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ORIGINAL ARTICLE

Management of Cerebral Microbleeds in Clinical Practice

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Abstract

Cerebral microbleeds (CMBs) are very frequent diagnoses with MRI imaging in the elderly or in patients with cerebral infarction, intracranial hemorrhage (ICH), and dementia. The mechanisms for CMBs are not fully understood but may be secondary to injury to the vascular wall from long-standing hypertension or amyloid deposition in the tissue. The presence of CMB increases the risk for stroke, dementia, and death. The increasing number of CMBs is also associated with a higher risk of hemorrhagic complications with the long-term use of anticoagulants in atrial fibrillation and in patients requiring thrombolysis for acute stroke. The presence of CMBs is however not a contraindication for anticoagulation or thrombolysis as was recently shown from the results of the CROMIS-2 study. This review will summarize our current understanding of the natural history of CMBs and offer suggestions on the best management in common clinical settings.

Keywords Cerebral microbleeds · Stroke · MRI · Dementia

Introduction

The widespread access to MR imaging of the brain in patients complaining of acute and chronic neurological symptoms leads to frequent detection of CMBs (Fig. 1), reported in 8–38% of the population [1–3]. Despite the high prevalence of CMBs, very little is known about their natural history or their impact on common vascular diseases. The characteristic hallmarks of "small MRI signal void" on T2*-gradient-echo (T2*-GRE) or susceptibility imaging (SWI) are easy to recognize and if numerous, quite dramatic in appearance (see Fig. 2). These focal remnant deposits of hemosiderin are most likely secondary to capillary and arteriolar damage from multiple mechanisms resulting in the leakage of blood products in the perivascular space. CMBs increase the risk of subsequent ischemic stroke and ICH, dementia, and death [3, 4]. The presence of CMBs may increase the risk of ICH with the long-term use of antithrombotic agents and when tissue plasminogen activator (tPA) is used in the treatment of an acute ischemic stroke.

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There have been several recent reviews outlining the incidence [1–4], pathophysiology [2], and significance of CMBs. The primary purpose of the current review is to offer clinicians a practical guideline on how best to evaluate and manage patients in whom brain imaging reveals CMBs. We review the current literature (MEDLINE, Embase, PubMed, Google Scholar, and references of review publications) over the last 15 years. Publications that specifically reviewed the incidence and prevalence in specific populations, imaging characteristics, clinical presentations, outcomes related to antithrombotic treatments, and prognosis were further reviewed in greater detail. We excluded reports with only individual case reports or where the clinical details were not available. This is a narrative review and not a meta-analysis on the subject of CMBs.

Incidence

The discovery of CMBs is relatively recent, reported first in 1994 as "black dots of signal loss" on T2-weighted MRI of the brain in patients with hypertension, ischemic stroke, and ICH and were initially termed hemorrhagic lacunes [5]. T2*-GRE and SWI MRI with greater sensitivity to detect blood breakdown products allows for easier detection. CMBs are rarely detected under 40 years of age [6]. In the Rotterdam Study, the prevalence increased from 17.8% in 60–69 years olds to 38.3% in over 80 years age [1]. In patients

