Cerebral microbleeds: detection, mechanisms and clinical challenges

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Review
Future Neurology

In the last decade or so, cerebral microbleeds (CMBs) – tiny perivascular hemorrhages seen as small, well-demarcated, hypointense, rounded lesions on MRI sequences that are sensitive to magnetic susceptibility – have generated increasing interest among neurologists and clinical stroke researchers. As MRI techniques become more sophisticated, CMBs are increasingly detected in various patient populations (including all types of stroke, Alzheimer's disease and vascular cognitive impairment) and healthy community-dwelling older people. Their presence raises many clinical dilemmas and intriguing pathophysiological questions. CMBs are emerging as an important new manifestation and diagnostic marker of cerebral small-vessel disease. They are a potential predictor of future intracerebral hemorrhage risk, a possible contributor to cognitive impairment and dementia and a potential key link between vascular and degenerative pathologies. In this article, we discuss the available pathological, neuroimaging and clinical studies in the field, and we provide a modern overview of the clinical and pathophysiological implications of CMBs in different disease settings.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe risk factors for CMBs and MRI findings
- Describe the histopathology and pathophysiology of CMBs
- Describe the clinical implications of CMBs

Keywords

■ cerebral amyloid angiopathy ■ cerebral microbleed ■ cerebral small-vessel disease ■ gradient-recalled echo ■ hypertensive vasculopathy ■ microhemorrhage ■ vascular cognitive impairment

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The past decade has witnessed increasing interest in cerebral microbleeds (CMBs), reflected by the proliferation of publications about them [1]. CMBs are defined radiologically as small, rounded, homogeneous, hypointense lesions on T2*-weighed gradient-recalled echo (T2*-GRE) and related MRI sequences that are sensitive to magnetic susceptibility (Figure 1) [2]. Scharf *et al.* were the first to report on small, intracerebral black dots of signal loss on T2-weighted spin-echo MRI in patients with hypertensive cerebrovascular disease and intracerebral hemorrhage (ICH) associated with ischemic white matter disease and lacunar infarcts [3]. They called these lesions 'hemorrhagic lacunes', and their further characterization using T2*-GRE MRI sequences led to the current radiologic definition of 'microbleeds', a term coined by Offenbacher and colleagues in 1996 [4]. A key feature of CMBs is that they are not seen well on conventional computed tomography or MRI scans (Figure 1). Available histopathological studies suggest that CMB radiological lesions are due to tiny bleeds adjacent to abnormal small vessels, being mainly affected by hypertensive angiopathy (arteriolosclerosis – usually lipohyaline degeneration related to hypertension) or cerebral amyloid angiopathy (CAA) [5].

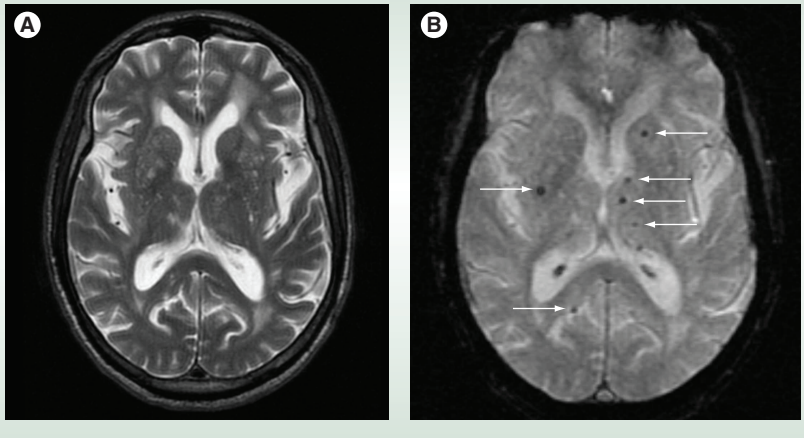

Figure 1. Cerebral microbleeds. (A) An axial T2-weighted MRI. **(B)** A T2*-weighted gradient-recalled echo (T2*-GRE) MRI. Note the microbleeds – small, dark dot-like lesions (arrows) visible only on the T2*-GRE image but not on the T2-weighted MRI.

The increasing recognition of CMBs in patients with cerebrovascular disease (including first-ever and recurrent ischemic or hemorrhagic stroke) [6,7], Alzheimer's disease [8,9], vascular cognitive impairment [10] and normal elderly populations (Figure 2) [11] raises many clinical dilemmas and intriguing pathophysiological questions [12]. CMBs are emerging as a manifestation and diagnostic marker of cerebral small-vessel disease (along with lacunar infarcts and white matter lesions – also termed white matter hyperintensities, white matter changes [WMC] or leukoaraiosis) (Box 1, Figures 3 & 4) [13–17]. They are a potential predictor of ICH risk, a possible contributor to cognitive impairment and dementia and may provide a new imaging tool to understand the links between vascular and degenerative pathologies [2]. CMBs are also occasionally detected in a variety of other conditions, including traumatic brain injury (traumatic microbleeds) [18,19], where they may have diagnostic or prognostic applications. However, these are beyond the scope of this article and are not considered further. The interested reader is referred to a recent summary of this field [1].

This article aims to provide a modern overview of the pathophysiological and clinical implications of CMBs in patients with cerebrovascular diseases, Alzheimer's disease, vascular cognitive impairment and in normal individuals. We will briefly discuss how the available pathological, neuroimaging and clinical studies could inform our understanding of the possible pathophysiological mechanisms underlying CMBs, and how these can provide novel

insights and future directions regarding the safety of antithrombotic use, the risk of recurrent symptomatic ICH, cognitive impairment and dementia.

What are CMBs? MRI detection, characteristics & differential diagnosis

Physical principles of microbleed MRI detection

The available data suggest that CMBs are composed of small collections of blood-breakdown products (in particular hemosiderin) contained within perivascular macrophages. Hemosiderin is an extremely paramagnetic material; this property, known as magnetic susceptibility, describes the degree to which a tissue (or any material) responds magnetically when placed in an exogenous magnetic field [20]. Consequently, when hemosiderin deposits are brought into the magnetic field of an MRI scanner, microscopic local magnetic fields develop, which create significant macroscopical inhomogeneities in the magnetic field surrounding CMBs, leading to fast decay of the local MRI signal, a phenomenon called the 'susceptibility effect' [12]. Similar distortions of the magnetic field are also caused by the close proximity of tissues with different magnetic susceptibilities (e.g., at the interface of soft tissues, bone and air).

In the most commonly used sequences in neuroimaging (incorporating T2- and T1-weighted images), magnetic susceptibility effects are largely corrected by the application of spin-echo techniques, which use a refocusing pulse [20,21]. However, in the case of CMB detection, rather than considering these local field inhomogeneities to be unwanted artefacts, such effects are positively exploited and optimized. GRE MRI sequences used for T2*-GRE imaging are considered to be very sensitive to the susceptibility effects and form the basis of blood-breakdown product detection (resulting from either 'macrohemorrhages' or CMBs) [2,22].

The resulting CMB signal hypointensities on T2*-GRE magnetic resonance images are typically larger than the physical size of the underlying hemosiderin deposits (2–10 vs 0.2–2.0 mm in diameter, respectively) [5,23]. This larger area of susceptibility-dependent dephasing on magnetic resonance images is called the 'blooming effect' and has important consequences in the visual interpretation of CMBs [2]. The extent of blooming varies according to the MRI sequence parameters, including magnetic field strength, echo time, slice thickness, flip angle, spatial resolution and image postprocessing techniques (such as susceptibility-weighted imaging [SWI]); therefore, altering these factors can lead to improved CMB detection [2,24–30]. Of these imaging parameters, echo time seems to be among the most influential for CMB identification [2]. A recent study of 22 patients seen in our stroke clinic and imaged using two separated T2*-GRE echo times demonstrated that although lengthening the echo time (thus giving more time for dephasing) substantially increased the total number of CMBs

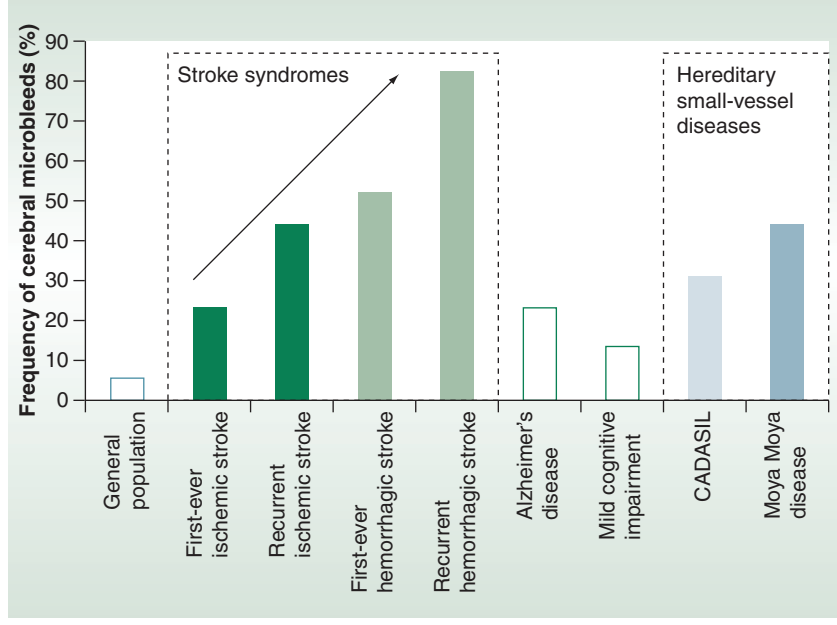

Figure 2. Frequency of cerebral microbleeds in different populations and disease states.
CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
Data taken from [6,9,162–164].

