ethnicity, the risk of ICH was stronger for Asian populations (OR 10.43; 95 % CI 4.59 to 23.72) and weaker for Western populations (OR 3.87; 95 % CI 0.91 to 16.40). However, the risk of ICH in western cohorts was only based on 7 ICH events and should be interpreted with caution. Conversely, in this meta-analysis, the risk of ischaemic stroke became stronger in Western cohorts (OR 2.23; 95 % CI 1.29 to 3.85) and weaker in Asian cohorts (OR 1.30; 95 % CI 0.88 to 1.93). However, by contrast, two recent prospective studies from Korea both in TIA cohorts and both with 500 patients found that CMBs were independently associated with recurrent ischemia. One study found that CMBs were associated with ischaemic stroke mortality (risk hazard ratio, 3.66; 95 % CI 1.47–9.09) [62], whilst the other found that CMBs were predictors of recurrent ischaemic stroke after adjusting for confounding factors (HR 3.66; 95 % CI 1.47–9.09) [81]. There were no ICH cases in the latter study although follow-up was only 90 days. Further prospective studies and pooled analyses are clearly required to further clarify the rapidly developing evidence in this area.

Relationship of CMBs to Anticoagulation

Whether the above results are applicable to AF-related ischaemic stroke populations exposed to anticoagulants is not clear: six of the 10 studies included in the above meta-analysis had anticoagulation rates below 5 %; one study excluded cardioembolic strokes and 2 studies did not report on anticoagulant use. A recent Korean study examined CMBs and mortality in ischaemic stroke patients with AF where 98 % of their cohort received anticoagulation [62]. CMBs were associated with increased mortality (42 % vs. 32 %, $p<0.028$). Greater than or equal to 5 CMBs were associated with all-cause mortality (HR 1.99; $p=0.004$) and ischaemic stroke death (HR 3.39; $p=0.007$) but not ICH mortality. Mixed CMBs were associated with all-cause mortality (HR 1.62; $p=0.043$) and strictly lobar CMBs with ICH mortality (HR 5.91; $p=0.008$). As this study only reviewed mortality data, those patients who suffered either ischaemic strokes or ICH and survived were not included. A pooled analysis of ischaemic and ICH cohorts found that CMBs were associated with warfarin use in ICH cohorts but not in ischaemic stroke or TIA cohorts [82]. A more recent retrospective study in ischaemic stroke and TIA patients showed a higher prevalence of CMBs in those with previous oral anticoagulation versus those without (36.7 % vs. 22.8 %, $p=0.03$); these CMBs tended to be lobar [83]. Other longitudinal studies in stroke patients (predominantly ischaemic stroke) have failed to show an association between warfarin and CMB incidence [55, 84].

A study in an ischaemic stroke cohort investigated the risk/benefit of antithrombotic treatment in regard to CMB count [85]. They found the risk of ICH increased as number of CMBs increased: 0.6, 1.9, 4.6 and 7.6 % - for 0 CMBs, 1CMB, 2–4CMBs and ≥5 CMBs, respectively ($p<0.001$). The authors concluded that the high risk of mortality and ICH in those with ≥5 CMBs outweighed the modest protective effect of antithrombotic agents. However, we cannot generalise this to AF populations treated with anticoagulants: this was a single centre study from Hong Kong; 82.5 % of CMBs were deep or mixed suggesting a high prevalence of hypertensive arteriopathy and only 4.3 % were on a vitamin K antagonist (92.5 % were taking a single antiplatelet agent).

In summary, in ischaemic stroke and TIA populations (to date mainly from Asia), CMBs are associated with both future ICH risk and ischaemic stroke risk. The balance of ICH and ischaemic stroke may vary with ethnicity, but more data are needed. Only very limited data are available on the effect of anticoagulation in this population. There is a trend to suggest 5 or more CMBs maybe signify a higher risk of mortality; one paper found this was driven by ICH whilst the other did not [62, 85]. Strictly lobar CMBs, signifying probable CAA, are associated with an increased risk of ICH-related mortality [62, 86]. There is currently not enough evidence to base anticoagulant decisions on CMB presence, location or numbers in this patient population. Prospective large cohort studies of ischaemic stroke and TIA cohorts (especially from non-Asian populations) - and, ideally, large-scale mata-analyses - with evaluation of CMBs at baseline are needed to determine the value of CMBs in ICH risk prediction [19].

CMBs in Intracerebral Haemorrhage

Prevalence, Dynamics and Associations

Studies in spontaneous ICH cases with MRI show a CMB prevalence from 23 [22] to 90 % [87]. The pooled prevalence from 15 such studies was 60.4 % [44]. CMBs are associated with older age, hypertension, antithrombotic or anticoagulant use, lacunar stroke and leukoaraiosis in this population [63, 88]. Cross-sectional studies show a significant association between CMBs and ICH [63, 89, 90]; furthermore, CMBs are more common in those with recurrent stroke (82.5 %; 95 % CI 70.6–90.2 %) than first-ever stroke (51.8 %; 95 % CI 47.3–56 %) [44]. Two studies suggest a regional relationship between CMBs and future ICH [63, 91]—that is, ICH occurs at site of previous CMBs - although this was not replicated in another study [43].

A causal relationship between CMBs and ICH can only be shown in longitudinal studies. Lobar ICH has a higher risk of recurrent ICH than deep ICH [92–95], and lobar ICH is a risk factor for recurrent ICH [93, 94]. Most studies regarding CMBs and ICH have been in lobar ICH, which reveal increasing ICH risk with increasing baseline CMB burden [57, 92,

96]. One study showed a cumulative graded effect; 1, 2, 3 to 5, or ≥6 baseline CMBs corresponding to a 3-year cumulative risk of symptomatic ICH of 14, 17, 38, and 51 %, respectively (p=0.003) [57]. The risk of symptomatic ICH was greater if new CMBs were found during follow-up. The association between CMBs and future ICH risk after deep ICH is less clear; one study of 80 deep ICH survivors was not able to draw any meaningful conclusions in respect of CMBs due to a low recurrence rate of ICH [92], while another study of ICH survivors (97 % attributed to hypertension) found that the number of baseline CMBs was significantly associated with recurrent ICH (p<0.0001) [97]. This last study defined recurrent ICH as "a newly appearing dark signal with a diameter >5 mm with or without corresponding symptoms on GRE"; thus, some of the "recurrent ICH" may not have been clinically significant and merely recurrent CMBs.

