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Cerebral microbleeds in neurological practice: concepts, diagnostics and clinical aspects

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ABSTRACT

Introduction: Due to the widespread use of magnetic resonance imaging (MRI) in neurological diagnostics, the number of patients detected as having cerebral microbleeds (CMBs) continues to increase. However, their clinical impact still remains controversial, especially the question of whether CMBs significantly increase the risk of life-threatening intracerebral haemorrhage (ICH) in patients undergoing intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT), or in patients on anticoagulant therapy or statins.

State of the art: The term 'CMB' is a radiological concept that aims to illustrate microscopic pathology of perivascular hemosiderin deposits corresponding most probably to small foci of past bleeding. MRI images in sequence T2*-GRE and susceptibility-weighted imaging (SWI) are used for a diagnosis of a CMB. This review summarises the current knowledge regarding the definition, prevalence, genetics, risk factors, radiological diagnosis and differential diagnosis of a CMB. We discuss its role as an indicator of future ischaemic or haemorrhagic events in high risk patients or those on antiplatelet or anticoagulant therapy, and its prognostic value for reperfusion strategies and for the development of dementia.

Future direction: The place of CMBs in current guidelines is explored herein. It must be emphasised that the recommendations relating to CMBs are expert opinions. Therefore, at the end of this review, we pose a number of questions that future clinical trials should answer.

Key words: cerebral microbleed, small vessel disease, intravenous thrombolysis, endovascular thrombectomy, antithrombotic therapy

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Introduction

Due to the ever-increasing use of head magnetic resonance imaging (MRI), the population of patients being diagnosed with cerebral microbleeds (CMBs) continues to increase [1, 2]. The term CMB is a radiological concept that aims to illustrate microscopic pathology of perivascular hemosiderin deposits corresponding to small foci of past bleeding. The detection of CMBs in neuroimaging mainly concerns the older population, patients with previous haemorrhagic and ischaemic strokes, patients with various types of dementia, patients with neurogenerative diseases of the nervous system, and patients with hypertension and amyloid angiopathy [2–4].

The most important clinical question is whether CMBs increase the risk of a life-threatening intracerebral haemorrhage (ICH), especially in patients undergoing intravenous thrombolysis (IVT), endovascular thrombectomy (EVT) or who are being treated with anticoagulants or statins. However,

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these important clinical problems in patients with CMBs are not yet fully understood, which means that the published recommendations are mainly based on observational studies or on the experience of experts [5–9].

This review summarises today's evidence-based clinical data regarding CMBs and their impact on IS and ICH risk.

State of the art

Definition and prevalence

Signs of small vessel disease (SVD) on conventional MRI include recent small subcortical infarcts, white matter magnetic resonance (MR) hyperintensities, lacunes, prominent perivascular spaces, cerebral microbleeds, and atrophy [10]. The term 'CMB' is in fact a radiological concept that aims to illustrate microscopic pathology of perivascular hemosiderin deposits corresponding to small foci of past bleeding [10, 11]. Support for this notion has been provided in post mortem correlative MR and histopathological studies. Histopathologically, areas of signal loss on gradient echo T2*-weighted sequences in the brains of deceased patients represent hemosiderin deposits indicating previous extravasation of blood [Supplementary reference 1, 2]. CMBs develop alongside small arteries, arterioles or capillaries, usually demonstrating fibrolipohyalinosis or amyloid microangiopathy. Therefore, hemosiderin-laden macrophages are presented in their proximity [Supplementary reference 3]. In the population-based Mayo Clinic Study of Ageing, the age- and sex-specific prevalence of core cerebrovascular disease lesions (infarctions, cerebral microbleeds, and white-matter hyperintensities detected with magnetic resonance imaging) were assessed. Among 1,462 participants without dementia, core cerebrovascular disease features increased with age. The prevalence of CMBs was 13.6%, of infarcts 11.7%, and of abnormal white-matter hyperintensities 10.7%. Infarcts and cerebral microbleeds are more common among men. In contrast, abnormal white-matter hyperintensities are more common among women aged 60 to 79 and men aged 80+ [10].

Hemosiderin deposits are superparamagnetic, and thus they show considerable internal magnetisation and magnetic susceptibility into the MRI magnetic field [10]. Their detection on MRI demands proper selection of appropriate sequences. CMBs are not visible in computed tomography. Consequently, the sensitivity of CMB detection varies with the MRI parameter i.e. pulse sequence, spatial resolution, magnetic field strength, and post-processing method [11]. It is estimated that CMBs occur in 3–7% of healthy people aged 45 to 50. Their presence increases with age: in people 80+, the prevalence of CMBs varies from 17.8% to 38.3% [1, 2] and is higher in men [Supplementary reference 3, 4]. In the Mayo Clinic Study of Ageing, CMB frequency increased with age with each succeeding decade (11% aged 60–69, 22% aged 70–79, and 39% aged 80+) [Supplementary reference 5]. A higher presence of CMBs in also reported in patients with first-ever and recurrent haemorrhagic or ischaemic stroke, Alzheimer's Disease, vascular cognitive impairment or vascular dementia, hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) [2, 12–15]. Apart from dementia, the presence of multiple CMBs is also associated with a global neuropsychiatric disorder burden, in particular symptoms of depression and disinhibition [Supplementary reference 6]. A high extent of CMBs may also induce parkinsonism and other motor symptoms such as gait disturbances. CMBs occur more commonly in PD patients with dementia than in those without dementia [Supplementary reference 7, 8].