Box 1. Cerebral small-vessel disease: the most prevalent brain condition ever described.

- Cerebral small-vessel disease refers to a group of pathological processes, of various etiologies that affect the small arteries, arterioles and capillaries of the brain [13]. They are considered to be among the most prevalent known neurologic processes and have major implications for stroke, dementia/cognitive impairment and aging [13,14]. Cerebral small vessels can either penetrate the brain cortex superficially, reaching the underlying structures of the white and deep gray matter, or stem from deeper arterial perforators at the base of the brain (Figure 3)
- Hypertensive small-vessel disease causes thickening of and damage to the arteriole wall, and typically affects the small-arterial penetrators to the white matter and the deep gray nuclei. Cerebral amyloid angiopathy is a chronic degenerative disease with progressive deposition of amyloid-β protein in the walls of small-to-medium-sized arteries, arterioles and capillaries in the cerebral cortex, overlying leptomeninges and gray–white matter junction [15,16]
- MRI is the most important tool for detecting and mapping cerebral small-vessel diseases. Their MRI manifestations include lacunes, white matter hyperintensities (areas of bright signal on T2-weighted or FLAIR images) and cerebral microbleeds (Figure 4). Small-vessel disease also has histopathological manifestations that may sometimes be beyond detection by currently available neuroimaging modalities (e.g., very small microinfarcts) [17]

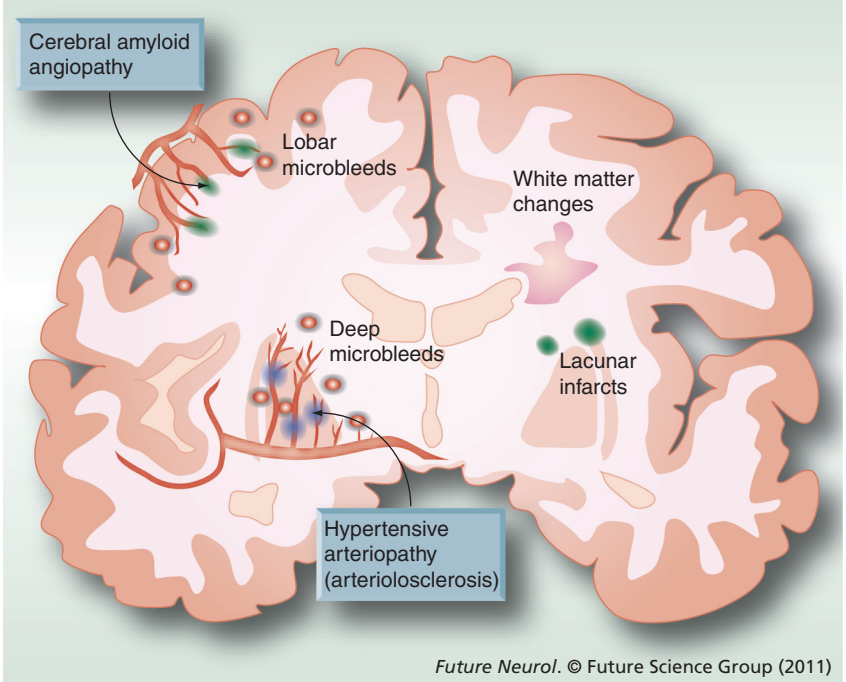

Figure 3. The spectrum of small-vessel diseases. The small vessels of the brain can mainly be affected by two types of pathologic abnormalities: arteriolosclerosis and/or cerebral amyloid angiopathy. Arteriolosclerosis typically affects small vessels originating from deep arterial perforators that penetrate the white matter and deep gray nuclei, whereas cerebral amyloid angiopathy preferentially affects the small arteries and arterioles of the cerebral cortex and gray–white matter junction by the deposition of amyloid-β in the vessel walls. Since small vessels cannot be visualized *in vivo*, the brain parenchymal lesions (detected on MRI) thought to be caused by the vessel changes described earlier have been adopted as a marker of the underlying cerebral small-vessel diseases. These brain parenchymal lesions include white matter changes, lacunar infarcts and cerebral microbleeds. It is important to note that the anatomic distribution of cerebral microbleeds is meant to reflect the underlying pathological vessel damage. Thus, cerebral microbleeds located in cortical–subcortical regions are presumably caused by cerebral amyloid angiopathy, while microbleeds located in deep brain regions are presumed to be the result of arteriolosclerosis.

detected, in some cases, the image quality was reduced, causing uncertainty in distinguishing lesions as CMBs or 'mimics' [24].

Despite the strong influence of MRI parameters on the number of CMBs detected, no consensus is yet available on an optimal imaging protocol for their identification. The heterogeneity in the sensitivity of CMB detection in different studies is most strikingly illustrated by the varying prevalence of CMBs reported in population-based studies (4.7–35.7%) [11,31].

MRI criteria for microbleed identification & differential diagnosis

Although precise MRI operational criteria to distinguish CMBs have varied between studies in the past [6], a consensus was recently published [2]: CMBs are defined as small, rounded or ovoid, blooming, homogeneous signal voids on T2*-GRE and related MRI sequences that are sensitive to susceptibility effects (Box 2 & Figure 1). A precise size definition does not appear to substantially influence the detection of CMBs: although the upper size limit is usually taken to be between 5 and 10 mm, a recent analysis revealed that the volume of microbleeds and macrobleeds (at least in a cohort of patients with CAA) is not a continuum, but shows a bimodal distribution [32].

In identifying CMBs, care must be taken to distinguish them from 'mimics' and artefacts (Figure 5). For example, blood vessels in the subarachnoid space, calcifications of the basal ganglia or cavernous malformations can all give rise to small, dot-like, low-signal areas on T2*-GRE MRI. Careful inspection of contiguous slices using different imaging modalities (CT, T2 MRI, FLAIR or DWI) and lesion geometry and location facilitates the identification of CMBs (Table 1).

The rating of CMB presence, number (burden) and anatomical distribution in the brain (e.g., lobar vs deep) is an essential prerequisite to investigate the important clinical questions in the field. CMB rating scales validated in hospital cohorts of stroke patients, including the Microbleed Anatomic Rating Scale (MARS) (see Supplementary Figure 1; www.futuremedicine.com/doi/suppl/10.2217/fnl.11.42), have been proposed [33,34], which include standardized defining criteria for CMBs as well as schemes to classify their anatomical location.

SWI & high-field imaging: mapping the future of CMB detection

The recently introduced SWI technique is increasingly being used in clinical practice and research [35,36]. SWI is a high-resolution, three dimensional T2*-GRE technique that enables us to visualize CMBs (and bleeds in general) with a sensitivity never seen before *in vivo* [26,36]. This technique is currently the most sensitive means to image CMBs. Recent data have shown that SWI can detect significantly more CMBs (at least 67% more) compared with conventional T2*-GRE [27]. In addition, due to its high sensitivity to hemosiderin, SWI can detect CMBs that are much smaller in size [26] than the 5.7-mm cut-off suggested by Greenberg *et al.* in a cohort of patients with CAA [32]. The *in vivo* identification of CMBs as small as 1 mm in size (or even smaller) could potentially inform the debate about pericapillary hemosiderin deposits within the submillimeter range, and has been recently described in some pathological studies [37,38].