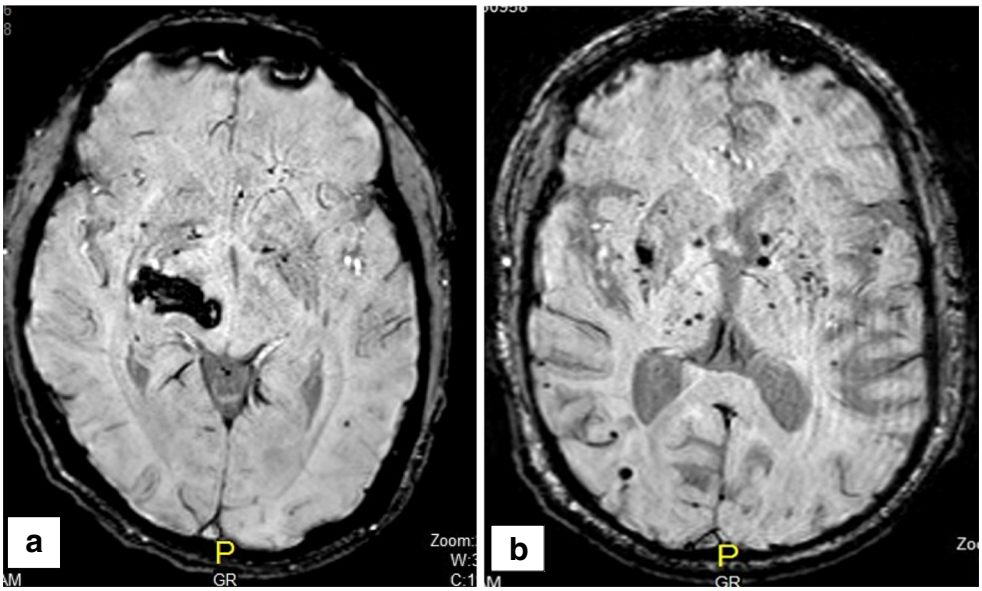

Fig. 1 Localization of a cerebral microbleed (a and b). The MRI of the patient shows a small right thalamic and basal ganglion hemorrhage. There are extensive cerebral microbleeds evident in the cortex and deep basal ganglion region

with acute stroke, CMBs have been reported in 30–70% of patients [7]. The prevalence is highest with lacunar stroke (53%), atherothrombotic stroke (36%), cardioembolic stroke (19%) [7], and with ICH (47–80%) [7]. The prevalence varies