Risk factors for CMBs

CMBs can be associated with some of the classical cerebrovascular risk factors, including male gender, advancing age, arterial hypertension (AH), and cigarette smoking [3, 16, 17]. However, any association between CMBs and diabetes [18] and dyslipidemia [19] has been inconsistent across published reports. In a population of patients from the Rotterdam Scan Study, the prevalence of CMBs gradually increased with age, from 6.5% in persons aged 45 to 50 to 35.7% in participants aged 80+ [2].

The number of CMBs is positively correlated with blood pressure values, and CMBs can be interpreted as a type of target organ damage due to chronic hypertension [20]. The results of a study on a general population in Sweden showed that both lobar and non-lobar CMBs were associated with the presence of AH [17]. Among cardiovascular risk factors determining the presence of CMBs in the lobar location, amyloid angiopathy and increased diastolic blood pressure have been identified [2]. A correlation between the duration of atrial fibrillation (AF) and the progression of CMBs during the observation period has been also reported [21].

Alcohol overuse may induce CMBs. In the AGES-Reykjavik study, heavy alcohol consumption increased the presence of CMBs in deep structures when compared to light or moderate consumption [1]. CMBs also constitute a ubiquitous manifestation of traumatic brain injury of all severities, and their presence is strongly associated with that of traumatic axonal injury (TBI). About 40% of the patients who died during the acute phase of TBI, and 47% of those who survived 12 months after a TBI, showed multifocal, perivascular and parenchymal CMBs in the grey matter [22].

CMBs develop in a high percentage of patients with brain tumours treated with radiation therapy within the first years after treatment. Significant factors for the development of a CMB include younger age at time of proton beam radiation therapy (PBT), a higher maximum radiation therapy dose, and a higher percentage and a higher volume of brain exposed to ≥ 30 Gy [23]. Bacterial endocarditis is also a condition often associated with the presence of CMBs [24]. A negative impact of obesity, and a positive impact of fish oil consumption, on the occurrence of CMBs have been observed [25]. The mere presence of a CMB is also a risk factor for its further progression [2, 26].

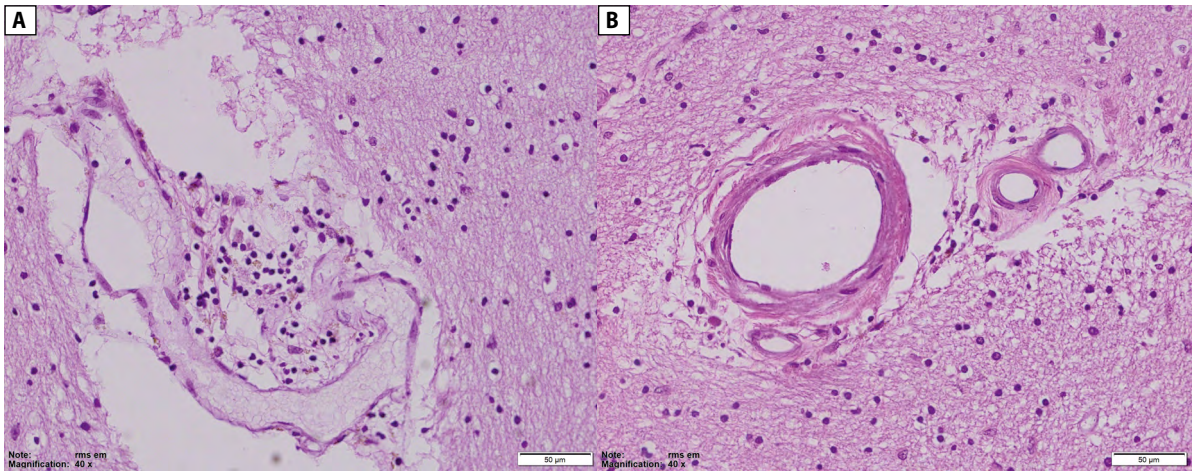

Figure 1. A. Perivenular space widening with accumulation of hemosiderin-laden macrophages and lymphocytes (HE, 400x) (Department of Pathology and Neuropathology, Medical University of Gdansk); **B.** Cerebral arterioles of different diameters presenting sclerotic changes and early perivascular space widening with single macrophages (HE, 400x) (Department of Pathology and Neuropathology, Medical University of Gdansk)

Neuropathology

Neuropathologically, SVD has been referred to using a wide range of terms, such as *status fibrosus*, *status lacunaris* or entity of hypertensive Binswanger's encephalopathy [27]. Age, vascular risk factors, and genetic predispositions are connected to neuro-vascular unit and cerebral small blood vessel (diameter 30–400 um) wall alterations. There are rare inherited forms and, sporadic types prevalent in older patients, with the most common being hypertensive arteriopathy (deep perforator arteriopathy) and cerebral amyloid arteriopathy (CAA).