Relationship of CMBs to Anticoagulation

There are few data on the interaction between anticoagulation and CMBs in ICH cohorts. Most available evidence is from cross sectional studies, which can only show association (with inevitable measured and unmeasured confounding factors) and not its causal direction. Nevertheless, in a cross-sectional study of warfarin users, CMBs were more prevalent in those with ICH versus those without (79 % vs. 22 %; p<0.001) [90] One further cross-sectional study of warfarin-associated ICH versus those on warfarin without ICH found after controlling for other variables associated with ICH, carriers of the ε2 allele had an OR of 3.8 (95 % CI 1.0 to 14.6) for lobar ICH [98]. Whilst this study did not specifically look at CMBs, the APOE ε2 allele is strongly associated with CAA, for which lobar CMBs are a specific marker. A pooled analysis of ICH cohorts also found an excess of CMBs in warfarin users versus non-users with ICH (OR 2.7; 95 % CI 1.6–4.4; p<0.001) [82]. A longitudinal study showed that in patients with ≥3 deep CMBs, warfarin use was associated with an increased incidence of deep ICH (14 % vs. 4 %; p=0.047) [99]; however, this was in a mixture of both ICH and ischaemic stroke patients in which ICH only made up 23 % of the cohort.

A decision analysis (based on best estimates rather than true prospective data and model validation) suggested that in lobar ICH a "do not anticoagulate" strategy leads to more favourable quality adjusted life years than an "anticoagulate" strategy (5.4 vs. 3.5); furthermore, available data suggests that whilst anticoagulation would prevent roughly 31 cardioembolic strokes per 1,000 lobar ICH patients in this setting, it is at the cost of 150 additional ICHs during the first year of treatment [95]. Since CMBs burden at baseline shows a graded relationship to the risk of recurrent ICH in patients with lobar ICH, the presence of CMBs may further tip the balance of net benefit away from anticoagulation [57]. The evidence for deep ICH is less clear, perhaps reflecting the lower recurrence of ICH in this group. The same decision analysis used above, based on an overall estimated recurrent ICH rate of 2.1 % per patient year for deep ICH concluded anticoagulation may benefit those with deep ICH if they carried a high risk of cardioembolism (>6.5 % per year; CHA(2)DS(2)VASC ≥5), or a low risk of recurrent ICH (<1.4 % per year) [95]. Nevertheless, the risk of recurrent ICH after deep ICH may exceed 1.4 % (2.3 % per year in one study) [93], especially in the presence of multiple CMBs [99] and has up to 73 % mortality [93].

Recent "real world" data somewhat contradicts the above decision analysis; a large German registry of 566 patients with AF and ICH [100••] found that patients resumed on anticoagulants had significantly reduced ischaemic events (5.5 % vs. 14.9 % p=0.08) and reduced mortality (HR 0.26; 95 % CI 0.13 to 0.53) with no significant effect on ICH recurrence (7.3 % vs. 5.7 %, p=0.53). A Danish registry study [100••] of over 1,000 patients with ICH and AF also noted that those with OAC resumption had reduced ischaemic complications (adjusted HR 0.52, 95 % CI 0.25–1.08), mortality (adjusted HR 0.49, 95 % CI 0.33–0.74) with no increase in "major bleeding". Neither study presented outcomes stratified by baseline ICH location (lobar or non-lobar) or diagnosis of likely underlying arteriopathy using MRI; further studies are required to investigate how baseline ICH characteristics and etiology might influence the future balance of ICH and ischaemic events or mortality.

Lobar ICH has a higher risk of ICH recurrence than deep ICH [92–94, 101]. In particular, in those with lobar ICH and strictly lobar CMBs (and a high probability of CAA), the risk of oral anticoagulation may outweigh the benefit on ischaemic stroke reduction. However, there are currently no randomised trials to support this, and such trials are likely to be challenging. In non-CAA related ICH, including deep ICH, the risks of future ICH and ischaemic stroke may be more finely balanced. If starting or restarting anticoagulation is necessary after ICH the optimal timing is unknown. In one study of 177 survivors of warfarin-ICH, 59 patients resumed warfarin after a median of 5.6 weeks (IQR 2.6–17). The hazard ratio for recurrent ICH with resumption of warfarin was 5.6 (95 % CI 1.8–17.2), and for ischemic stroke, it was 0.11 (95 % CI 0.014–0.89). The combined risk of recurrent intracranial haemorrhage or ischemic stroke was lowest if warfarin was resumed after approximately 10 to 30 weeks [102]. In some situations, anticoagulation may be needed more urgently (e.g. pulmonary embolism), and in this situation, it is reasonable to consider starting treatment once acute bleeding is likely to have stopped (e.g. after a few days). Alternatives to vitamin K antagonists should be considered such as NOACs, which have a ~50 % lower risk of ICH in AF cohorts [103••]. A small observational cohort study suggested that left atrial appendage occlusion devices are safe after ICH, and this may also be a reasonable option in those judged to be at high risk of ICH

[104]. A randomized controlled trial of NOACs versus standard care (antiplatelets or no treatment) in ICH survivors with an indication for oral anticoagulation is currently underway (APACHE-AF) and in cases of clinical equipoise enrolment into this or similar studies should be considered.

Other Markers of SVD and Risk of ICH

Other non-CMB markers of small vessel disease seen on MRI may also be associated with increased ICH risk with implications for anticoagulation use. White matter hyperintensities (WMH) of presumed vascular origin (Fig. 1c) are associated with an increased risk of ICH in both ischaemic stroke [67, 105] and ICH cohorts [106]. The relationship between CMBs, WMHs and recurrent stroke was evaluated in two studies [107, 108], which showed CMBs without advanced WMHs are associated with increased risk of ICH whilst CMBs with advanced WMHs are not. Interestingly, in those with advanced WMHs without CMBs, there were no ICH events [107]. By contrast, a recent Korean TIA registry study suggested that CMBs are a stronger predictor for future ischaemic stroke risk than are WMH [81]. There is currently no evidence to suggest anticoagulant decisions should be based on WMH even in the context of CMBs.