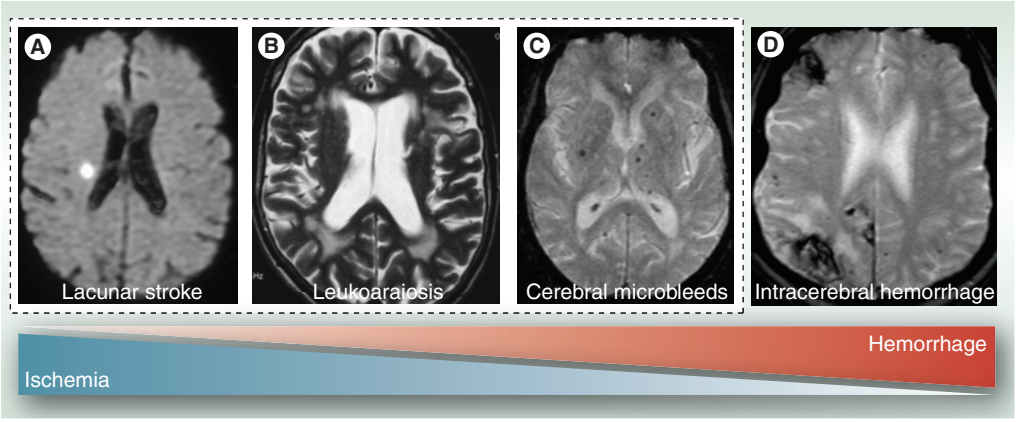

Figure 4. MRI manifestations of small-vessel disease of the brain. (A) An acute lacunar infarct in an axial diffusion weighted MRI. **(B)** An axial T2-weighted MRI showing confluent white matter changes (leukoaraiosis). **(C)** An axial T2*-weighted gradient-recalled echo image showing multiple cerebral microbleeds (dark, rounded lesions) in lobar distribution. **(D)** The right panel is also an axial T2*-weighted gradient-recalled echo, which shows two lobar macrobleeds, fulfilling the Boston criteria for probable cerebral amyloid angiopathy.

Another benefit of SWI is that it can discriminate between some CMB 'mimics' and true microbleeds. For example, calcifications that usually appear to be hypointense on T2*-GRE and thus are difficult to differentiate from microbleeds have an opposite signal intensity in SWI (because calcifications tend to be diamagnetic and iron paramagnetic), and thus appear hyperintense [39]. SWI can also minimize other 'mimics' such as vessel flow voids and the presence of deoxyhemoglobin [36].

Despite the increased sensitivity of SWI, a recent study has questioned the clinical relevance of improved microbleed detection using this method [40]. Goos and colleagues evaluated 141 patients presenting at a memory clinic and found no differential independent associations of microbleeds detected on GRE versus SWI in terms of vascular risk factors and imaging markers of small-vessel disease (although more CMBs were detected by SWI) [40]. The authors suggested that CMBs may be considered the 'tip of the iceberg' for underlying small-vessel pathology; thus, SWI simply exposes a larger tip of the iceberg, already captured by T2*-GRE, but may not lead to important reclassification of CMB groups. However, this study was limited by the heterogeneity of the population (essentially composed of several relatively small subgroups), which may have limited the power of detecting meaningful differences. Further research is clearly needed to define any added value that might be provided by SWI.

The clinical relevance of improved microbleed detection using SWI may lie in the improved sensitivity to dynamic changes during the natural history of small-vessel diseases, rather than in cross-sectional 'snapshots' [26]. SWI in conjugation with the introduction of higher-field scanners [41] should improve our ability to see the development of CMBs and their accumulation over time (discussed later), which could in turn lead to improved early recognition, diagnosis and therapeutic monitoring of different patient populations.

Histopathological correlates of CMBs

The combination of MRI and direct correlation with small vessel and tissue histopathological changes associated with CMBs (detected in life or by post-mortem MRI) can provide significant insights into the underlying disease processes. A limited number of studies focusing on direct radiological–pathological correlations of CMBs is available [5,23,42,43]. Fazekas and collaborators were the first to demonstrate that the pathological substrates of 21 CMBs seen as hypointense

Box 2. Current consensus MRI criteria for cerebral microbleed identification.

- Hypointense lesions (black) on T2*-GRE MRI
- Rounded or ovoid in shape
- Well defined
- Small†
- Surrounded by brain parenchyma (at least half of the lesion)
- Not seen well on T1- or T2-weighted MRI
- Clinical history excluding traumatic diffuse axonal injury
- Differentiated from other hypointense lesions or artefacts ('microbleed mimics' – see Table 1)

†Size should be used very conservatively in the identification of cerebral microbleeds, and a precise upper limit is probably not critical.
T2-GRE: T2*-weighted gradient-recalled echo.*

Table 1. Nonhemorrhagic and hemorrhagic causes of small, dot-like, low-signal areas on T2*-weighted gradient-recalled echo besides cerebral microbleeds and the strategy for their differential diagnosis.

Microbleed 'mimics'	Distinguishing features/strategy for diagnosis
Nonhemorrhagic	
Flow voids from blood vessels	Linear/curvilinear lesions in subarachnoid space, usually cortical or juxtacortical (visible on T2 MRI)
Calcifications	Usually found in the globi pallidi or dentate nuclei. Often symmetrical hypointensities (may be bright flecks on CT)
Air–bone interfaces (partial volume artefacts)	Particularly seen in the frontal/temporal lobes (because of the adjacent orbit and mastoid bone, respectively) and artefact at the edges of the cerebellum. Reviewing adjacent T2*-GRE slices will help reduce misinterpretation as CMBs)
Hemorrhagic	
Cavernous malformations (essentially clusters composed of a single layer of endothelium and an absence of BBB components and neuronal tissue. These thinly walled vessels resemble sinusoidal cavities filled with stagnant blood)	Visible on T2 MRI. Familial cavernous malformations (subtypes I–IV) type II have a distinctive 'popcorn-like' appearance with a hypointense hemosiderin rim and a core of variable signal intensity. Type IV malformations (punctuate hypointensities) may be more difficult to differentiate
Hemorrhagic micrometastases (especially from melanoma or renal cell carcinoma)	Concomitant presence on T1 MRI as hyperintensity or as surrounding edema. The clinical history and examination may also help
Diffuse axonal injury	Clinical history, concomitant imaging abnormalities (e.g., parenchymal contusions and/or skull fractures)
Hemorrhages within or along the margin of an area of infarction	Look at the T2, FLAIR or DWI MRI sequences to identify infarction
Small hemorrhages close to a large ICH or to an infarct	Visible on T2*-GRE MRI and on T2, FLAIR or DWI MRI, respectively

CMB: Cerebral microbleed; DWI: Diffusion-weighted imaging; ICH: Intracerebral hemorrhage; T2-GRE: T2*-weighed gradient-recalled echo.*

lesions on T2*-GRE MRI of 11 autopsied brains were focal accumulations of hemosiderin-laden macrophages adjacent to abnormal small vessels [5]. Their subjects were mostly hypertensive patients who suffered an ICH, and in the majority of the brains, CMBs were associated with hypertensive vasculopathy (fibrohyalinosis) [5]. In two brains, CAA of variable extent was detected and found to be associated with foci of remote blood leakage. In the brains with underlying hypertensive vascular changes, CMBs were preferentially located in the basal ganglia/thalami and sometimes at cortical–subcortical locations. A recent study combined SWI and histopathology in eight brains from patients with Alzheimer's disease [42], and confirmed that CMBs indeed seem to correspond to areas of microscopic bleeding – although a minority of these lesions were found to be microaneurysms, small lacunes or vessel wall dissections. In this study, the majority of CMBs were found in cortical–subcortical locations, and the adjacent arterioles were affected by advanced CAA (vessel wall thickening with amyloid-β (Aβ) deposition and lacking a muscularis layer) [42].

Taken together, the findings of neuroimaging–pathological correlation studies, as well as other histopathological analyses of CMBs [38,44–47], show that CMBs are commonly associated with two different small-vessel pathologies: hypertensive vasculopathy and CAA. Moreover, these two microangiopathic disorders seem to influence CMB topography. Typically, hypertensive vasculopathy results in CMBs in the basal ganglia, thalamus, brainstem and cerebellum, while CAA is characterized by a lobar, cortical–subcortical distribution (Figure 6) [2]. Indeed, the differential patterns of CMB locations correlate well with the distribution of the vascular pathology; hypertensive vasculopathy (arteriolosclerosis) affects small, deep arterial perforators to the white matter and deep nuclei, whereas CAA involves the small-to-medium-sized arteries, arterioles and capillaries of the cerebral cortex and gray–white matter junction (Figure 3). Nevertheless, this notion may be an oversimplification since the neuroimaging–pathological correlation studies described earlier mainly included patients likely to have advanced small-vessel disease – either CAA or hypertensive arteriopathy. For example, in the study by Fazekas *et al.*, most patients were hypertensive and died from ICH [5]; by contrast, in the study by Schrag and coworkers, the majority of the patients had advanced CAA [42]. As both CAA and hypertension-associated vasculopathy are age-related conditions, they commonly coexist in elderly patients with (or without) CMBs. Therefore, in many patients seen in clinical practice, CMBs have a 'mixed'

lobar and deep distribution, which is challenging to interpret and will require pathological validation studies.

Risk factors & associations

Apart from being associated with specific underlying vasculopathies, CMBs are strongly associated with a number of clinical syndromes including ischemic and hemorrhagic stroke, Alzheimer's disease and vascular cognitive impairment (Figure 2) [12]. In these patient populations, as well as in healthy elderly individuals, studies of risk factors for CMBs and associations have been extensively reviewed [2,6,9,12,48–51]. Aging (partly reflecting the increasing prevalence of hypertension and CAA), hypertension and *APOE* genotype along with other neuroimaging correlates of brain small-vessel disease (lacunar infarcts and WMCs) show the most consistent associations with CMBs across different studies.