Pathological changes of blood vessels in hypertensive arteriopathy include arteriosclerosis, fibrinoid necrosis and, although this is a term now less commonly used, lypohyalinosis. These changes are caused initially by endothelial and blood-brain barrier dysfunction. The molecular pathogenesis of arteriolosclerosis is not well understood, but its main steps encompass structural changes of the basement membranes, progressive loss of smooth myocytes, intimal thickening, replacement by collagen fibres (fibrosis), and protein depositions.

A second form, sporadic CAA, can occur in or outside an AD setting, and is characterised by blood vessel wall deposition of amyloid B protein (mainly AB40). AB in the soluble form is eliminated from the brain within the interstitial fluid along the vessels and along glial water channels of the glymphatic system. CAA intensity and presence have been shown to correlate with APOE specific alleles, and cerebral B-amyloid burden in PET studies.

CMBs correspond to perivascular hemosiderin-laden macrophages, hemosiderin deposits, iron-positive siderophages and small erythrocytic extravasations (Fig. 1A, B). They are identified in the setting of ICH and ischaemic stroke, and in AD, and are more frequently seen with increasing age. Some studies show also relations to the ischaemic mechanisms. In hypertensive arteriopathy, CMBs are found in the deep grey matter, white matter, and infratentorially, while lobar (cortico-subcortical) mainly occipital or frontal lesions correspond to CAA.

The mixed type of CMB distribution points to the coexistence of both types of vascular pathology; in addition, some authors have proposed that these two diseases create a continuum of age-related vascular pathology [28]. Some studies have shown no neuropathological evidence for a topographical relation between CMB and CAA [29]. However, there have been few radiological-neuropathological correlation studies in CMB . Pathophysiologically, the causes and consequences of CMB are multifactorial: impaired vasodilatation and autoregulation, loss of elasticity, vessel stiffening, aberrant blood flow, interstitial fluid drainage, fluctuation in blood flow, hypoperfusion, inflammation (microglial activation), myelin dysfunction, and finally neurodegeneration [30, 31].

Genetics

Genetic factors determining the presence of CMBs include polymorphisms linked with sporadic CMBs and less common mutations seen with familial conditions. The most common gene polymorphism associated with sporadic CMBs is the apolipoprotein E (APOE) gene on chromosome 19. Apolipoprotein E (ApoE) is genetically associated with cerebral β-amyloidosis (Aβ). ApoE has a determining role in the progression of Aβ deposition, since having the APOE ε2 and APOEε4 alleles is the major risk factor for CAA and Alzheimer's Disease (AD). APOE ε2 and APOE ε4 have each been independently associated with lobar CMBs [31]. Essential hypertension is a disease with a complex and multifactorial aetiology inherited by poligenes. Allelic variants, so-called 'candidate genes', only predispose to higher pressure values,

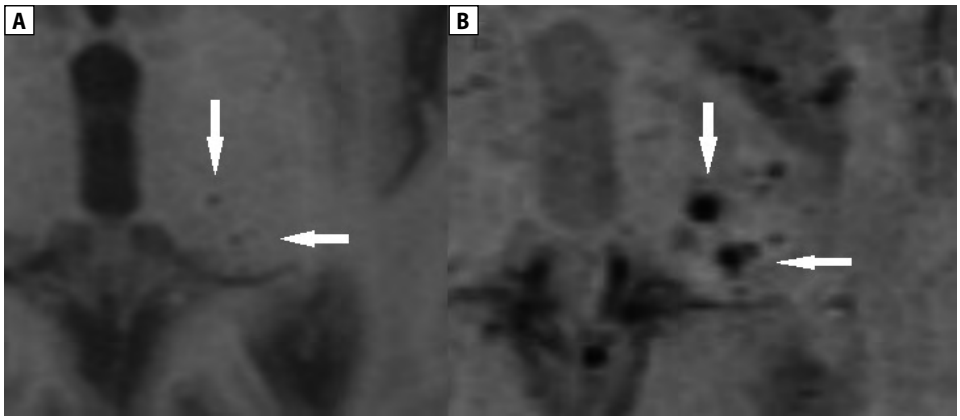

Figure 2. 'Blooming effect' in T1 (**A**) and T2* GRE (**B**) images (Department of Radiology of Holy Spirit Specialist Hospital in Sandomierz)

and only their combined action with environmental factors leads to an increase in blood pressure [32].