Cortical superficial siderosis (cSS) describes linear residues of blood in the superficial layers of the cerebral cortex seen on blood-sensitive MRI techniques [109] (Fig. 1d). cSS is common in CAA related ICH (40–47 %) but rarer in other forms of ICH (4.6–15 %) [69, 110]; it is rare (<1 % prevalence) in the general population [68]. cSS has recently been validated as a diagnostic marker of CAA [69]. Two studies have shown that cSS (in the context of CAA) is a significant independent risk factor for intraparenchymal ICH and intracranial haemorrhage [110, 111]. The most recent study revealed ICH rate at 4 years was 25 % (95 % CI 7.6–28.3 %) for patients without siderosis, 28.9 % (95 % CI 7.7–76.7 %) for patients with focal siderosis and 74 % (95 % CI 44.1–95.7) for patients with disseminated cSS (defined as siderosis in more than 3 sulci). The majority of patients (88 %) with CAA in this trial initially presented with ICH; thus, the risk of subsequent ICH in CAA patients without ICH is less clear. cSS in the context of CAA may, thus, be a powerful imaging marker of future ICH risk. In patients with ICH, anticoagulation should probably be avoided in the presence of disseminated cSS attributed to CAA.

Current Scoring Systems for Ischaemic Stroke and Bleeding Risk in Atrial Fibrillation: Could Cerebral Microbleeds Improve Risk Prediction?

The commonly used scoring systems to aid anticoagulation decisions in AF are CHADS2, CHA(2)DS(2)VASC, HAS-BLED, ATRIA and HEMORR(2)HAGES. None were primarily designed to predict ICH, and many of the component variables (heart failure, diabetes, renal failure, liver disease, anaemia or platelet/coagulation defect, alcohol abuse and malignancy) are not consistent significant predictors of ICH [112]. Of the commonly used bleeding risk scores, only HASBLED has demonstrated a significant predictive performance for ICH [113]. Furthermore, both the bleeding risk scores (e.g. HASBLED) and the ischaemic stroke risk scores (e.g. CHA(2)DS(2)VASC) share similar predictor variables (e.g. hypertension, age, previous stroke) and are correlated.

A retrospective Korean study in 550 ischaemic stroke patients with AF found that higher CHADS2 and CHA(2)DS(2)VASC scores were associated with the presence and number of CMBs. This trend was true for both lobar and deep CMBs. However, recurrent ICH was only associated with CMBs (HR 3.79; 95 % CI 1.09 to 13.15) and not CHADS2 or CHA(2)DS(2)VASC scores, suggesting that neuroimaging of CMBs might have better predictive value for ICH than the existing clinical scores. Further large prospective studies are needed to investigate how adding neuroimaging or other biomarker data might improve the accuracy of both bleeding and ischaemia prediction models.

A patient-specific scoring model for AF has suggested in a patient without prior stroke, anticoagulation was preferred if there was a moderate risk (4.5 %/year) of thromboembolism, regardless of the presence of CMBs [114]. This was based on the assumption that CMBs conferred a twofold risk for ICH and did not consider number or location of CMBs. However, if CMBs were found to confer a 3.2-fold risk of ICH, MRI screening for CMBs would be beneficial in patients at lower risk for thromboembolism (e.g. 1.5 %/year) [114]. Recent pooled estimates in ischaemic stroke and TIA cohorts suggest that CMBs may confer a higher hazard than estimated in this paper (n=3,067; overall odds ratio for ICH 8.52; 95 % CI 4.23–17.18, p=0.007) [78••]

Future Directions

Ongoing Observational Studies of CMBs and Anticoagulation

Further longitudinal studies are required before MR brain imaging can be used to guide anticoagulation decisions. To our knowledge, there are four such prospective cohort studies underway, two in Europe, both recruiting over 1,000 patients with ischaemic stroke or TIA: The Clinical Relevance of Microbleeds in Stroke (CROMIS-2) [19] and Intracerebral Haemorrhage Due to Oral Anticoagulants: Prediction of the Risk by Magnetic Resonance (HERO) (https://clinicaltrials.gov/ct2/show/NCT02238470); and two in Asia: Intracerebral Haemorrhage in Patients Taking Oral Anticoagulant for Atrial

Table 2 Suggested recommendations on anticoagulation decisions in different AF populations based on available evidence

	Healthy older population		Ischaemic stroke		Lobar ICH		Deep ICH	
	Evidence	Recommendations	Evidence	Recommendations	Evidence	Recommendations	Evidence	Recommendations
CMBs present	Associated with both IS and ICH [52, 71, 75]	Best practice oral anticoagulation according to existing ischaemia and bleeding risk scores (e.g. CHADS2 and CHADS(2)VASC) and HASBLED)	Risk of both IS (overall OR 2.3) and ICH (overall OR 8.5) [78••] Associated with increased all cause mortality [62]	Best practice oral anticoagulation according to existing ischaemia and bleeding risk scores (e.g. CHAD S2 and CHAD S(2)VASC) and HASBLED). Enrol into observational studies, e.g. CROMIS-2	High risk of ICH recurrence regardless of CMBs (2-year recurrence rate 15–22 %) [92, 95, 96] CMB number associated with increasing risk of recurrent ICH in CAA [57, 92]	Consider avoiding long-term oral anticoagulation [95] Consider enroling into trials such as APACHE-AF Consider LAA occlusion device if thromboembolic risk is high	No reliable evidence exists. Rate of recurrence ~2 % per year [93], may be increased by CMBs (~3-fold increase if >3 CMBs [93].	Decision model suggests anticoagulation preferred if <3 CMBs and cardioembolic risk high (>6.5 % per year) [95]. Recent observational data suggest anticoagulation may be preferred in most patients [100••] Consider LAA occlusion device if bleeding risk judged to be high (e.g. high HASBLED score, many CMBs, poorly controlled hypertension, etc.) Consider enroling into trials such as APACHE-AF
Strictly lobar CMBs	Associated with ICH [76••] Associated with IS [72] If >5 CMBs increased risk of all cause and stroke related mortality.	Best practice oral anticoagulation according to existing risk scores (e.g. CHADS2, CHADS(2)VASC and HASBLED)	Associated with ICH mortality [62] If >5 CMBs Risk of ICH 7.5 %/year [85]	Best practice anticoagulation oral anticoagulation according to existing ischaemia and bleeding risk scores (e.g. CHAD S2 and CHAD S(2)VASC) and HASBLED). Enroll into observational studies, e.g. CROMIS-2	Increased hazard ratio of ICH if multiple [96]. For >5 CMBs increased risk of ICH compared with no CMBs (in CAA cohort; HR 5.25; $p<0.001$) [96] 3-year cumulative risk 51 % for recurrent ICH [57]	These patients have probable CAA. Suggest avoid long-term oral anticoagulation, especially if multiple CMBs present. Consider LAA occlusion device if thromboembolic risk is high	No reliable evidence exists	Consider enroling into trials such as APACHE-AF Consider anticoagulation if cardioembolic risk high (>6.5 % per year) [95] Consider LAA occlusion device if risk of future ICH judged to be high