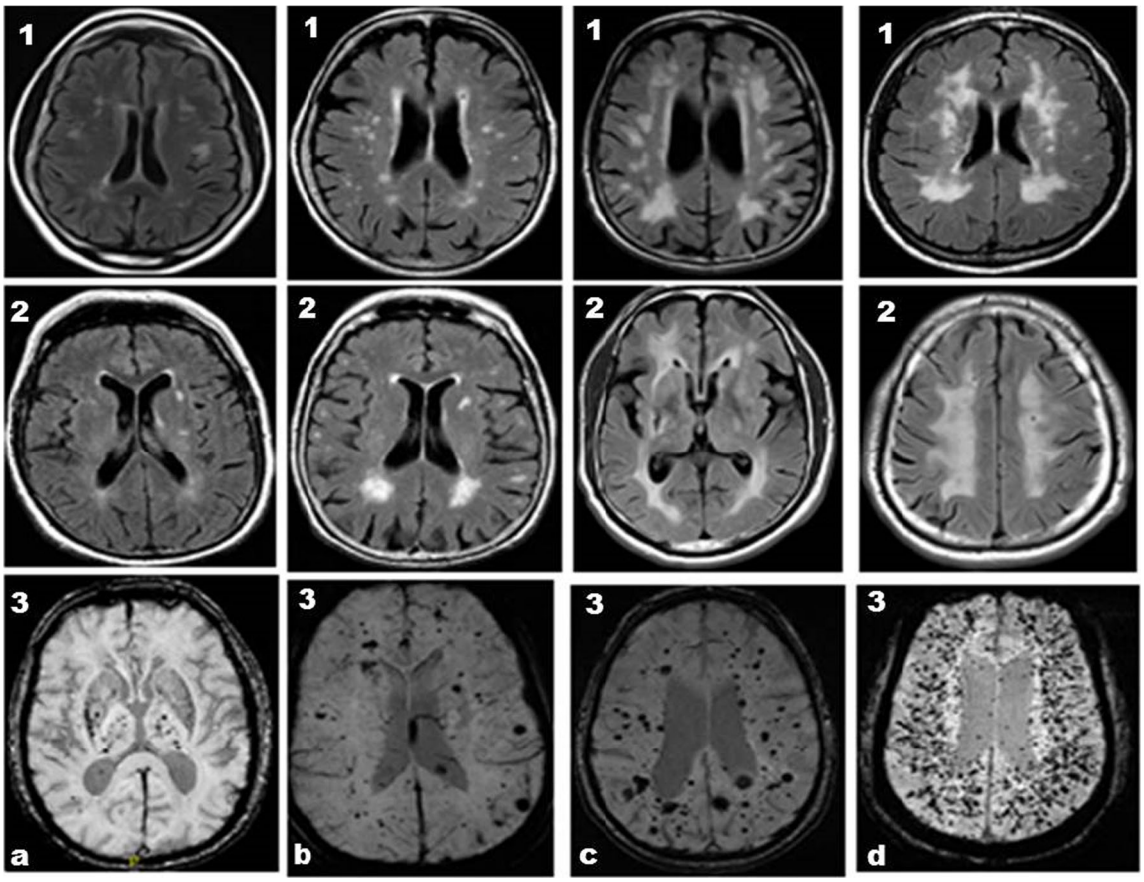

Fig. 2 Detection of microbleeds. CMBs are best detected on GRE *Gradient or SWI sequences. FLAIR and T2 may not show the abnormalities (first and second row of images). 2a shows CMBs located only in the basal ganglion. This pattern is most frequency seen in patients with long-standing hypertension. 2b and 2c show increasing CMBs located predominantly in the cortex. These locations are most often associated with amyloid angiopathy. 3d is the SWI MRI of our patient with extensive CMBs in the cortex. CMBs were also extensive in the subcortical and brainstem regions (data not shown)

according to age, etiology (CAA or hypertension), and ethnicity of the subjects [2, 6, 7]. The frequency of CMBs is lower when atherosclerosis is evident in other vascular beds, reported in 4% of patients with coronary artery disease and 13% of patients with peripheral arterial disease [8].

CMBs numbers increase over time. In the Rotterdam Study, new lesions were reported in 10% of subjects during a 3-year time period [9]. Similarly, new CMBs were reported in 30% of patients within a week following an acute ischemic stroke [10] and in 26% following an ICH [11]. Once established the lesions are visible on MRI indefinitely and it is not possible to distinguish between new and older lesions [12].

Conditions Associated with Increased Risk of CMBs Are Listed in Table 1

Etiological Mechanisms and Pathology

A continuous endothelium, tight inter-endothelial junctions, and presence of a robust muscular medial layer together with surrounding pericytes are likely the best defense against extravasation of red cells [13]. Several diverse and possibly interrelated pathological mechanisms explain the development of CMBs in patients with microvascular disease, ischemic stroke, and ICH [2, 14, 15].

In patients with CAA, CMBs are located in the cerebral cortex in regions with high amyloid-Beta concentrations [16]. Amyloid is deposited in the vessel wall where it promotes inflammation, smooth muscle loss, vasomotor dysfunction and an increase in reactive oxygen species leading to leakage of intravascular material including RBCs [17, 18] although a recent report failed to show such an association [18]. In patients with Alzheimer's disease, leukoaraiosis is also seen frequently in the presence of CMBs, suggesting that the two may have similar pathological mechanisms (see Fig. 3) [20].

Whereas leakage of blood is the most likely mechanism, the MRI appearance of microbleeds, other etiologies include fibrinoid necrosis, small cavernomas, calcium deposits, hemorrhagic exudates related to previous trauma, micro-dissection, micro-aneurysms, metastatic lesions and flow voids in pial spaces [16, 21]. MRI only detects only 50% of CMBs that are evident in autopsy studies, often missing lesions less than 1 mm [15, 22]. High field (i.e., 7-T MRI) is more sensitive to microbleeds [15]. The rate of false-positive MRIs for CMBs was 20% in one recent study [15]. Calcium deposits or lacunes were the most common conditions accounting for false-positive lesions [15]. The differentiation between CMBs and calcium deposits can be better appreciated with quantitative susceptibility mapping (QSM) with one study showing a specificity of 96.7% compared to 50.3% on GRE imaging [23].