CMBs in population-based studies: recent insights

As well as in populations of patients with clinical syndromes or diseases, CMBs have been studied in several populations of community-dwelling elderly individuals (see Supplementary Table 1; www.futuremedicine.com/doi/suppl/10.2217/fnl.11.42) [31,52–54]. Most of these studies have highlighted hypertension [52–54] and age [31,52,54] as key risk factors of CMBs; some also showed an association with male gender [31]. However, no independent relationships were found with other cardiovascular risk factors, MRI findings or *APOE* status. A pooled analysis of these population-based cohorts revealed an increased risk of CMBs in hypertensive people (odds ratio [OR]: 3.9; 95% CI: 2.4–6.4) [6], which is comparable with the risk for CMBs demonstrated in hypertensive stroke populations (OR: 2.3; 95% CI: 1.7–3.0) [6].

Recent population-based studies (including a larger number of participants with a higher mean age and using advanced MRI scanning protocols) have provided more evidence about the associations with CMBs. In the Age, Gene/Environment Susceptibility (AGES)–Reykjavik study of older people (n = 1962, with a mean age of 76 years), as expected, the prevalence of CMBs increased with age [55]. Interestingly, 70% of the detected CMBs were located in the cerebral lobes and over a third of these lesions were in posterior hemispheric regions (parietal and occipital lobes) (Figure 7). This topographical pattern, along with the significant association of CMBs with *APOE ε4*/*ε4* genotype, is suggestive of underlying CAA in many of these participants. Recently, the Rotterdam scan study has revealed evidence of a possible differential influence on the anatomical distribution of CMBs [11,56]. In the analysis of this cohort (now including 3979 persons), Vernooij *et al.* [56] and Poels *et al.* [11] showed that cardiovascular risk factors (including systolic blood pressure, hypertension and smoking) and the presence of lacunar infarcts and white matter lesions were related to CMBs in deep or infratentorial regions, while the *APOE ε4* allele was associated with CMBs in a strictly lobar anatomical distribution (Figure 8).

A recent subanalysis of the Rotterdam scan study specifically investigated the spatial distribution of lobar microbleeds over the different lobes [57]. After taking into account the volumetric differences between the lobes and the clustering effects of multiple microbleeds [58], this study found that lobar CMBs (including strictly lobar CMBs) showed a significant predilection for the temporal ($p < 0.001$) and parietal lobes ($p = 0.04$) [58]. In these regions, microbleeds were not uniformly distributed; instead, they were primarily found on the posterior part in the temporal and parietal lobes. This study adds evidence to the association between lobar microbleeds and CAA. In addition, the spatial distribution pattern of lobar CMBs found in the general elderly population may shed light on our understanding of the pathophysiology of CAA. Previous studies that have investigated the distribution of CMBs in CAA and Alzheimer's disease

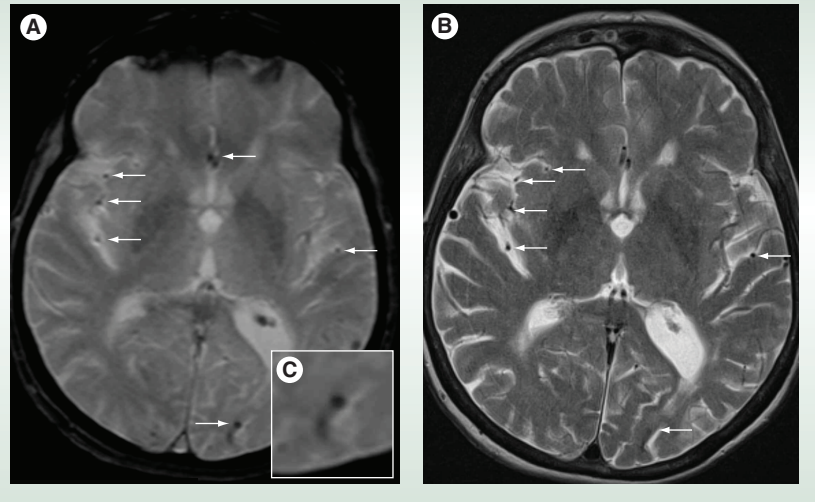

Figure 5. How many microbleeds can you count? (A) An axial T2*-weighted gradient-recalled echo sequence showing some small, round, hypointense lesions resembling cerebral microbleeds (arrows). However, careful comparison with the T2-weighted sequence shows that these are consistent with vessel flow voids (a common microbleed 'mimic'; arrows in **[B]**). Note the linear vessel leading up to the lowest black dot (magnified in **[C]**). By contrast, microbleeds generally appear as blind-ended round or ovoid lesions.

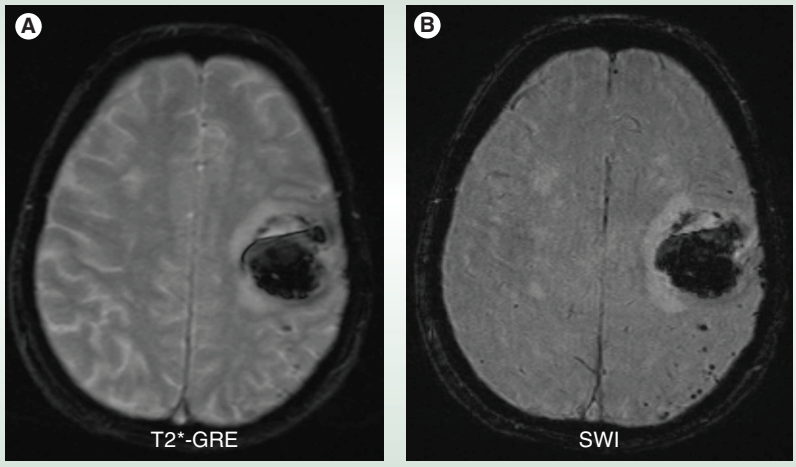

Figure 6. Susceptibility-weighted imaging is a more sensitive method for cerebral microbleed detection compared with conventional T2-weighted gradient-recalled echo. (A) The axial T2*-GRE image of this patient who suffered an intracerebral hemorrhage contains four definite microbleeds. **(B)** The corresponding SWI image of the same patient (taken on the same day) shows three-times as many cerebral microbleeds as that in **(A)**.
SWI: Susceptibility-weighted imaging; T2*-GRE: T2*-weighed gradient-recalled echo.

have also found a predilection for the occipital lobe [8,58]. However, these studies were conducted in patients with clinical CAA (according to the Boston diagnostic criteria [59]) or Alzheimer's disease, probably representing more advanced CAA-related pathology.

In summary, the results of these population-based cohorts [11,55,56], as well as other studies, suggest that CMB location in the brain (deep/infratentorial vs strictly lobar) is related to the underlying arteriopathy (hypertensive or CAA-associated, respectively). The strong association between strictly lobar (but not deep) CMBs and *APOE ε4* is consistent with the well-known relationship of this allele with CAA [60], in which cortical–subcortical areas are the preferential sites of vessel amyloid deposition [16]. Hence, strictly lobar CMBs (Figure 6A) may be a useful diagnostic marker for CAA; however, this hypothesis requires further pathological validation. On the other hand, the close link of deep and infratentorial CMBs with traditional cardiovascular risk factors such as severe hypertension and systolic blood pressure, as well as with lacunar infarcts and white matter lesions (expressions of 'ischemic small-vessel disease'), points to hypertension-related microangiopathy as their primary cause (Figure 6B). The link between arterial hypertension and CMBs (especially deep CMBs) is further supported by studies highlighting their close relationship with left ventricular hypertrophy [61], higher ambulatory blood pressure [62,63], retinal microvascular abnormalities [64] and lacunar strokes [65]. By contrast, CAA does not seem to be accounted for by conventional cardiovascular risk factors.

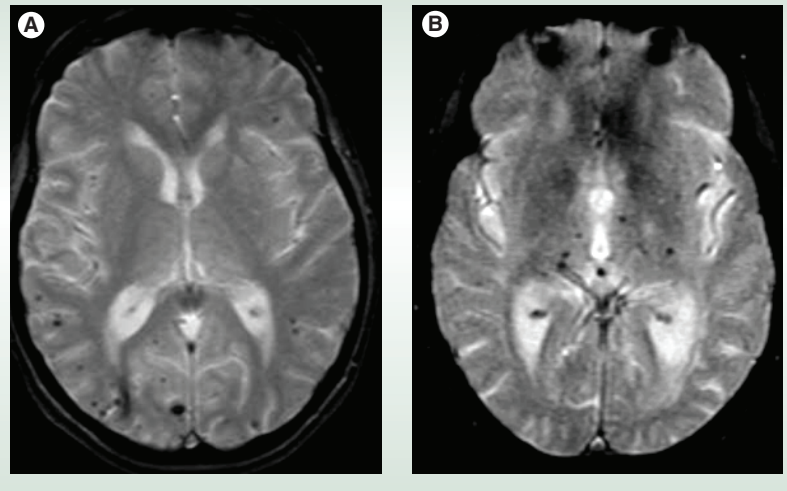

Figure 7. Patterns of cerebral microbleed distribution. (A) Axial T2*-weighted gradient-recalled echo of an elderly individual without a history of hypertension, showing microbleeds in strictly lobar brain regions (cortical and cortical–subcortical). This topographical pattern may be suggestive of cerebral amyloid angiopathy. **(B)** Axial T2*-weighted gradient-recalled echo of an elderly individual with a history of hypertension. Microbleeds are strictly located in deep brain areas (basal ganglia and thalamus).