ICH intracerebral haemorrahge, *IS* ischaemic stroke, *LAA* left atrial appendage, *LAA* left atrial appendage, *CMBs* cerebral microbleed, *cSS* convexity/cortical superficial siderosis, *CAA* cerebral amyloid angiography

Fibrillation with Cerebral Microbleeds (IPAAC-warfarin) and its counterpart using NOACs (IPAAC-NOAC) [115]. The major challenge with these studies is that the outcome of interest (ICH) is rare, requiring large numbers of patients followed up for a long period of time to provide enough statistical power. Nevertheless, pooling data from these large cohort studies should provide strong data on the additional predictive value provided by including neuroimaging data in risk scores.

Minimizing the Risk of ICH Using Non-VKA Treatments

Both NOACs and left atrial appendage (LAA) occlusion devices have been shown to be as efficacious as warfarin in preventing cardio embolic stroke in AF [103••, 116, 117]. A recent meta-analysis of phase 3 randomised control trials shows NOACs to have a reduced risk of stroke and systemic embolism compared with warfarin (RR 0.81, 95 % CI 0.73–0.91; $p<0.0001$) and significantly reduced all-cause mortality (RR 0.90, 95 % CI 0.85–0.95; $p=0.0003$) and intracranial haemorrhage (RR 0.48, 0.39 to 0.59; $p<0.0001$) [103••]. However, trial patients may be younger, healthier and more compliant with medications; thus, we may to be able to generalise to patients with CMBs who are often older and suffer from hypertension. There have been concerns that in the absence of any specific antidote, NOAC-related ICH may be larger and have poorer outcome than VKA-ICH. Few data are available, but a small study from Japan comparing rivaroxaban-related ICH to warfarin-related ICH found rivaroxaban had smaller haemorrhages compared with warfarin (median, 4 mL versus 11 mL; $p=0.03$) despite the rivaroxaban subgroup having more CMBs [118]. These findings need to be replicated in larger cohorts.

Left atrial occlusion devices have similar efficacy to warfarin in preventing cardioembolic stroke, at least over follow-up for up to several years [117]. LAA devices, as the name suggests, occlude the left atrial appendage, which echocardiography studies suggest may account for 90 % of emboli in AF-related stroke [119]. As these devices only require a short period of anticoagulation or antiplatelet therapy, the risk of subsequent ICH is lower than a long-term oral anticoagulation