MRI diagnostics

The basis of blood-breakdown product detection in patients with CMBs is sequence T2*-GRE. MRI images in this sequence are typically larger than the physical size of the underlying hemosiderin deposits. This phenomenon is called the 'blooming effect' and significantly aids visual interpretation of CMBs [Fig. 2A, B]. The extent of blooming varies according to the MRI sequence parameter, especially echo, but also magnetic field strength (7T > 3T > 1,5T), slice thickness, flip angle, spatial resolution (3D > 2D) and image postprocessing technique (susceptibility-weighted imaging, SWI) [10, 15, 34]. SWI is another particularly effective diagnostic technique in the detection of CMBs (Fig 2A, B) [3, 34]. Studies have shown that SWI can detect significantly more CMBs (at least 67% more) compared to conventional T2*-GRE [35]. CMBs are characterised by a lack of signal hyperintensity in the T1 and T2 sequences.

According to the current consensus, CMBs are defined as: hypointense lesions (black) on T2*-GRE MRI, round or ovoid, well defined, small, not seen well on T1- or T2-weighted MRI, with the necessary exclusion of clinical history of traumatic diffuse axonal injury, and where at least half of the lesion is surrounded by brain parenchyma [15, 34].

Differential diagnosis

CMBs are by definition smaller than 5-10 mm in diameter. CMBs should be distinguished from mimics and artifacts. Various structures in the brain can give small, dot-like, low-signal areas on T2*-GRE or SWI MRI e.g. blood vessels in the subarachnoid space, calcifications of the basal ganglia, cavernous malformations, haemorrhagic micrometastases especially from melanoma or renal cell carcinoma, and post-traumatic changes. Hence, the diagnostician must carefully review contiguous scans using different MRI sequences and sometimes compare the suspected areas using CT scans [15, 36].

Distribution on MRI

Yakushiji et al. analysed data from 8,595 stroke-free individual participants aged between 55 and 75 from 11 studies for the presence and distribution of CMBs. The authors compared eastern (East Asian) and western (Caucasian) populations. They found that Eastern and Western general populations have different anatomical distributions of CMBs. In their analysis, Eastern populations had higher odds of deep and/or infratentorial or mixed CMBs [37]. CMBs in the lobar and deep locations are associated with hypertensive arteriopathy [20] [Supplementary figure 1a]. Age and APOE4 carrier status act through amyloid load to increase the risk of lobar CMBs, especially located in the occipital and parietal regions of the brain [38], although in patients with amyloid angiopathy CMBs have also been observed located infratentorially [39] [Supplementary figure 1b]. Mixed-location CMBs have been found to be a biomarker of neurodegeneration in a memory clinic population [40]. Also, the Framingham population study showed that hypertension increased the risk of any CMB and, in deep and mixed locations, low total cholesterol and APOE ε4 increased the risk of lobar CMB, and that statin use increased the risk of lobar and mixed location CMB [Supplementary reference 4]. Different distributions of CMBs have been observed in patients with Parkinson's Disease [4], although some studies have indicated an occurrence of strict lobar CMBs in patients with non-dementia Parkinson's Disease [41].

In order to assess the location of, and increase in, the number of CMBs, scales called 'MARS' (*Microbleed Anatomical Rating Scale*, Tab. 2, Supplementary reference 1) and 'BOMBS' (*Brain Observer Microbleed Scale*, Tab. 2, Supplementary reference 2) have been created with the possibility of mapping brain structures.

Clinical implications

Risk of ischaemic and haemorrhagic stroke

In patients with ischaemic stroke (IS), the presence of CMBs is associated with advanced age, diabetes and the previous use of antithrombotics. CMBs located in deep structures

are also associated with the presence of arterial hypertension [18, 42]. An increased risk of ischaemic and haemorrhagic stroke itself has been also reported in patients with CMBs [21, 43, 44]. In a meta-analysis of 13,864 patients from five population-based studies, CMB presence was significantly associated with the incidence of IS and ICH. Pooled analysis of 7,672 patients with ischaemic stroke/TIA (CMBs vs.no CMBs) from 19 studies showed that CMB was associated with an increased risk of recurrent IS and a crude risk of ICH during follow-up [36]. Patients with IS or TIA with CMBs are three times more likely to have a subsequent ICH [21, 45] or recurrent IS [45]. The predictors of ICH in AIS are age, high NIHSS score, and deep, lobar and cortico-subcortical distribution of CMBs. The risk and mortality of ICH increase with the quantity of CMBs [21, 46].

An observational prospective study based on 168 ICH survivors who underwent 1.5T MRI at ICH onset (median follow up 3.4 years) showed that prognostic and associated factors of incident CMBs differed according to the index ICH location. Whereas in lobar ICH, incident CMBs were associated with haemorrhagic biomarkers, in non-lobar ICH the ischaemic burden increased [47]. In the MISTRAL study (MIcrobleeds predict STRoke in ALzheimer's) carried out in 333 patients with AD (in one in three of whom a CMB was imaged), the main measures were stroke-related mortality, incident stroke, and ICH. Patients with AD with lobar CMBs had an increased risk of stroke and stroke-related mortality, and the presence of non-lobar CMBs was associated with an increased risk of cardiovascular events and cardiovascular mortality [48].