Table 1 Conditions associated with high risk of CMBs

A. Common causes of CMBs	B. Uncommon causes of CMBs
1. Increasing age	1. Moyamoya
2. Hypertension	2. Trauma
3. Amyloid-related disorders	3. Obstructive sleep apnea
i. CAA	4. Paroxysmal cold hemoglobinuria
ii. Hereditary cerebral hemorrhage with amyloidosis-Dutch type	5. Cardiac valvular surgery
4. Chronic use of antithrombotic medications	6. Infectious endocarditis
5. Genetic defects	7. Chronic disease states
i. CADASIL	8. Paroxysmal autonomic instability
6. Race (Africans, African-Americans, Asians, Arabs, Indians)	9. Familial Mediterranean fever
	10. CNS intoxication
	11. Renal disease
	12. Severe weight loss
	13. Left ventricular assist devices
	14. Substance abuse (e.g., cocaine)

Clinical Presentation, Diagnosis, and Management

CMBs mostly remain asymptomatic and undiscovered and come to medical attention when MRI is completed for unrelated reasons (for example, routine investigation of non-specific headache, dizziness, or numbness). In such situations, the discovery of CMBs requires no additional investigations and the patient may be advised improved lifestyle. In older patients, especially with cortical CMBs and cognitive impairment, the diagnosis of early (pre-symptomatic) CAA may be considered.

The presence of CMBs increased the risk of ischemic stroke 2–3 fold and ICH 5 fold [22]. The risk is highest in patients with associated hypertension and CAA [22]. In a recent meta-analysis of 3067 patients with TIA/ischemic stroke, there was a twofold increase in the risk of stroke in patients with CMBs versus no CMBs [22]. The presence of CMBs is also associated with an increased risk of early stroke following transient ischemic attacks (TIAs) [21, 23]. The risk of recurrent ischemic stroke is higher in the population from Europe and North America and for ICH in patients from Asia [24]. In the presence of CMBs, ICH tends to be larger, especially if lobar or putaminal [25], leading to increased length of stay in hospital [26] and increase mortality [27].

Cerebral Microbleeds and Vascular Disease: Common Management Dilemmas

The presence of CMBs poses management challenges [28]. Clinical situations where the presence of CMBs may require attention include (1) long-term antithrombotic treatment, (2) reperfusion strategies in acute stroke, and (3) antithrombotic medications in patients with ICH.