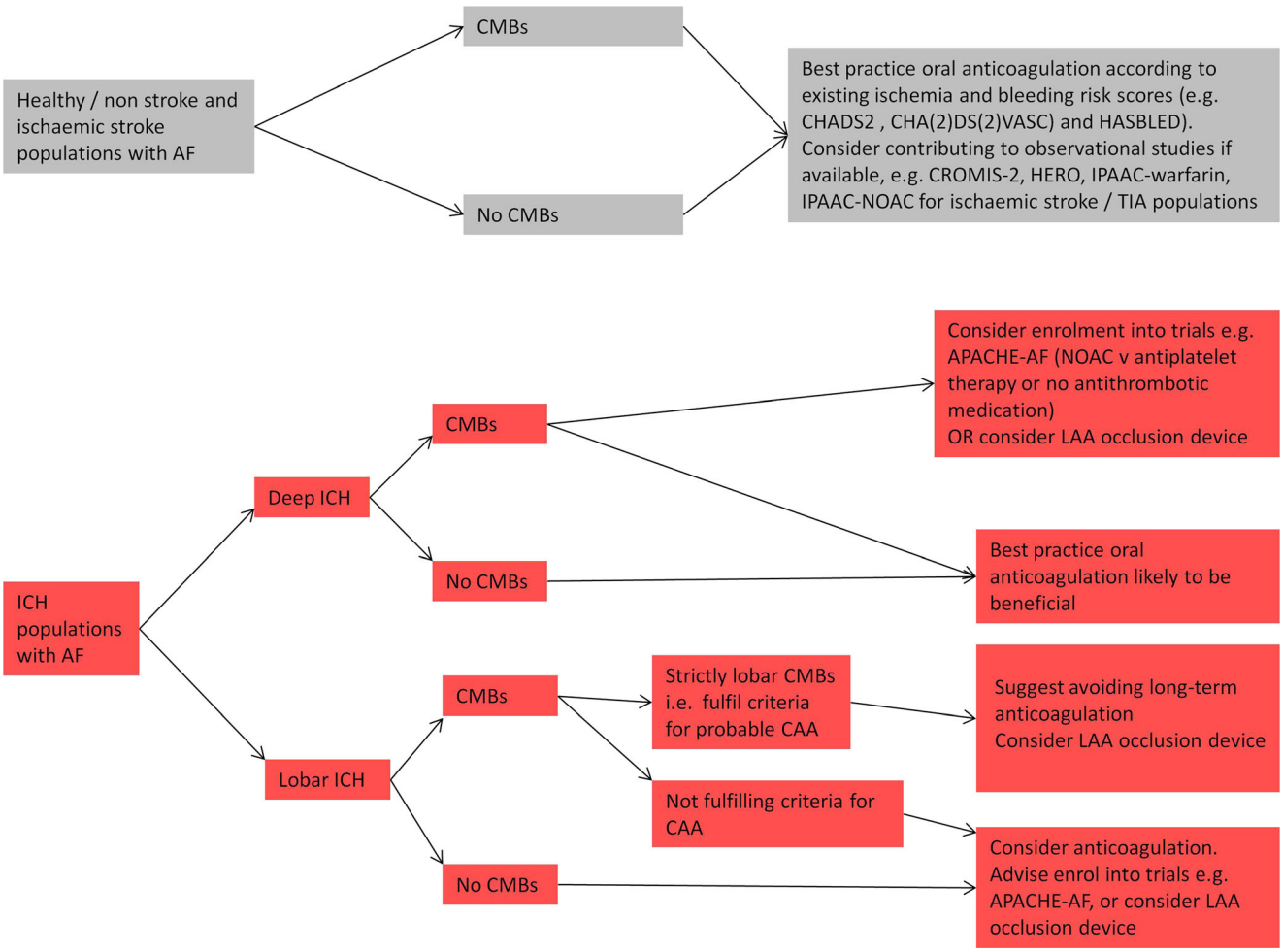

Fig. 2 Flow chart showing authors' recommendations on anticoagulation decisions in different AF populations based on evidence available with different imaging markers. *ICH* intracerebral haemorrhage, *LAA* left atrial appendage, *CMBs* cerebral microbleed. For supporting evidence, see Table 2

with warfarin (RR 0.15; 95 % CI 0.03–0.49) [117]. This approach seems attractive for patients at high risk of ICH on long-term oral anticoagulation (e.g. those with ICH due to bleeding-prone arteriopathies [CAA and hypertensive arteriopathy]), but no randomized controlled studies have been undertaken. One observational study reviewed the safety of LAA occlusion devices in those with ICH and AF. The mean CHA(2)DS(2)VASC and HASBLED scores were 4.5 and 4.7, respectively. Patients received dual antiplatelet medication (aspirin 100 mg/day and clopidogrel 75 mg/day) for 3 months, followed by aspirin monotherapy thereafter. There were no ICH or ischaemic events after a 1-year follow-up [104]. These data suggest that LAA occlusion may be a reasonable option in ICH survivors in whom the risk of recurrent ICH on long-term oral anticoagulation is judged to be unacceptably high.

The Challenge of Anticoagulation in AF Associated with ICH

More data are needed to guide the decision of whether to start anticoagulation after ICH, ideally from randomized controlled trials. APACHE-AF (http://apache-af.nl/) is currently underway in the Netherlands and will randomize patients with AF and a recent ICH to apixaban or standard care (antiplatelet therapy or no antithrombotic medication). Trials of anticoagulation after ICH may be challenging to perform, as clinicians may not have equipoise in some patients, for example those with probable CAA in whom any aggravation of future ICH risk may be considered unacceptable.

Conclusions

CMBs are common in patients likely to be exposed to anticoagulant drugs, including healthy elderly and stroke cohorts. CMBs are a marker of small vessel disease, and in the majority of cases, seem to be due to extravasation of blood from damaged small vessels. The distribution of CMBs is a useful guide to the likely underlying small vessel arteriopathy: strictly lobar CMBs have high specificity for CAA, while deep CMBs likely reflect hypertensive arteriopathy. Since CAA typically spares the deep structures, a mixed pattern may reflect either a mixture of pathologies (hypertensive arteriopathy and CAA) or advanced and anatomically widespread hypertensive arteriopathy. There is clear evidence that CMBs dynamically evolve over time in all populations so far studied (including healthy older populations, memory and cognitive clinic, and stroke patients), and that baseline CMBs are associated with an increased risk of incident CMBs over time. CMBs in patients with ischaemic stroke or TIA are associated with an increased risk of future stroke, with most studies suggesting an increased risk for ICH greater than that for ischaemic stroke. CMBs also predict the risk of recurrent ICH after an index ICH. There may be ethnic differences in risk associated with CMBs, but further studies are required. Although cross-sectional studies suggest an association between anticoagulant exposure and CMBs, there are currently no large-scale prospective follow-up studies available on CMBs in patients treated with anticoagulation. CMBs are one of many MRI markers of small vessel disease; other emerging markers include cortical superficial siderosis, which seems to be a characteristic of CAA and a high risk of future ICH, especially if disseminated.

Given the lack of available high quality evidence, it is currently not possible to make clear evidence-based recommendations of how CMBs should influence treatment decisions in patients with AF. Nevertheless, Table 2 provides a summary of opinion-based recommendations, based on the available supporting evidence. A simple figure with suggested options is also presented (Fig. 2).

Compliance with Ethics Guidelines

Conflict of Interest D Wilson and HR Jäger declare no conflicts of interest. DJ Werring has received fees from Bayer for advisory board participation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham heart study. Circulation. 2004;110(9):1042–6.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119–25.
3. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke J Cereb Circ. 2005;36(6):1115–9.
4. Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. Heart. 2014;100(5):396–405.
5. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses. Stroke J Cereb Circ. 1995;26(8):1471–7.
6. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115(21):2689–96.

7. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med. 2007;120(8):700–5.
8. Dowlatshahi D, Butcher KS, Asdaghi N, Nahirniak S, Bernbaum ML, Giulivi A, et al. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke J Cereb Circ. 2012;43(7):1812–7.
9. Bejot Y, Cordonnier C, Durier J, Aboa-Eboule C, Rouaud O, Giroud M. Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study. Brain J Neurol. 2013;136(Pt 2):658–64.
10. Lovelock CE, Molyneux AJ, Rothwell PM, Oxford Vascular S. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. Lancet Neurol. 2007;6(6):487–93.
11. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007;68(2):116–21.
12. Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. J Neurol Neurosurg Psychiatry. 2012;83(2):124–37.
13. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. JAMA J Am Med Assoc. 2001;285(22):2864–70.
14. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the euro heart survey. Chest. 2010;138(5):1093–100.
15. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] working group on thrombosis. Thromb Haemost. 2011;106(6):997–1011.
16. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
17. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
18. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
19. Charidimou A, Shakeshaft C, Werring DJ. Cerebral microbleeds on magnetic resonance imaging and anticoagulant-associated intracerebral hemorrhage risk. Front Neurol. 2012;3:133.
20. Haeusler KG, Wilson D, Fiebach JB, Kirchhof P, Werring DJ. Brain MRI to personalise atrial fibrillation therapy: current evidence and perspectives. Heart. 2014;100(18):1408–13.
21. Fisher M. MRI screening for chronic anticoagulation in atrial fibrillation. Front Neurol. 2013;4:137.
22. Offenbacher H, Fazekas F, Schmidt R, Koch M, Fazekas G, Kapeller P. MR of cerebral abnormalities concomitant with primary intracerebral hematomas. AJNR Am J Neuroradiol. 1996;17(3):573–8.
23. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol. 1999;20(4):637–42.
24. Tanaka A, Ueno Y, Nakayama Y, Takano K, Takebayashi S. Small chronic hemorrhages and ischemic lesions in association with spontaneous intracerebral hematomas. Stroke J Cereb Circ. 1999;30(8):1637–42.
25. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001;56(4):537–9.
26. Reijmer YD, Fotiadis P, Martinez-Ramirez S, Salat DH, Schultz A, Shoamanesh A, et al. Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. Brain J Neurol. 2014.
27. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovasc Dis. 2011;32(6):528–34.
28. Schommer K, Kallenberg K, Lutz K, Bartsch P, Knauth M. Hemosiderin deposition in the brain as footprint of high-altitude cerebral edema. Neurology. 2013;81(20):1776–9.
29. 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 magnetic resonance imaging (MRI) microbleeds. Neuropathol Appl Neurobiol. 2014;40(3):258–69.
30. 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. Sci Transl Med. 2014;6(226):226ra31.
31. Tanskanen M, Makela M, Myllykangas L, Rastas S, Sulkava R, Paetau A. Intracerebral hemorrhage in the oldest old: a population-based study (vantaa 85+). Front Neurol. 2012;3:103.
32. Fisher M. Cerebral microbleeds: where are we now? Neurology. 2014;83(15):1304–5.
33. Poels MM, Vernooij MW, Ikram MA, Hofman A, Krestin GP, van der Lugt A, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke J Cereb Circ. 2010;41(10 Suppl):S103–6.
34. Dierksen GA, Skehan ME, Khan MA, Jeng J, Nandigam RN, Becker JA, et al. Spatial relation between microbleeds and amyloid deposits in amyloid angiopathy. Ann Neurol. 2010;68(4):545–8.
35. Fisher CM. The arterial lesions underlying lacunes. Acta Neuropathol. 1968;12(1):1–15.
36. Park JH, Seo SW, Kim C, Kim GH, Noh HJ, Kim ST, et al. Pathogenesis of cerebral microbleeds: in vivo imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment. Ann Neurol. 2013;73(5):584–93.
37. Smith EE, Nandigam KR, Chen YW, Jeng J, Salat D, Halpin A, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. Stroke J Cereb Circ. 2010;41(9):1933–8.
38. Ritter MA, Droste DW, Hegedus K, Szepesi R, Nabavi DG, Csiba L, et al. Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. Neurology. 2005;64(7):1233–7.
39. Roob G, Schmidt R, Kapeller P, Lechner A, Hartung HP, Fazekas F. MRI evidence of past cerebral microbleeds in a healthy elderly population. Neurology. 1999;52(5):991–4.
40. Hanyu H, Tanaka Y, Shimizu S, Takasaki M, Abe K. Cerebral microbleeds in Alzheimer's disease. J Neurol. 2003;250(12):1496–7.
41. Hanyu H, Tanaka Y, Shimizu S, Takasaki M, Fujita H, Kaneko N, et al. Cerebral microbleeds in Binswanger's disease: a gradient-echo T2*-weighted magnetic resonance imaging study. Neurosci Lett. 2003;340(3):213–6.
42. Kato H, Izumiyama M, Izumiyama K, Takahashi A, Itoyama Y. Silent cerebral microbleeds on T2*-weighted MRI: correlation with stroke subtype, stroke recurrence, and leukoaraiosis. Stroke J Cereb Circ. 2002;33(6):1536–40.
43. Roob G, Lechner A, Schmidt R, Flooh E, Hartung HP, Fazekas F. Frequency and location of microbleeds in patients with primary