Dementia and neurodegenerative diseases

No strong association between the presence of CMBs and the development of dementia has been shown in prospective studies. However, adjusted meta-analysis of three population-based studies (Rotterdam, Framingham Heart and AGES Reykjavik), which included dementia-free participants at baseline, revealed that CMBs were independently associated with a marginally increased risk of all-cause incidence of dementia [5, 49]. In studies on an elderly population, CMB presence at baseline was associated with a doubled risk of dementia in the crude meta-analysis, although this was not confirmed in the adjusted meta-analysis [50, 51].

In a Japanese observational study, the presence of CMBs in patients with dementia was not associated with deterioration of memory function. But the presence of more than one CMB, and their mixed location, affected the development of dementia regardless of its clinical picture [52]. A report concerning stroke clinic patients showed that CMBs were consistently associated with frontal-executive impairment and had prognostic relevance for long-term cognitive outcome [53].

CMBs are associated with decreased cerebrospinal fluid amyloid levels and are related to the ApoE e4 allele, as well as other imaging manifestations typical of small vessel disease [Supplementary reference 9]. CMBs are found in c.24-33% of Alzheimer's Disease dementia patients [Supplementary reference 10–12]. In patients with AD or vascular dementia, those with lobar-only CMBs have a higher amyloid burden than those with mixed lobar and deep CMBs or deep-only CMBs. Apolipoprotein E ε4 homozygosity is associated with a greater risk of lobar CMBs [Supplementary reference 13].

The mixed location of CMBs is thought to be associated with neurodegenerative diseases of the nervous system [54]. CMBs are often detected in Parkinson's Disease, but different localisations of CMBs, including deep brain hemispheres, are more often given in this disease [4]. Kim et al. compared the occurrence of CMBs in patients with PD and multiple system atrophy (MSA), and found no difference between the number and distribution of CMBs in both groups of patients [55]. No reports of CMBs in other neurodegenerative diseases have been found.

Chronic Kidney Disease and haemodialysis

Chronic kidney disease is mentioned as one of the risk factors for CMBs, especially in patients treated with haemodialysis. A decrease in eGFR (estimated glomerular filtration rate) is associated with the occurrence of CMBs and an increase in their number [56]. MRI studies of cohorts of dialysed patients have shown asymptomatic markers of small vessel disease, including silent cerebral infarction, white matter hypersensitivity, and CMBs. However, all studies evaluating the problem of CMBs in dialysis patients to date have been conducted in Asian populations. The presence of these changes was associated with the future occurrence of strokes, memory impairment, and dementia [57]. Among 180 patients examined by Qian et al., 36.1% had detected CMBs. Deeply located CMBs were significantly associated with haemodialysis treatment, mean arterial pressure (MAP) and the number of lacunar infarctions, but were not associated with dialysis modality or heparin use [58].

Stroke course and treatment

Global risk and outcome

Sakuta et al. found that the presence of CMBs is predicts poor outcome in minor ischaemic stroke patients [59]. Among 1,963 participants of the Framingham Heart Study, with an average follow-up of 7+ years, CMBs were not strongly associated with increased mortality of any cause, and after adjusting for cardiovascular risk factors and preventative medication, there was no statistical significance [60]. In the Rotterdam Study, 3,979 participants were observed for 5+ years. Localisation of CMBs in deep structures of the brain and subtentorial areas was significantly associated with an increased risk of mortality of any cause, regardless of cardiovascular risk factors. The risk of mortality increased with the number of CMBs [61].

The results of the PROspective Study of Provastatin in the Elderly at Risk (PROSPER) showed that in the 7-years follow up, the presence of CMBs was associated with a six-times

greater risk of stroke-related death. Individuals with lobar CMBs had a seven-fold increase in stroke-related deaths (but not cardiovascular deaths), and individuals with non-lobar CMBs had a doubled risk of cardiovascular (but not stroke-related) death [62].

Data from the prospective study by Soo et al. showed that the risk of increase in mortality from ICH with quantity of CMBs was as follows: 0.6% (no CMBs); 0.9% (1 CMB); 1.5% (2–4 CMBs); and 3.8% (5 or more CMBs). Mortality from IS and myocardial infarction did not increase with quantity of CMBs [46].

In an overall meta-analysis including studies across different populations (IS/TIA; memory clinic high risk elderly cohort and patients from population-based studies) of 14,433 participants, CMB presence was an independent predictor of all-cause mortality [46]. In the MISTRAL study, in a cohort of patients with Alzheimer's Disease, lobar CMBs increased the risk of fatal stroke by more than 30 times, and CMBs located in deep structures of the brain led to a 12-fold increased risk of cardiovascular death [48].