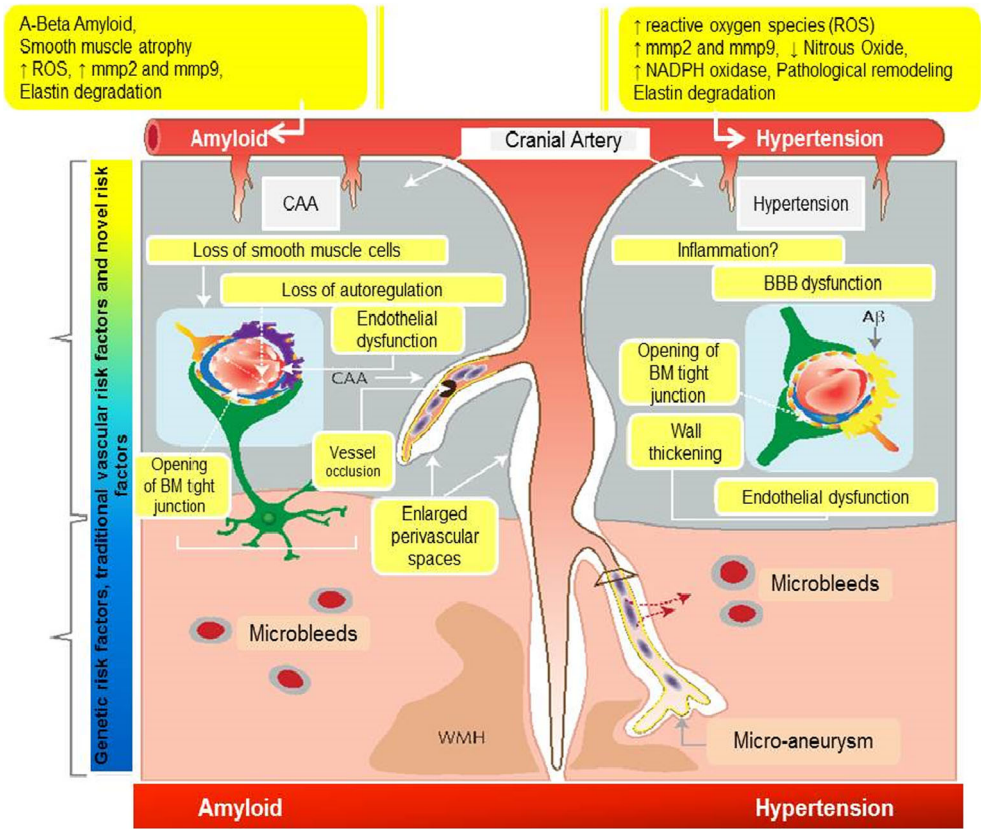

Fig. 3 Factors leading to cerebral microbleeds. The most important factors leading to the development of cerebral microbleeds (CMBs) are hypertension and cerebral amyloid angiopathy (CAA). The contributing factors to the damage to arterioles and capillaries in the two conditions may have important differences. Modified from figure 3 of reference [19]

1. Long-term use of antithrombotic medication in patients with CMBs

CMBs are seen with higher frequency in patients with vascular risk factors [1, 29] and a previous history of stroke, cognitive deficits or dementia [1, 29]. Can long-term antithrombotic medications lead to an increase in CMBs? Does treatment with antithrombotic medications in the presence of CMBs increase the risk of ICH or recurrent stroke? Is the risk dependent on the number and location of the CMBs and the type of medication (antiplatelet versus anticoagulants)?

The use of ASA can lead to an increase in CMBs, especially in the elderly [22, 29, 30]. In the Rotterdam Study, long-term ASA or clopidogrel was associated with an increase in CMBs [31]. CMBs are more frequent in patients with atrial fibrillation and significantly more frequent in atrial fibrillation patients treated with long-term anticoagulation [32]. When compared to patients on no antithrombotic medications, the odds for developing CMBs were 2.8 higher for antiplatelet medications and 8 times higher with warfarin use [30].

Secondly, the risk of ICH is higher in patients with CMBs in whom antithrombotic medications are used [33]. Warfarin-treated atrial fibrillation patients with ICH have higher rates of CMBs compared to similarly treated patients with no ICH [32–34]. The increased numbers of CMBs in warfarin-treated patients with ICH are independent of age, INR or hypertension [35]. In a meta-analysis comprising of 1460 patients with ICH and 3817 patients with TIA/stroke, the risk of recurrent ICH or ischemic stroke was evaluated with long-term use of antithrombotic medications [30]. The presence of CMBs increased the risk of ICH with long-term use of warfarin. A similar but weaker link was evident with the use of antiplatelet medications [30]. The recently published CROMIS-2 [36] study provides further evidence for the risk of ICH in patients with atrial fibrillation and recent TIAs or acute ischemic stroke who are treated with oral anticoagulants. In the study, 1490 patients were followed for at least 2 years after initiation of anticoagulants. Forty percent of patients were treated with direct oral anticoagulants (DOACs). The risk of ICH was low but at least three times higher in patients with CMBs (9.8 [95% CI 4.0–20.3] versus 2.6 [95% CI 1.1–5.4] per 1000 patient-years follow-up). Patients treated with DOACs had fewer hemorrhages compared to warfarin-treated patients. The risk of ICH was however significantly lower than the risk of recurrent stroke. While the study may be helpful for risk stratification, we believe that long-term anticoagulation is still the best option for prevention of cerebrovascular disease in patients with CMBs and recent vascular disease.