intracerebral hemorrhage. Stroke J Cereb Circ. 2000;31(11):2665–9.
44. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain J Neurol. 2007;130(Pt 8):1988–2003.
45. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165–74.
46. Stehling C, Wersching H, Kloska SP, Kirchhof P, Ring J, Nassenstein I, et al. Detection of asymptomatic cerebral microbleeds: a comparative study at 1.5 and 3.0 T. Acad Radiol. 2008;15(7):895–900.
47. Gregoire SM, Werring DJ, Chaudhary UJ, Thornton JS, Brown MM, Yousry TA, et al. Choice of echo time on GRE T2*-weighted MRI influences the classification of brain microbleeds. Clin Radiol. 2010;65(5):391–4.
48. Cheng AL, Batool S, McCreary CR, Lauzon ML, Frayne R, Goyal M, et al. Susceptibility-weighted imaging is more reliable than T2*-weighted gradient-recalled echo MRI for detecting microbleeds. Stroke J Cereb Circ. 2013;44(10):2782–6.
49. Goos JD, van der Flier WM, Knol DL, Pouwels PJ, Scheltens P, Barkhof F, et al. Clinical relevance of improved microbleed detection by susceptibility-weighted magnetic resonance imaging. Stroke J Cereb Circ. 2011;42(7):1894–900.
50. Shams S, Martola J, Cavallin L, Granberg T, Shams M, Aspelin P, et al. SWI or T2*: which MRI sequence to use in the detection of cerebral microbleeds? The karolinska imaging dementia study. AJNR. 2015.
51. Kakar P, Charidimou A, Werring DJ. Cerebral microbleeds: a new dilemma in stroke medicine. JRSM Cardiovasc Dis. 2012;1(8):2048004012474754.
52. Poels MM, Ikram MA, van der Lugt A, Hofman A, Krestin GP, Breteler MM, et al. Incidence of cerebral microbleeds in the general population: the Rotterdam scan study. Stroke J Cereb Circ. 2011;42(3):656–61.
53. Goos JD, Henneman WJ, Sluimer JD, Vrenken H, Sluimer IC, Barkhof F, et al. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. Neurology. 2010;74(24):1954–60.
54. Gregoire SM, Brown MM, Kallis C, Jager HR, Yousry TA, Werring DJ. MRI detection of new microbleeds in patients with ischemic stroke: five-year cohort follow-up study. Stroke J Cereb Circ. 2010;41(1):184–6.
55. Lee SH, Lee ST, Kim BJ, Park HK, Kim CK, Jung KH, et al. Dynamic temporal change of cerebral microbleeds: long-term follow-up MRI study. PLoS One. 2011;6(10), e25930.
56. Klarenbeek P, van Oostenbrugge RJ, Rouhl RP, Knottnerus IL, Staals J. Higher ambulatory blood pressure relates to new cerebral microbleeds: 2-year follow-up study in lacunar stroke patients. Stroke J Cereb Circ. 2013;44(4):978–83.
57. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke J Cereb Circ. 2004;35(6):1415–20.
58. van Dooren M, Staals J, de Leeuw PW, Kroon AA, Henskens LH, van Oostenbrugge RJ. Progression of brain microbleeds in essential hypertensive patients: a 2-year follow-up study. Am J Hypertens. 2014;27(8):1045–51.
59. Jeerakathil T, Wolf PA, Beiser A, Hald JK, Au R, Kase CS, et al. Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham study. Stroke J Cereb Circ. 2004;35(8):1831–5.
60. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam scan study. Neurology. 2008;70(14):1208–14.
61. Chatzikonstantinou A, Willmann O, Szabo K, Hennerici MG. Cerebral microbleeds are uncommon in ischemic stroke associated with nonvalvular atrial fibrillation. J Neuroimaging Off J Am Soc Neuroimaging. 2011;21(2):103–7.
62. Song TJ, Kim J, Song D, Nam HS, Kim YD, Lee HS, et al. Association of cerebral microbleeds with mortality in stroke patients having atrial fibrillation. Neurology. 2014;83(15):1308–15.
63. Lee SH, Bae HJ, Kwon SJ, Kim H, Kim YH, Yoon BW, et al. Cerebral microbleeds are regionally associated with intracerebral hemorrhage. Neurology. 2004;62(1):72–6.
64. Naka H, Nomura E, Wakabayashi S, Kajikawa H, Kohriyama T, Mimori Y, et al. Frequency of asymptomatic microbleeds on T2*-weighted MR images of patients with recurrent stroke: association with combination of stroke subtypes and leukoaraiosis. AJNR Am J Neuroradiol. 2004;25(5):714–9.
65. Li L, Simoni M, Kuker W, Schulz UG, Christie S, Wilcock GK, et al. Population-based case–control study of white matter changes on brain imaging in transient ischemic attack and ischemic stroke. Stroke J Cereb Circ. 2013;44(11):3063–70.
66. Hopkins RO, Beck CJ, Burnett DL, Weaver LK, Victoroff J, Bigler ED. Prevalence of white matter hyperintensities in a young healthy population. J Neuroimaging Off J Am Soc Neuroimaging. 2006;16(3):243–51.
67. Smith EE, Rosand J, Knudsen KA, Hylek EM, Greenberg SM. Leukoaraiosis is associated with warfarin-related hemorrhage following ischemic stroke. Neurology. 2002;59(2):193–7.
68. Vernooij MW, Ikram MA, Hofman A, Krestin GP, Breteler MM, van der Lugt A. Superficial siderosis in the general population. Neurology. 2009;73(3):202–5.
69. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17):1346–50.
70. Charidimou A, Jager RH, Fox Z, Peeters A, Vandermeeren Y, Laloux P, et al. Prevalence and mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy. Neurology. 2013;81(7):626–32.
71. Bokura H, Saika R, Yamaguchi T, Nagai A, Oguro H, Kobayashi S, et al. Microbleeds are associated with subsequent hemorrhagic and ischemic stroke in healthy elderly individuals. Stroke J Cereb Circ. 2011;42(7):1867–71.
72. Akoudad S, Ikram MA, Koudstaal PJ, Hofman A, Niessen WJ, Greenberg SM, et al. Cerebral microbleeds are associated with the progression of ischemic vascular lesions. Cerebrovasc Dis. 2014;37(5):382–8.
73. Akoudad S, Ikram MA, Koudstaal PJ, Hofman A, van der Lugt A, Vernooij MW. Cerebral microbleeds and the risk of mortality in the general population. Eur J Epidemiol. 2013;28(10):815–21.
74. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Ann Neurol. 2011;70(6):871–80.
75. Akoudad S, Darweesh SK, Leening MJ, Koudstaal PJ, Hofman A, van der Lugt A, et al. Use of coumarin anticoagulants and cerebral microbleeds in the general population. Stroke J Cereb Circ. 2014;45(11):3436–9.
76.•• van Etten ES, Auriel E, Haley KE, Ayres AM, Vashkevich A, Schwab KM, et al. Incidence of symptomatic hemorrhage in patients with lobar microbleeds. Stroke J Cereb Circ. 2014;45(8):2280–5. **Study suggests patents with CMB without ICH carry a similar risk to those with CMB and ICH for recurent ICH**.
77. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke J Cereb Circ. 1991;22(8):983–8.
78.•• Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and recurrent stroke risk: systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts.