Outcome after reperfusion strategies

Due to the destruction of the walls of the small arteries and arterioles adjacent to CMBs by lipohyalinosis, formed microaneurysms, hypertension and/or cerebral amyloid angiopathy, there is a predisposition towards brain haemorrhage. The risk of intracerebral haemorrhage increases if the patient is undergoing reperfusion therapy or is being treated with anticoagulants.

Therefore, multiple CMBs should serve as an especially loud warning of a potential risk for major brain bleeding when thrombolytics and antithrombotic agents are being considered [Supplementary reference 14].

IV-thrombolysis

Intravenous thrombolysis with rt-PA is the most widely used treatment for AIS [8, 9] Clinical studies and meta-analyses evaluating the association of CMBs with outcomes of AIS patients treated with IVT have shown contradictory results [63–70]. Some of these studies did not indicate a relationship between high CMB burden and poor long-term outcome [66, 67], but in contrast other studies did point to such an association [68–70]. A multicentre prospective European study and a meta-analysis by Arca et al. showed that only a high number of CMBs (≥ 10) was associated with higher mortality in patients treated with intravenous thrombolysis (IVT) [63]. Similar conclusions resulted from the multistep algorithm to model 90-day modified Rankin Scale scores in patients with ≤10 vs. >10 CMBs who did or did not receive IVT developed by Schlemm et al. [64]. In the meta-analysis by Wang et al., no effect of CMBs on mortality in IVT patients was found [65].

The results of studies in the context of occurrence of sICH after IVT in patients with CMBs detected before treatment are also contradictory [71, 72]. Zand et al. indicated that a high CMB burden (> 10) is associated with a higher risk of sICH [73]. The same conclusion was confirmed by other studies and meta-analyses [65, 73]. The recent meta-analysis by Yan et al. of 2,407 participants from nine studies showed that pretreatment CMBs were associated with increased incidence of sICH in AIS patients receiving IVT. However, these results were not convincing enough to establish the presence of a CMB as a contraindication to IVT [74].

Endovascular thrombectomy (EVT)

Prospective data regarding the impact of CMBs on the safety and efficacy of mechanical thrombectomy in patients with ASI remains limited. Choi and al. analysed the impact of CMBs on long-term outcome following recanalisation in patients with AIS. They found that the presence of a CMB, and high burden and lobar location, are independent predictors of poor outcomes, and may increase sICH especially in patients with recanalisation after large vessel occlusion, more than in those without recanalisation [75]. In the study by Shi et al., 6.8% had ≥ 2 CMBs, and only 1 patient had ≥ 5 CMBs. The authors showed that the presence of a CMB did not increase haemorrhagic transformation (HT) and mortality following EVT for AIS [76].

To date, only one meta-analysis based on the results of four studies with a total of 598 patients has been published. CMBs were present in 18%, and ≥ 5 CMBs in only 1% of patients. The risk of ICH after EVT did not significantly differ between patients with and without CMBs [77].

Carotid endarterectomy (CEA) and angioplasty with stenting (CAS)

Only two reports have discussed the problematic presence of CMBs in patients undergoing CAS. Among the whole group of patients treated by Kakumato et al., 20.5% had CMBs initially, and 8% developed new CMBs straight after CAS. New CMBs appeared on the same side of CAS in all patients. New CMBs appeared significantly more frequently in the CMB-positive group than in the CMB-negative one [78]. This observation confirmed the results of the study conducted by Ito et al., which found that new CMBs also developed after CAS, mostly in the territory of the treated carotid artery [79].

In a multicentre European study, 162 patients were treated with CEA or CAS. In both groups, there was no manifestation of ICH after surgery. CMBs appeared in only 6.0% of patients after CAS, and in 6.4% after CEA, without statistical significance between the groups [80].

Antithrombotic therapies

Antiplatelets

There has been long-running uncertainty as to whether during chronic use of antiplatelet agents there is incidence of CMBs or an increase in the number of them, and what their location is, and whether IS and/or ICH occurs more frequently.

Many studies have been carried out on this subject, but they have mainly been observational studies.

There have been some systemic reviews and meta-analyses discussing the relationship between antiplatelet drug use and CMBs [81–83]. The meta-analysis by Liu et al., based on 11 studies involving 10,429 participants, revealed a significant relationship between antiplatelet therapy and the occurrence of CMBs in both ICH and IS patients. In the case of stratification based on ethnicity, the relationship between antiplatelet therapy and CMBs was at a similar level of significance for ICH and IS for an Asian population, but was not significant for ICH and IS for patients from European countries [81]. A review of the literature including 1,460 patients with ICH and 3,817 with IS/TIA showed that CMBs were almost three times more common in the group of ICH, and almost six times more often seen in patients using antiplatelet drugs [82]. The meta-analysis conducted by Wang at al., based on the results of 10 studies, showed that patients with multiple CMBs had an almost quadrupled risk of developing ICH compared to patients with a single CMB. A very strong relationship has been found between the presence of CMBs and the subsequent occurrence of ICH in patients treated with antiplatelet agents [83]. The meta-analysis by Qui et al. was based on the results of 37 studies with a total of 20,988 participants. The analysis showed that CMBs were more frequent in antiplatelet users, and in those in strictly lobar rather than in than deep or infratentorial locations. ICH was higher in participants with CMBs than in those without CMBs [84].