Pathophysiology of CMBs: a key role for BBB dysfunction?

Cerebral microbleeds are unique among the MRI manifestations of cerebral small-vessel disease, in that they seem to provide direct evidence of microvascular leakiness, causing blood-breakdown products to extravasate through the vessel wall. By contrast, WMCs lack pathological specificity and may result from a wide range of both vascular and inflammatory conditions. In the setting of small-vessel disease, the vascular endothelium of small arterioles and capillaries seems to become permeable to elements such as red blood cells, inflammatory cells and plasma proteins [66], which are normally excluded by the BBB [67]. Thus, it seems highly plausible that endothelial/BBB derangement could play a key role in CMB formation [68], although direct evidence for this hypothesis is limited so far.

The BBB is a dynamic structure that consists of a microvascular endothelial cell monolayer connected by tight junctions and resting on a basal lamina, adjoined by smooth muscle cells (at the arteriolar level), pericytes, microglia and perivascular macrophages and covered by astrocytic end-feet. These cellular elements form a complex mechanism by which central nervous system homeostasis is maintained, partly by

controlling cerebral blood flow and partly by providing a dynamic barrier at the blood–brain interface. Disordered interaction between these cellular elements and inter- and intra-cellular signaling pathways also mediates disease: specific perturbations in any of the components of this complex system could potentially disrupt the BBB and lead to microbleeding.

How could small-vessel diseases cause the BBB to fail and give rise to CMBs? As we have seen, at least two pathophysiological mechanisms can lead to CMBs: CAA and hypertension (Figure 9). In CAA, the deposition of Aβ protein, mainly in cortical and leptomeningeal small-caliber vessels (e.g., in the smooth muscle layer) can alter elements of the BBB, up to years before neuroimaging findings and symptoms begin; as the damage accumulates, microvascular endothelial walls become leaky and thickened. Focal wall fragmentation can give rise to MRI-detectable microhemorrhages in a predominantly lobar distribution [69]. For deep CMBs to occur, hypertension-mediated small-vessel damage could also compromise the BBB and vessel wall integrity, but possibly with different molecular/cellular defects [70,71].

There may be interactions between these two pathways, since both CAA and hypertensive arteriopathy may coexist in elderly people (Figure 9). However, their relative contribution in different disease states may vary; for example, in Alzheimer's disease, a more degenerative picture (CAA-related) seems likely to prevail [9].

The proposed cascade of pathophysiological events leading to CMBs is speculative at present, but could explain a number of epidemiological, neuroimaging, pathological and clinical observations. For example, it provides a putative mechanism linking small-vessel disease to tissue damage and neuronal dysfunction, since the BBB is an integral part of the neurovascular unit that incorporates the connection of astrocytes to neuronal synapses and also blood cells (e.g., leukocytes, polymorphonuclear cells, monocytes, lymphocytes and erythrocytes) [67]. In addition, this extended view of the BBB may help to explain recent findings of significantly increased levels of free, active MMP-9 and C-reactive protein among patients with microbleeds [72]. Furthermore, this model predicts that if breakdown of the BBB is an early event in the natural history of CMBs, the toxic extravasation of plasma proteins, including plasmin and thrombin, may contribute to neuronal injury and neurodegeneration even before microhemorrhages reach the threshold for MRI-detection.

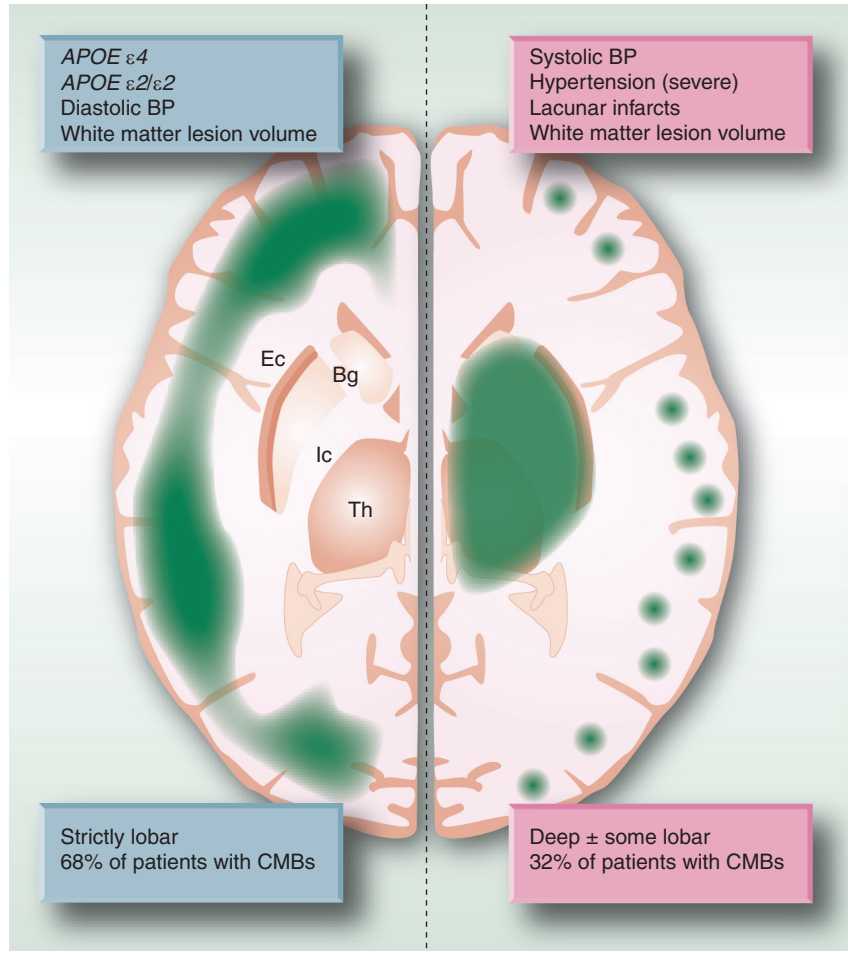

Figure 8. The distribution of cerebral microbleeds and their significant associations in the Rotterdam Scan Study.
Bg: Basal ganglia; BP: Blood pressure; CMB: Cerebral microbleed; Ec: External capsule; Ic: Internal capsule; Th: Thalamus.
Data taken from [56].

The failure of the BBB as a central theme in the pathogenesis of CMB, could also be relevant for other expressions of cerebral small-vessel disease (such as WMCs and lacunar infarcts), which are traditionally considered to be ischemic in nature [13,68] and are strongly associated with CMBs. The cells that constitute the BBB not only maintain microvessel integrity, but also play a part in the control of cerebral blood flow. It could also help account for a previously unsuspected interplay between the hemorrhagic and ischemic components in small-vessel diseases, which has been observed in recent reports (Box 3) [73–77].

Clinical implications of CMBs

CMBs & clinical impairment, disability & mortality

It is now becoming evident that CMBs can contribute to neurologic dysfunction, long-term disability and cognitive impairment. Histopathological studies show brain tissue