Stroke J Cereb Circ. 2013;44(4):995–1001. **Meta analysis on prospective stroke cohorts outlining risk of stroke with CMBs**.
79. Song TJ, Kim J, Lee HS, Nam CM, Nam HS, Heo JH, et al. The frequency of cerebral microbleeds increases with CHADS(2) scores in stroke patients with non-valvular atrial fibrillation. Eur J Neurol Off J Eur Fed Neurol Soc. 2013;20(3):502–8.
80. Werring DJ, Coward LJ, Losseff NA, Jager HR, Brown MM. Cerebral microbleeds are common in ischemic stroke but rare in TIA. Neurology. 2005;65(12):1914–8.
81. Lim JS, Hong KS, Kim GM, Bang OY, Bae HJ, Kwon HM, et al. Cerebral microbleeds and early recurrent stroke after transient ischemic attack: results from the Korean transient ischemic attack expression registry. JAMA Neurol. 2015;72(3):301–8.
82. Lovelock CE, Cordonnier C, Naka H, Al-Shahi Salman R, Sudlow CL, Edinburgh Stroke Study G, et al. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. Stroke J Cereb Circ. 2010;41(6):1222–8.
83. Horstmann S, Mohlenbruch M, Wegele C, Rizos T, Laible M, Rauch G, et al. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. Eur J Neurol Off J Eur Fed Neurol Soc. 2014.
84. Jeon SB, Kwon SU, Cho AH, Yun SC, Kim JS, Kang DW. Rapid appearance of new cerebral microbleeds after acute ischemic stroke. Neurology. 2009;73(20):1638–44.
85. Soo YO, Yang SR, Lam WW, Wong A, Fan YH, Leung HH, et al. Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. J Neurol. 2008;255(11):1679–86.
86. Thijs V, Lemmens R, Schoofs C, Gorner A, Van Damme P, Schrooten M, et al. Microbleeds and the risk of recurrent stroke. Stroke J Cereb Circ. 2010;41(9):2005–9.
87. Wong KS, Chan YL, Liu JY, Gao S, Lam WW. Asymptomatic microbleeds as a risk factor for aspirin-associated intracerebral hemorrhages. Neurology. 2003;60(3):511–3.
88. Jeong SW, Jung KH, Chu K, Bae HJ, Lee SH, Roh JK. Clinical and radiologic differences between primary intracerebral hemorrhage with and without microbleeds on gradient-echo magnetic resonance images. Arch Neurol. 2004;61(6):905–9.
89. Alemany M, Stenborg A, Terent A, Sonninen P, Raininko R. Coexistence of microhemorrhages and acute spontaneous brain hemorrhage: correlation with signs of microangiopathy and clinical data. Radiology. 2006;238(1):240–7.
90. Lee SH, Ryu WS, Roh JK. Cerebral microbleeds are a risk factor for warfarin-related intracerebral hemorrhage. Neurology. 2009;72(2):171–6.
91. Lee SH, Kwon SJ, Kim KS, Yoon BW, Roh JK. Cerebral microbleeds in patients with hypertensive stroke. Topographical distribution in the supratentorial area. J Neurol. 2004;251(10):1183–9.
92. Viswanathan A, Rakich SM, Engel C, Snider R, Rosand J, Greenberg SM, et al. Antiplatelet use after intracerebral hemorrhage. Neurology. 2006;66(2):206–9.
93. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke J Cereb Circ. 1995;26(7):1189–92.
94. Neau JP, Ingrand P, Couderq C, Rosier MP, Bailbe M, Dumas P, et al. Recurrent intracerebral hemorrhage. Neurology. 1997;49(1):106–13.
95. Eckman MH, Rosand J, Knudsen KA, Singer DE, Greenberg SM. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke J Cereb Circ. 2003;34(7):1710–6.
96. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. Neurology. 2010;75(8):693–8.
97. Jeon SB, Kang DW, Cho AH, Lee EM, Choi CG, Kwon SU, et al. Initial microbleeds at MR imaging can predict recurrent intracerebral hemorrhage. J Neurol. 2007;254(4):508–12.
98. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology. 2000;55(7):947–51.
99. Imaizumi T, Inamura S, Kohama I, Yoshifuji K, Nomura T, Komatsu K. Antithrombotic drug uses and deep intracerebral hemorrhages in stroke patients with deep cerebral microbleeds. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2013;22(6):869–75.
100.•• 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 J Am Med Assoc. 2015;313(8):824–36. **Recent review outlining risk of recurrent ICH in those with AF who restart OACs vs those who do not**.
101. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2013.
102. Majeed A, Kim YK, Roberts RS, Holmstrom M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. Stroke J Cereb Circ. 2010;41(12):2860–6.
103.•• Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62. **Meta analysis of NOAC RCT trials**.
104. Horstmann S, Zugck C, Krumsdorf U, Rizos T, Rauch G, Geis N, et al. Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage. Neurology. 2014;82(2):135–8.
105. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. Stroke Prevention In Reversible Ischemia Trial (SPIRIT). European Atrial Fibrillation Trial (EAFT) study groups. Neurology. 1999;53(6):1319–27.
106. Smith EE, Gurol ME, Eng JA, Engel CR, Nguyen TN, Rosand J, et al. White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. Neurology. 2004;63(9):1606–12.
107. Naka H, Nomura E, Takahashi T, Wakabayashi S, Mimori Y, Kajikawa H, et al. Combinations of the presence or absence of cerebral microbleeds and advanced white matter hyperintensity as predictors of subsequent stroke types. AJNR Am J Neuroradiol. 2006;27(4):830–5.
108. Kim DE, Bae HJ, Lee SH, Kim H, Yoon BW, Roh JK. Gradient echo magnetic resonance imaging in the prediction of hemorrhagic vs ischemic stroke: a need for the consideration of the extent of leukoariosis. Arch Neurol. 2002;59(3):425–9.
109. Linn J, Herms J, Dichgans M, Bruckmann H, Fesl G, Freilinger T, et al. Subarachnoid hemosiderosis and superficial cortical hemosiderosis in cerebral amyloid angiopathy. AJNR Am J Neuroradiol. 2008;29(1):184–6.
110. Charidimou A, Peeters AP, Jager R, Fox Z, Vandermeeren Y, Laloux P, et al. Cortical superficial siderosis and intracerebral hemorrhage risk in cerebral amyloid angiopathy. Neurology. 2013;81(19):1666–73.
111. Linn J, Wollenweber FA, Lummel N, Bochmann K, Pfefferkorn T, Gschwendtner A, et al. Superficial siderosis is a warning sign for future intracranial hemorrhage. J Neurol. 2013;260(1):176–81.
112. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500–10.
113. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006

compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol. 2012;60(9):861–7.
114. Eckman MH, Wong LK, Soo YO, Lam W, Yang SR, Greenberg SM, et al. Patient-specific decision-making for warfarin therapy in nonvalvular atrial fibrillation: how will screening with genetics and imaging help? Stroke J Cereb Circ. 2008;39(12):3308–15.
115. Wang Z, Soo YO, Mok VC. Cerebral microbleeds: is antithrombotic therapy safe to administer? Stroke J Cereb Circ. 2014;45(9):2811–7.
116. Holmes Jr DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014;64(1):1–12.
117. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA J Am Med Assoc. 2014;312(19):1988–98.
118. Hagii J, Tomita H, Metoki N, Saito S, Shiroto H, Hitomi H, et al. Characteristics of intracerebral hemorrhage during rivaroxaban treatment: comparison with those during warfarin. Stroke J Cereb Circ. 2014;45(9):2805–7.
119. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol. 1995;25(2):452–9.