Thirdly, the number and location of CMBs may influence the subsequent risk of ICH and ischemic stroke. The risk of ICH rises with increasing number of CMBs especially if the

Table 2 Risk evaluation of patients with cerebral microbleeds (CMBs) according to underlying clinical conditions

A. Detection of CMBs in routine MRI imaging (no history of vascular disease or risk factors)		
1. < 5 CMBs and age > 65	No further investigations required	Healthy lifestyle
2. > 5 CMBs and age < 50	Consider CADASIL in the presence of moderate to severe WMD	Health lifestyle watch for hypertension
3. > 5 CMBs and age > 65	Consider amyloid angiopathy/Alzheimer disease, especially in the presence of cognitive decline	Caution in use of ASA or AC, especially in the presence of numerous CMBs
B. CMBs, known ischemic vascular disease, and antiplatelet medications		
1. < 5 CMBs and requires long-term antiplatelet medications	Caution in older individuals (> 80 years old)	Risk of intracerebral hemorrhage low with long-term use of ASA or AC
2. > 5 CMBs with minimal WMD + long-term antiplatelet treatment	Evaluate for hypertension and other vascular risk factors	Risk of intracerebral hemorrhage low. Consider low-dose ASA and manage risk factors, especially hypertension aggressively
3. > 5 CMBs with extensive WMD + long-term antiplatelet medications	Consider amyloid angiopathy/Alzheimer disease, especially if cognitive decline	Rick of intracerebral hemorrhage slightly increases, especially with long-term use. Low-dose ASA, caution patient of the risk of ICH especially in the presence of amyloid angiopathy
C. CMBs, ischemic vascular disease, and anticoagulation		
1. < 5 CMBs, short-term AC and < 65 years	No WMD	Low risk for intracerebral hemorrhage
2. <5 CMBs, long-term AC and < 65 years age	Risk factors, especially hypertension	Risk of intracerebral hemorrhage slightly increases. Treat hypertension aggressively
3. > 5 CMB, long-term AC age > 65	Increase risk of intracerebral hemorrhage, especially in the presence of WMD, suspected CAA or hypertension	Consider DOACs or atrial appendix closure device if the risk is very high
4. CMBs and reintroduction of AC following acute stroke	Imaging to ensure that there is no ICH	No evidence that the presence of CMBs increases the risk of symptomatic intracerebral hemorrhage. Initiate AC 7–10 days following acute stroke
5. CMBs and a combination of antiplatelets and AC. No recent stroke or ICH	Imaging not required	Risk not known but likely higher than single antithrombotic therapy
D. CMBs, recent ICH and require antiplatelet or anticoagulation medications		
1. CMBs, "deep" intracerebral hemorrhage related to hypertension or idiopathic	Repeated brain imaging	Risk of recurrent intracerebral hemorrhage higher in patients with higher CMB count and WMD. May consider ASA or AC 4–6 weeks following intracerebral hemorrhage. Consider DOACs
2. CMB and cortical intracerebral hemorrhage	Investigate for CAA/Alzheimer's disease	Risk of recurrent ICH high, caution with the use of AC, including DOACs
E. CMBs and risk of ICH with thrombolysis/thrombectomy		
1. < 5 CMBs and rtPA or thrombectomy	Minimal increase in the risk of Intracerebral hemorrhage	No precautions or special imaging
2. > 5 CMBs and rtPA or thrombectomy	Increased risk of intracerebral hemorrhage	Thrombolysis not contraindicated. Avoid fluctuations in blood pressure and tight glucose control

CMB, cerebral microbleeds; *WMD*, white matter disease; *ASA*, aspirin; *AC*, anticoagulation, *CAA*, cerebral amyloid angiopathy

CMBs were located in the cerebral cortex (suggestive of CAA) [22, 37].

Caution is recommended in the long-term use of warfarin in patients with an increased number of CMBs, especially if these are related to CAA. The risk of developing CMBs with direct oral anticoagulants (DOACs) is likely lower than with warfarin use and may be similar to ASA [38, 39]. In patients with higher counts of CMBs, DOACs may be preferred choice if the risk of embolism is high and long-term anticoagulation is deemed necessary [39, 40].

2. Acute stroke management and CMBs

There are recent reports on the increased risk of ICH in patients with CMBs treated with rtPA [40, 41]. The odds of developing an ICH were 2.36 higher in patients with CMBs versus no CMBs. Patients with 1–10 CMBs had an odds ratio of 3.20 that increased to 4.35 in patients with more than 10 CMBs [38]. The increase in ICH is mostly asymptomatic [42]. Functional outcome was worsened with increasing CMBs count [42]. While CMBs have been shown to increase following thrombectomy, this does not increase the risk of ICH [43, 44].