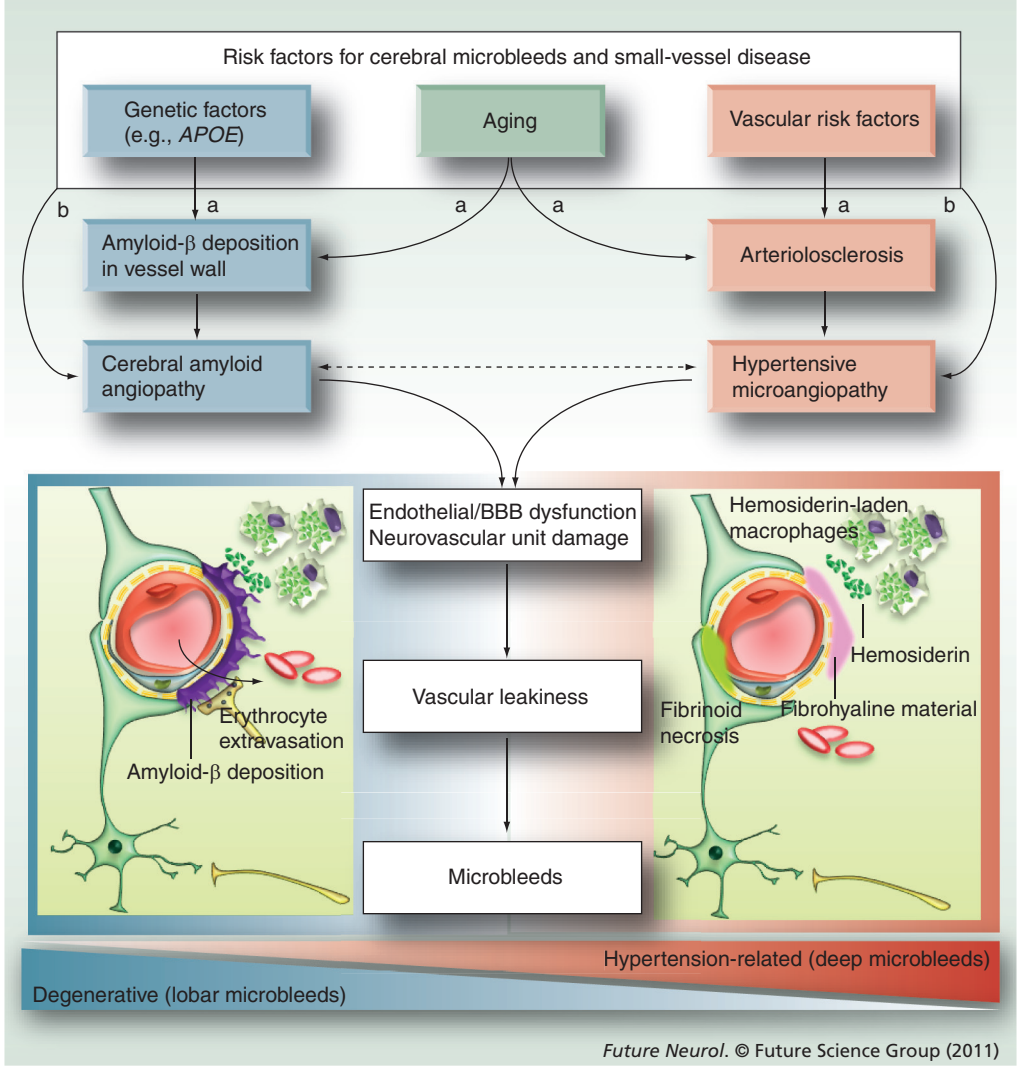

Figure 9. A proposed model of the pathophysiological pathways that can give rise to cerebral microbleeds. The available pathological, epidemiological and neuroimaging evidence suggests that at least two distinct pathophysiological pathways can lead to cerebral microbleeds in the context of small-vessel disease of the brain: the cerebral amyloid angiopathy-related pathway (left side) and hypertensive microangiopathy-associated pathway (right side). The former can be thought of as a neurodegenerative process, while the latter as a more 'pure' vascular process. Through different genetic, morphological and functional alterations, both pathways can culminate in endothelial/BBB disruption, vascular leakiness and microbleeding. Note that these two pathways have distinct risk factors (which can affect them at multiple levels during the disease process; they could act to initiate the disease process [a] or contribute directly to the already established disease mechanism [b]), but may overlap in elderly individuals. The two routes can contribute to the burden of cerebral microbleeds to a different extent (e.g., the degenerative cerebral amyloid angiopathy-related pathway may prevail in Alzheimer's disease, while the vascular hypertension-related pathway may predominate in patients with intracerebral hemorrhage). The cellular and molecular details of the proposed representation remain to be elucidated.

damage surrounding CMBs, providing a possible substrate for clinical impairment [5,23,42,43]. Besides causing direct structural damage to the surrounding tissue (presumably induced in part by toxic/inflammatory effects of leaking elements such as inflammatory and red blood cells and various plasma proteins), recent experimental data suggest that microbleeding can potentially disturb the function of nearby neurons [78] or even affect the cortical electrical activity (due to the high concentration of hemosiderin) [79,80]. Broadly, CMBs could affect brain function either acutely, if they develop rapidly in a strategic location, or they could have a cumulative effect on anatomically distributed functions (e.g., cognition or gait).

Could microbleeds cause acute clinical symptoms?

A seizure-like mechanism may account for the transient focal neurological attacks described in some patients with CAA and could possibly be associated with CMBs [81,82]. The episodes consisted of recurrent, mostly stereotyped transient motor or sensory symptoms (focal weakness, numbness or paresthesias) of gradual and spreading onset (unlike 'typical' transient ischemic attacks, which start abruptly with negative neurological phenomena). In a report by Roth and coworkers, four out of six patients with these transient symptoms responded to anticonvulsant drugs, while the other two patients showed improvement after the cessation of their antiplatelet therapy [82]. Patients similar to those described in case series raise interesting therapeutic dilemmas [81,82]. For instance, if microbleeding is causing these atypical transient neurological symptoms through a seizure-like mechanism, then antithrombotic medication should probably be avoided, while anticonvulsant medication is the most reasonable and safe treatment.

It remains uncertain whether a single CMB – with an absolute order of size of less than a millimeter in diameter – can disrupt the brain function to cause an acute stroke or transient ischemic attack syndrome. This may be the case if CMBs form rapidly in a strategic location, by analogy to acute lacunes, which are by definition smaller than 15 mm. Only one case report in the literature suggests that this can actually happen [83]. Whether CMBs could be a clinically important cause of lacunar-type stroke or transient ischemic attack symptoms requires further study. However, the most likely mechanism by which CMBs can be associated with clinical impairment may lie in their accumulation over time, and as a biomarker of underlying small vessel disease progression.

Accumulation of CMBs over time

Only limited data are available on how CMBs accumulate over time. Gregoire and colleagues studied a cohort of 21 surviving patients with ischemic stroke or transient ischemic attacks screened for microbleeds at baseline and followed-up after a mean interval of 5.5 years [84]. During this period, half of the patients with CMBs at baseline developed new CMBs compared with only 8% of patients without baseline CMBs [84]. In this small cohort, the presence of CMBs at baseline and mean systolic blood pressure predicted the development of new lesions [84]. A recently published study, part of the Rotterdam scan study, presented the first longitudinal data on the incidence of CMBs in the general population [85]. Poels *et al.* reported that the incidence of CMBs in this elderly population followed-up

Box 3. Are cerebral microbleeds a potential link between ischemic and hemorrhagic mechanisms in cerebrovascular disease?

- Cerebrovascular disorders have traditionally been thought to be dichotomized along hemorrhagic versus ischemic mechanisms
- A recent investigation [74] and a case report [75], found an unexpectedly high prevalence of positive diffusion-weighted imaging (DWI) lesions, indicative of small infarcts, in patients with advanced cerebral amyloid angiopathy. These DWI lesions were associated with microbleed burden, suggesting shared pathophysiological pathways for hemorrhagic processes and ischemia [73]. A multicenter cross-sectional MRI study has recently expanded these findings [76]. Gregoire and colleagues found that acute, subclinical ischemic brain lesions are frequent (but previously underestimated) after ICH, and are three-times more common in cerebral amyloid angiopathy-related ICH than other ICH types [76]. Ischemic brain lesions were associated with white matter changes and strictly lobar microbleeds, suggesting that they result from an occlusive small-vessel arteriopathy. This imaging study indicates that DWI lesions contribute to the overall burden of vascular-related brain damage in ICH, and thus may be a useful surrogate marker of ongoing ischemic injury from small-vessel damage
- Jeon and coworkers reported the rapid appearance of cerebral microbleeds (CMBs) in 12.7% of patients (n = 237) who underwent serial T2*-weighted gradient-recalled echo imaging at presentation and after a median of 4 days [77]. The presence of CMBs at baseline and the presence of severe small-vessel disease were independent predictors of new CMBs, demonstrating the rapidly evolving nature of CMBs in the acute phase of ischemic stroke
- Taken together, these data suggest an intriguing interplay between the hemorrhagic and ischemic components in small-vessel diseases [73]. Rather than being separate entities, 'microbleeding' and 'microinfarction' are in a dynamic continuum. Thus, it may be important to reframe our thinking from the classic dichotomous etiologies and mechanisms of cerebrovascular disease (hemorrhagic vs ischemic) to a continuum of causative factors. CMBs may be a marker of abnormal small vessels that are prone not only to future bleeding, but also to occlusion

after a 3-year interval increased from 24.4% at baseline to 28.0% at follow-up [85]. A total of 85 persons (10.2%) developed new CMBs; the presence of microbleeds at baseline predicted the development of new CMBs (OR: 5.38; 95% CI: 3.34–8.67) [85]. Strong predictors of the incidence of CMBs were found to differ depending on their anatomical distribution in the brain, being similar to population-based studies of the prevalence of CMBs. Traditional cardiovascular risk factors, the presence of lacunar infarcts and larger WMC volume at baseline were associated with incident deep or infratentorial CMBs, whereas *APOE ε4*/*ε4* genotype or larger WMC volumes had a higher risk of incident strictly lobar CMBs [85]. Another recent longitudinal study evaluated the frequency and risk factors of newly occurring CMBs over an average period of 2 years in a memory clinic cohort (n = 254; including patients with Alzheimer's disease) and found that 12% of patients developed new CMBs; the burden (presence and number) of baseline CMBs was a strong predictor for the development of new CMBs [86]. The results of these studies show that in a variety of healthy and neurological patient populations, CMBs accumulate over time and are related to baseline CMBs. The development of new CMBs may reflect the progression and severity of the underlying small-vessel disease, providing one mechanism by which CMBs relate to neurological function or outcome. The evaluation and mapping of CMBs on sequential MRI may help to monitor the severity of the underlying disease, the effect of risk-modifying measures and to tailor therapeutic decisions.