The results of a recently conducted study emphasise that the duration of antiplatelet therapy can influence the prevalence of CMBs and the incidence of ICH [85].

Oral anticoagulants

Atrial fibrillation (AF) quintuples the risk of IS. Therefore, to reduce this risk, anticoagulants are indicated [86]. For this reason, for many years vitamin K antagonists (VKAs) have been used. We have had the results of several studies assessing the risk of ICH in patients using VKAs, although most of these studies did not take into account the presence of CMBs. NOACs (novel oral anticoagulants) have been used for several years, but the issue of any correlation between the occurrence of a CMB and the safety of treatment has not been properly studied.

Previous studies, not assessing the presence of CMBs in the MRI, showed that NOAC-related ICH patients had lower baseline haematoma volume and were less likely to have severe neurological deficits (> 10 points according to NIHSS-National Institutes of Health Stroke Scale score) on admission than VKA-ICH patients [87].

In turn, in the international collaborative multicentre pooled analysis CROMIS-2 (Clinical Relevance of Microbleeds In Stroke), no differences in baseline ICH volume, haematoma expansion, 90-day mortality, or functional outcome in ICH-patients treated with NOAC and VKA were found [88].

Graff-Radford et al. showed that anticoagulant use correlated with the presence of CMBs in the general population, and that the predictors for presence/absence of CMBs included older age at magnetic resonance imaging and male sex. The predictors of CMB count in the CMB-positive group were male sex and amyloid load detected with positron emission tomography (PET) [Supplementary reference 15].

In the multicentre prospective, observational study RASUNOA (Rationale and Design of the Registry of Acute Stroke Under Novel Oral Anticoagulants) location and counts of CMBs in patients with IS and ICH prior treated with NOAC were analysed. The proportion of patients with at least one CMB, and the absolute number of CMBs, were higher in the ICH group [89]. Lioutas et al. evaluated the incidence of CMBs in ICH patients treated with anticoagulants before stroke onset. In the study group, CMB prevalence was 51% (52% in VKA, 48% in NOAC). NOAC patients had a lower CMB count, and ≥ 5 CMBs were less prevalent in the NOAC group [90].

Balancing the risks of recurrent ischaemic stroke and intracranial haemorrhage is important for patients treated with antithrombotic therapy after ischaemic stroke or transient ischaemic attack.

In the aforementioned CROMIS-2 study of patients with atrial fibrillation anticoagulated after recent IS or TIA, CMBs were independently associated with sICH risk [91]. The results of the meta-analysis by Charidimou et al. based on a group of 1,552 patients pointed to a particular risk of ICH in patients in whom ≥ 5 CMBs had been detected [92].

In the pooled analysis of individual patient data from the Microbleeds International Collaborative Network (MICON), which includes 38 hospital-based prospective cohort studies from 18 countries, the authors found the novel MICON-intracranial haemorrhage (MICON-ICH) and MICON-ischaemic stroke (MICON-IS) risk scores — which include clinical variables and MRI-detected cerebral microbleeds — to predict intracranial haemorrhage in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack. These scores are new means by which to assess the long-term risk of intracranial haemorrhage and ischaemic stroke [Supplementary reference 16]. In Greenberg's opinion, the MICON-ICH risk score is substantially better than the discrimination offered by scales such as HASBLED that do not incorporate CMBs [Supplementary reference 17].

Statins

The results of studies assessing the impact of lipid levels and the effect of drugs used to regulate their level are inconsistent [19, 93]. Some of them have indicated that low serum cholesterol level and/or triglyceride level is associated with an increased risk of ICH. A meta-analysis based on 43 studies with a combined total of 317,291 patient-years of follow-up indicated that, in patients with ICH, statins did not increase recurrent ICH. In survivors of IS, although statins substantially and significantly reduced IS, there was a non-significant increase

Table 1. Cerebral microbleeds in the guidelines of expert groups and scientific societies