Heparin and low molecular heparin are used frequently in patients with crescendo TIAs, progressing stroke, arterial dissection, venous thrombosis and in patients with large thrombus burden in the cranial vessels or the heart although this is not supported by high-level clinical evidence. Currently, no information is available on the ICH risk if anticoagulation is initiated following an acute stroke in patients with high CMBs count. Imaging to determine CMB burden prior to anticoagulation treatment in such situations is not recommended. Similarly, the decision to treat with single or dual antiplatelet agent in similar settings does not require any additional imaging.

3. Introduction of antithrombotic medications in patients with CMBs and intracerebral hemorrhage

Intracerebral hemorrhage is one of the most feared complications of long-term anticoagulation. The risk of ICH is lower with direct oral anticoagulants (DOACs) [45]. The risk of development of CMBs or ICH in patients treated with apixaban, a DOAC is similar to ASA [39] making it a preferred agent in patients with CMBs who may require long-term anticoagulation.

The decision to restart anticoagulation in patients with anticoagulation-related ICH is often difficult. [46] A history of previous ICH, especially if recent, remains an important relative contraindication to initiation of anticoagulation treatment. The location of the ICH also has some bearing on the decision to reintroduce anticoagulation. Since lobar hemorrhages are most likely related to CAA and more likely to rebleed, it is generally recommended that anticoagulation not be offered to such patients. Patients with hypertensive or traumatic ICH may have cautious reintroduction of anticoagulation, preferably with DOACs in 4–6 weeks following the hemorrhage (see Table 2). [47]

Future Directions

CMBs remain one of the most important understudied problems in modern medicine. While the relationship between CMBs and risk of development of stroke, ICH, and dementia is well established, there are no recommendations on the use of screening for detection of CMBs in high-risk subjects. The number of CMBs increases over time, especially in the presence of hypertension and in some ethnic groups. If early aggressive treatment of risk factors, especially hypertension or improvement in lifestyle habits, might slow the development of new CMBs is not known but preliminary evidence is suggestive [48].

CMBs are almost exclusively diagnosed with T2*-GRE or SWI MRI studies. While higher field MRI improves the yield of detection, autopsy studies show that many small lesions can be missed on imaging. Pathological studies show that CMBs are not a single entity but can result from various multiple mechanisms that lead to the breakdown of the blood-brain barrier and include occlusion or aneurysmal damage secondary to the effects of hypertension, deposition of beta-amyloid, or leakage in a cavernous malformation [49]. Remodeling and biochemical changes associated with hypertension and aging may result in progressive atrophy of the medial endothelial layer and abnormalities in the MMP2/MMP9 and cytokine concentrations, promoting microaneurysmal formation, loss of vessel wall integrity, and hemorrhage from cerebral arterioles (see also Fig. 3). [50] Further studies are needed to better understand the pathophysiology.

Several clinical trials are evaluating antithrombotic treatment in patients with CMBs that may provide answers on how best to manage the problem. Two studies in Europe are recruiting patients with TIAs and stroke. The Clinical Relevance of Microbleeds in Stroke (CROMIS-2) is enrolling up to 1425 subjects from 79 hospitals in the UK (ClinicalTrials. Gov:

Table 3 Cerebral microbleeds: a proposed clinical classification

A. Incidental CMBs not requiring any restriction on the use of antithrombotic medications	B. CMBs (> 5) in patients with high risk of intracranial hemorrhage: caution with the use of anticoagulation medications	C. CMBs and intracranial hemorrhage (ICH): risk of recurrent intracranial hemorrhage high
a. Discovered on MRI imaging for unrelated condition	a. Acute stroke and thrombolysis/thrombectomy	a. Hemorrhage related to amyloid angiopathy and Alzheimer's disease
b. CMBs in the presence of vascular risk factors requiring ASA	b. Acute stroke and early anticoagulation therapy (AF, arterial dissection, cerebral venous thrombosis)	b. ICH related to AC use
c. Incidental with hypercholesterolemia requiring statins	c. Acute stroke/TIA and dual antiplatelet therapy)	c. ICH in patients with mechanical cardiac valves
d. Incidental with atrial fibrillation requiring anticoagulation (AC)	d. "Stroke in progression" and heparin use	
e. CMBs in the presence of symptomatic cardiovascular disease or peripheral vascular disease requiring ASA or AC	e. Acute ischemic stroke and hemorrhagic conversion	
f. CMBs and long-term AC for venous thrombosis or systemic embolism including PE and mechanical cardiac valves	f. Idiopathic ICH	
g. Renal disease, CMBs, and chronic dialysis	g. Hypertensive ICH	