A 4-year longitudinal study which used SWI to monitor changes of CMBs annually in a cohort of elderly patients (28 healthy controls and 75 individuals with mild cognitive impairment) has recently presented interesting data [26]. While none of the cognitively normal participants had more than three microbleeds, six of the subjects with mild cognitive impairment had more than three microbleeds. In five out of these six patients, the number of CMBs progressively increased over serial scans, and all six went on to develop progressive cognitive impairment based on their dementia rating [26]. The late-onset cognitive decline observed in these patients most probably reflects the synergistic effects of small-vessel disease and degenerative changes (discussed later in the 'Cognition' section). However, this study provides preliminary data that CMBs may relate to cognitive outcome, particularly if they evolve over time.

CMBs & outcome

A population-based study of elderly people (n = 435) with or at high risk of cardiovascular disease investigated the prognostic value of CMBs regarding overall, cardiovascular-related and stroke-related mortality [87]. Compared with subjects without any CMBs, subjects with more than one CMB had a sixfold risk of stroke-related death (hazard ratio: 5.97; 95% CI: 1.60–22.26; p = 0.01) [87]. However, the most striking findings were that deep CMBs were found to be significantly and independently associated with cardiovascular mortality (hazard ratio: 2.67; 95% CI: 1.23–5.81; p = 0.01), whereas strictly lobar CMBs were significantly associated with stroke-related mortality (hazard ratio: 7.20; 95% CI: 1.44–36.10; p = 0.02) [87]. Also in a previous study, the presence of CMBs (especially multiple CMBs) was the strongest predictor of mortality (among other MRI markers of vascular damage, such as WMCs) in a memory clinic population of 1138 patients [88].

As well as affecting mortality and stroke risk, the accumulation of multiple CMBs could have a cumulative effect on brain functions subserved by distributed networks, such as gait or cognition. It is important to note that there are many potential confounders in the study of how CMBs could affect brain function and cause clinical impairment. Their close relationship and overlap with other imaging correlates of cerebral small vessel disease such as lacunes and white matter damage, as well as all types of clinical stroke syndromes, makes it challenging to dissect their independent effects.

CMBs & neurological function

Gait

In a cross-sectional study, De Laat *et al.* reported the first indications that CMBs (especially in the temporal and frontal lobe, basal ganglia and thalamus) may be associated with gait disturbances, independently of other coexisting markers of cerebral small-vessel disease [89]. In addition, in a prospective cohort of elderly patients (n = 94) presenting with spontaneous lobar ICH, Greenberg and colleagues showed that a high number of CMBs at baseline was associated with a high 3-year cumulative risk of cognitive impairment, functional dependence or death (being more than 50% in individuals with more than six CMBs) [90]. CMBs have also been associated with clinical disability in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy [91].

Cognition

There has been increasing attention given to CMBs in relation to cognition. Werring and colleagues systematically examined the cognitive impact of CMBs [92] in a neurovascular clinic population. Consecutive patients with CMBs (n = 25) were compared with a control group without CMBs (n = 30) that was closely matched for age, WMC severity, prevalence and location of cortical infarctions and ischemic stroke subtype (i.e., factors likely to influence cognition) [92]. A striking difference in the prevalence of executive dysfunction was found between the two groups: 60% of patients with CMBs were impaired in frontal executive function (i.e., initiation, planning and higher-order problem-solving behaviors among others), compared with only 30% of non-microbleed patients (p = 0.03) [92].

New studies have expanded these observations [93]. The great majority of the studies published to date had cross-sectional designs and used Mini-Mental State Examination (MMSE) as an outcome measure, a test that has been criticized for its insensitivity to subtle or focal cognitive deficits (especially executive dysfunction). Nevertheless, studies in memory clinic patients with vascular cognitive impairment [94], Alzheimer's disease [95] and normal individuals [96] suggest a relationship between CMBs and cognition [97]. The fact that a relationship was found despite the insensitivity of the outcome measure implies a possible strong impact of CMBs on cognition.

A recent community-based, cross-sectional study assessed the associations of CMBs and retinopathy with cognitive impairment and dementia in 3906 older adults in the AGES–Reykjavik study [98]. Using a battery of neurocognitive tests, this study found that CMBs were associated with lower scores on tests sensitive to processing speed and executive function (even after adjusting for potential confounders such as WMCs, brain infarcts and major cardiovascular risk factors) [98]. The associations with poor cognitive performance in these domains were also stronger in patients with multiple CMBs or patients with concomitant multiple CMBs and retinopathy lesions (mainly microaneurysms and retinal hemorrhages, which are indicative of retinal-blood barrier breakdown) [98]. In addition, having multiple CMBs and retinopathy was significantly associated with an increased OR (3.10; 95% CI: 1.11–8.62) of vascular dementia [98]. This large study provides robust evidence supporting an association between microvascular damage, reflected by the presence of CMBs and retinopathy lesions, and cognitive dysfunction in people living in the community.

The study of the impact of CMBs on cognitive function faces many methodological challenges. First, a demonstration of a direct relationship between microbleeds and cognition is hampered by their strong correlation with other neuroimaging markers of small-vessel disease (including WMCs and lacunes). Moreover, dissecting the independent cognitive impact of microbleeds in cohorts of old people (with either sporadic cerebrovascular disease or population-based cohorts), is potentially confounded by the presence of multiple pathologies (such as Alzheimer's-type pathology and/or CAA). For example, some key population-based clinicopathological studies assessing CAA and dementia (such as the Honolulu Asia Aging Autopsy Study [HAAS] [99] and the Medical Research Council Cognitive Function and Ageing Studies [MRC CFAS] [100]) have found CAA prevalence to be consistently higher in demented compared with nondemented subjects [101]. This supports a significant independent contribution for CAA to the pathogenesis of dementia [101,102]. One way to circumvent these confounding effects is to focus on 'purer' genetic forms of disease. In cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a disease often considered to be a model of 'pure' vascular dementia (with affected individuals progressing to dementia at 40–60 years of age), the neuroimaging features resemble those of sporadic small-vessel disease (with a high prevalence of CMBs) (Figure 2), but the presence of coexistent Alzheimer's pathology and CAA in unlikely [103,104]. On the other hand, patients with autosomal-dominant forms of familial Alzheimer's disease, who have a younger age at symptom onset (and can be diagnosed definitively during life), are much more likely to have 'pure' Alzheimer's disease without coexisting sporadic small-vessel disease, but seem to have a prevalence of microbleeds similar to sporadic Alzheimer's disease [105].

The specific impact of CMBs on cognitive function in different patient populations and disease settings remains uncertain. A consistent pattern emerging from cerebrovascular cohorts is the association of microbleeds with executive dysfunction. Taken together, cross-sectional studies suggest that CMBs may provide some insights into disentangling the underlying mechanisms of vascular cognitive impairment, in diagnosis and in monitoring its severity and prognosis [93]. Vascular cognitive impairment, being second only to Alzheimer's disease as a cause of dementia, is a key healthcare challenge, especially given the aging of western societies [106]. In

general, cerebral small-vessel diseases are today thought to be among the most common substrates of vascular cognitive impairment [13]. In post-stroke dementia [107], it is hypothesized that pre-existing small-vessel damage (or Alzheimer's disease) increases the risk of future cognitive decline [108]. CMBs might be a surrogate marker for the severity of small-vessel damage (either hypertension or CAA-related) and could therefore have relevance for cognitive prognosis [93]. However, few prospective data on this topic are available. A pilot 6-year follow-up study of stroke patients suggests that CMBs at baseline had a heightened risk of frontal–executive cognitive impairment at follow-up [109]. If these results are replicated in larger prospective cohorts, CMBs, along with other MRI parameters, could be a useful prognostic marker in identifying patient subpopulations at the highest risk of future cognitive decline, who can subsequently be managed with aggressive therapies targeting vascular risk factors (predominantly hypertension) [110]. Moreover, if their topography can help identify underlying small-vessel arteriopathies, CMBs may be a useful addition to radiological criteria for vascular cognitive impairment [111].