American Heart Association/ American Stroke Association: Scientific rationale for inclusion and exclusion criteria for intravenous alteplase in acute ischaemic stroke [97]	Intravenous alteplase has not been shown to increase sICH rates in patients with CMBs. Intravenous alteplase administration in these patients is therefore reasonable (Class IIa; benefit > risk)
American Heart Association/ American Stroke Association: Prevention of stroke in patients with silent cerebrovascular disease [98]	We suggest that, for patients with nonvalvular atrial fibrillation in whom anticoagulation is indicated but who are considered at particularly high risk of future ICH on basis of microbleed number and location, it may be reasonable to administer dabigatran, rivaroxaban, apixaban, or edoxaban in preference to warfarin. Another alternative to warfarin anticoagulation that might be considered is percutaneous closure of left atrial appendage
American Heart Association/ American Stroke Association: 2018 guidelines for early management of patients with acute ischaemic stroke [9]	In eligible patients who have previously had a small number (10 or fewer) of CMBs demonstrated on MRI, administration of IV alteplase is reasonable (Class IIa; benefit > risk); In eligible patients who have previously had a high burden of CMBs (more than 10) demonstrated on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and benefits of treatment are uncertain (Class IIb; benefit ≥ risk)
European Stroke Organisation — Karolinska Stroke Update Conference: Consensus statements and recommendations from ESO Karolinska Stroke Update Conference [99]	Routine MRI assessment of small vessel disease including CMBs is not recommended (Grade C; benefits outweigh risk); Oral anticoagulants in patients with evidence of CMBs should not be withheld (Grade C); NOACs should preferentially be used over VKA in NVAF (Grade C)
European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke [Supplementary reference 23]	For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden is unknown or is known to be low (< 10), we suggest intravenous thrombolysis with alteplase. Quality of evidence: Low; Strength of recommendation: Weak For patients with acute ischaemic stroke of < 4.5 h duration, for whom cerebral microbleed burden has been previously reported to be high (> 10), we suggest no intravenous thrombolysis. Quality of evidence: Low; Strength of recommendation: Weak
Decision algorithms for direct oral anticoagulant use in patients with nonvalvular atrial fibrillation: a practical guide for neurologists [100]	In patients after ICH, when anticoagulation is contraindicated (among other things on detection of > 5 cortical CMBs), surgical ablation or percutaneous left atrial appendage closure should be considered
European Society of Cardiology (ESC) guidelines for management of atrial fibrillation developed in collaboration with EACTS [8]	Among factors supporting lack of return to anticoagulation in patients with atrial fibrillation after ICH, numerous (> 10) CMBs are listed

of ICH. Nonetheless, statins show clear benefits in reducing mortality and improving functional outcome, irrespective of stroke subtype [94]. The conclusion of the Rotterdam Study was that low serum triglyceride level was associated with the presence of deep or infratentorial CMBs [95].

A recent review based on seven studies of 3,671 participants presented the hypothesis that statins treatment is not associated with CMBs overall, but may increase the risk of lobar CMBs formation [96].

Current guidelines

Nowadays, reperfusion therapy is widely used in AIS patients, and stroke prevention relies on chronic anticoagulation with a tendency towards aggressively initiating treatment. Unfortunately, the eligibility criteria for reperfusion procedures and the scales currently used to qualify for secondary stroke prevention, do not take the presence of CMBs into account [Supplementary reference 18–24].

All recommendations regarding the use of antiplatelet, anticoagulant or IVT and EVT in patients with CMBs are experts' opinions mostly based on the results of observational studies or on randomised clinical trials with relatively small groups of patients. However, despite omitting the issue of CMBs, they constitute a guideline for managing patients in various clinical cases.

In 2013, Fisher proposed MRI screening for chronic anticoagulation in AF [Supplementary reference 25]. The algorithm developed by Fisher recommends MRI screening in patients aged 60+. Among those patients who have CMBs demonstrable on MRI, a distinction is made between cortical vs. subcortical CMBs, and between findings of five or more subcortical vs. less than five subcortical CMBs. According to this algorithm, treatment should be considered in patients with cortical CMBs or at least five subcortical CMBs [97].

Following the current AHA/ASA Guidelines, no RCT of IVT and EVT in AIS with baseline MRI to identify CMBs have been conducted, so no determination of effect of baseline CMBs on the treatment safety and efficacy of alteplase and EVT with CMBs is available. In the absence of any evidence that IVT and EVT provide no benefit or cause harm in eligible patients with CMBs, withholding treatment on the basis of the presence of CMBs could lead to the exclusion of patients who would benefit from it.

The AHA/ASA also recommend the use of antiplatelet drugs and oral anticoagulants in the prevention of cardiovascular events in patients with CMBs [8, 97, 98]. The problem of CMBs in the European Stroke Organisation (ESO) [99, Supplementary reference 26] and European Association of Cardiology (ESC) [7] documents and in the Practical Guide for Neurologists published in 2019 by Canavero et al. [100] is under discussion. The current recommendations are set out in Table 1.

Therefore, future studies should determine the number of CMBs above which we should not perform reperfusion therapy and not use anticoagulant therapy, and also answer the questions as to whether the number is the same for different CMB locations and whether the presence of other cardiovascular risk factors could correct this number. It is also important to identify those groups of patients that should be scanned by MRI before making therapeutic decisions.

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