CMBs, cerebral mircobleeds; *ICH*, intracerebral hemorrhage; *ASA* aspirin; *AC*, anticoagulation; *TIA* transient ischemic attack

NCT02513316). The Intracerebral Hemorrhage Due to Oral Anticoagulants (HERO) has enrolled 1000 patients in Spain (ClinicalTrial.Gov; NCT02238470). Two cohort studies, Intracerebral Hemorrhage in Patients Taking Oral Anticoagulants for Atrial Fibrillation with Microbleeds (IPAAC-warfarin) and Intracerebral Hemorrhage in Patients Taking Oral Anticoagulants for Atrial Fibrillation with Microbleeds with NOACs (IPAAC-NOAC) (Prevention of Cardiovascular Events in Ischemic Stroke Patients With High Risk of Cerebral Hemorrhage (PICASSO) (ClinicalTrials.gov Identifier: NCT01013532) are enrolling patients in Asia where the risk of ICH appears to be high. The COMPASS trial [51] and CURE-MRI are studying the impact of long-term anticoagulation on CMBs while the ASPREE-NEURO trial [52]is evaluating the relationship between antiplatelet medications and CMBs.

Current Guidelines for Suggested Management

There are scarce "expert" recommendations on the diagnosis, prevention, and management of CMBs, likely because of their innocuous nature and relatively benign natural history, unless symptomatic. [28] Their presence however increases the risk of stroke approximately 2–4-fold and ICH 5-fold [22]. Treatment with antithrombotic medications may lead to an increase in the number of CMBs and warfarin use may increase the risk of ICH. The recent publication from the AHA/ASA offers advice on the risk of ICH in patients with CMBs, while advising that caution does not suggest discontinuation or withholding the use of antithrombotic agents even with patients with high count. DOACs may be the preferred medication for stroke prevention in patients with high CMB count and atrial fibrillation [36]. See Tables 2 and 3 for recommendations on antithrombotic medication management in patients with CMBs.

Conclusions

Intracranial hemorrhage and ischemic stroke remain amongst the leading causes of death and the leading causes of acquired disability in North America and most of the world. With wider availability and use of brain MR imaging, an increasing segment of the population is being identified with CMBs and white matter abnormalities and their presence may be one of the most important markers for future risk of ischemic stroke, ICH, and dementia. While there is preliminary evidence that treatment of hypertension may lead to fewer recurrent strokes in patients with CMBs, [48] ongoing trials will allow for better understanding of this observation.

The risk of ICH is higher in patients with CMBs who are on long-term antithrombotic medications. A personalized approach to treatment is warranted in such subjects. The risk is highest with warfarin use but exists for ASA and DOACs. Current evidence suggests caution but no change in treatment strategy for patients with atrial fibrillation with less than 5 CMBs and no previous history of ICH. In patients with higher sub-cortical CMB count and a previous history of ICH, the DOACs may be a better choice of treatment in patients with atrial fibrillation and high CHAD2 scores [53]. The risk of recurrent hemorrhage may be higher in patients with lobar hemorrhage, CAA, and cortical CMBs. In such patients, it may be appropriate to consider closure of the atrial appendix as a treatment option for atrial fibrillation management as the risk of recurrent ICH is high.

Author's Contribution All authors, i.e., Dr. Ashfaq Shuaib, Dr. Saadat Kamran, Dr. Naveed Akhtar, and Dr. Richard Camicioli contributed equally to the review article.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study, formal consent is not required.

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