The approach to dementia and cognitive impairment is changing [112,113]. Traditionally considered as separate entities, Alzheimer's disease and vascular cognitive impairment are now increasingly conceptualized as a continuum of overlapping syndromes in older people, in which underlying neurodegenerative and cerebrovascular pathology coexist [114]. Evidence is accumulating that vascular and degenerative processes have a complex interplay and shared risk factors [114,115]. Chronic hypertension is often present in patients with Alzheimer's disease [116] and may exacerbate the deleterious effect of neurodegenerative pathology on the brain [115]. A critical question in elucidating these mechanisms is exactly how vascular and neurodegenerative pathologies are linked; CAA (common in both Alzheimer's disease and in advancing age) may provide a connection between these processes [9,93]. In CAA, Aβ deposition in small vessels alters their function and disrupts the BBB, resulting in CMBs (found in ~23% of Alzheimer's disease patients [9]) and parenchymal damage. In parallel, small-vessel damage and dysfunction (caused by both CAA and hypertensive microangiopathy) can lead to impaired clearance of Aβ, resulting in its further deposition in the vessel wall, establishing a vicious cycle [93]. CMBs appear to be at the center of these complex processes, and may help to unravel the relationships between CAA, hypertensive microangiopathy and Alzheimer's disease for understanding mechanisms of cognitive impairment.

CMBs as prognostic markers of recurrent stroke

Whether CMBs are a marker of increased future stroke risk (particularly ICH) is one of the most clinically relevant questions at present, yet few longitudinal data of good quality are available. A previous systematic review demonstrated that CMBs were more prevalent among patients with recurrent stroke rather than patients with a first-ever stroke (Figure 1) [6]. Although this general conclusion was derived from a small number of patients (n = 1021), it suggests that CMBs may be a useful imaging marker of ongoing cerebrovascular damage [6], which can add additional information about stroke recurrence (to that obtained using standard MRI sequences).

Many prospective cohort studies that have examined the association between CMBs and the risk of subsequent stroke in patients with a history of transient ischemic attack or ischemic stroke were performed in Asian populations [117–120]. On aggregate, these studies have shown an increased risk of recurrent stroke (mainly hemorrhagic stroke) in patients with CMBs (especially multiple CMBs [120]) who suffered a lacunar or other type of ischemic stroke [117–120]. This is in line with the emerging role of CMBs as markers of underlying hemorrhagic-prone vasculopathy [2]. A study performed in a Canadian population with acute ischemic stroke or transient ischemic attacks also found an elevated risk of recurrent cerebrovascular events in patients with CMBs; however, the risk was mainly assumed to be for recurrent ischemic stroke rather than hemorrhage [121]. In a small prospective study from our research group of 21 surviving patients with ischemic stroke or transient ischemic attack followed-up after a mean interval of 5.5 years, we found only one recurrent ICH among eight patients with CMB, compared with no ICH in 13 patients without CMBs [84].

A recently published prospective follow-up study (median 2.2 years) of a European cohort of 487 hospitalized patients with a transient ischemic attack or ischemic stroke found that patients with microbleeds had a higher risk of developing new ischemic strokes rather than ICHs [122]. During follow-up, only two patients developed ICH compared with 32 patients who developed recurrent ischemic stroke and three with undetermined stroke [122]. Interestingly, only strictly lobar CMBs (or in combination with

deep microbleeds) had an independent effect on the risk of recurrent stroke (p = 0.018) [122]. An interpretation of this study (which awaits replication form larger cohorts) is that in patients with ischemic stroke, the presence of CMBs in a strictly lobar or mixed distribution might signal the presence of unsuspected CAA pathology, which, although generally considered to be a hemorrhagic disorder, is also characterised by frequent ischemic lesions related to the severity of small vessel disease [74,75], and could also increase the future risk of ischemic stroke.

With the accumulating evidence that microbleeds reflect an underlying bleeding-prone arteriopathy, it is speculated that they can be a useful factor for recurrent hemorrhagic stroke risk stratification in the future. Greenberg *et al.* prospectively evaluated a cohort of CAA patients and found that the count of microbleeds or macrobleeds on baseline MRI predicted an increased risk of hemorrhagic stroke (proportional to the count) in survivors of lobar ICH [90]. Jeon and colleagues also noted an elevated risk of recurrent ICH development associated with CMBs (but not with other clinical and laboratory data) in a prospective study of 112 survivors of ICH [123].

The predictive value of the presence of CMBs for the risk of occurrence of cerebrovascular disease in the general population is currently unknown. The only large-scale, high-quality evidence so far comes from a recent prospective study of 2102 healthy elderly individuals followed for a mean interval of 3.6 years in Japan [124]. This study demonstrated a significant association between CMBs and subsequent hemorrhagic stroke (hazard ratio: 50.2; 95% CI: 16.7–150.9) and ischemic stroke (hazard ratio: 4.48; 95% CI: 2.20–12.2) [124]. These important findings await exploration in further longitudinal population-based studies.

Overall, the association of CMBs with spontaneous ICH raises a clinical dilemma concerning the safety of antithrombotic treatments. Since CMBs provide direct evidence of blood leakage from pathologically fragile small vessels, their presence may be a risk factor for antithrombotic-associated ICH, raising the important question of whether CMBs may shift the risk–benefit balance away from antithrombotic use in some patients.

CMBs & treatment: balancing the risks

CMBs & antithrombotic treatment

Antiplatelet and anticoagulant treatments are widely used in patients at high risk of cardiovascular or cerebrovascular disease (e.g., ischemic stroke, ischemic heart disease or atrial fibrillation). In our aging population, the lifetime risk for developing atrial fibrillation is one in four people over the age of 40 years [125]. If left untreated, atrial fibrillation increases the risk of ischemic stroke fivefold, with the highest risk seen in elderly patients who have had a previous stroke or transient ischemic attack. In this setting, anticoagulation reduces ischemic stroke risk by approximately 65%. However, this benefit has to be balanced against an increased risk of ICH, which is the most feared complication of anticoagulation, causing death or severe disability in up to 75% of patients [126]. A recent observational inception cohort study of patients treated with anticoagulation (of whom a quarter had a previous history of stroke) reported a 2.5% (95% CI: 1.1–4.7%) risk of ICH in 1 year [127]. Over the last decade, increasing use of warfarin to prevent cardioembolic stroke due to atrial fibrillation has led to a fivefold increase in the incidence of anticoagulant-related ICH, which now accounts for approximately 15% of all ICH [128]. This trend is set to continue and will be a huge future healthcare, social and economic challenge. With the potential availability of new oral anticoagulants such as dabigatran [129], it is likely that even more acute cardioembolic stroke patients will be using oral anticoagulation for secondary stroke prevention. It is a paradox that many of these elderly patients at the highest risk of cardioembolic stroke are also at the highest risk of ICH. In many patients, this makes it extremely difficult to balance the antiocclusive and prohemorrhagic effects of antithrombotic drugs; improving this risk–benefit assessment for individual patients remains a major goal of research in cerebrovascular medicine.

Because anticoagulation-related ICH is associated with increased age and previous stroke, and it often occurs with anticoagulation intensity within the therapeutic range [130], it is likely that the mechanism underlying this high risk is related to individual patient factors (e.g., an age-related disorder of small brain vessels, such as CAA or hypertensive small-vessel disease). In keeping with this hypothesis, some studies suggest that WMCs (a marker of small-vessel disease) increase the risk of anticoagulant-related ICH [131,132]. Because they provide direct evidence of blood leakage from pathologically fragile small vessels, CMBs might be a stronger independent predictor of anticoagulation-associated ICH. The available studies on CMBs and anticoagulation-associated ICH risk have many limitations, with most being cross-sectional studies in Asian cohorts, so their findings cannot

clearly show causative relationships and may not be generalizable to other populations [120,133–146]. Nonetheless, existing data support the hypothesis that the presence of CMBs increases the risk of ICH as a complication of antithrombotic medication [135,142,145]. A prospective study reported CMBs in 87% of patients with ICH following warfarin treatment for atrial fibrillation [142], while a recent case–control study also reported more CMBs in warfarin-associated ICH than in matched warfarin users without ICH [141].

A meta-analysis of published data [120,133–146] and unpublished data on stroke patient cohorts treated with antithrombotic drugs attempted to systematically bring together the available evidence [147]. Lovelock and coauthors pooled the data of 1461 patients with ICH and 3817 patients with ischemic stroke or transient ischemic attack, and through case–case comparisons, they showed that CMBs are more common in warfarin-related ICH than 'spontaneous' ICH [147]. In addition, in pooled follow-up data for 768 patients treated with antithrombotics, the presence of CMBs at baseline was associated with a significantly increased risk of future ICH (OR: 12.1; 95% CI: 3.4–42.5; $p < 0.001$) [147]. These results provide important indications that warfarin could indeed be harmful in patients with CMBs, but there was no standardization of imaging data or CMB ratings because individual patient data were not available. Moreover, previous studies have not fully investigated the effect of CMB burden on the risk of ICH on anticoagulant treatment, which may be important [130].

Given the lack of definite evidence at present, antithrombotic treatment should not be avoided in patients with CMBs and a clear indication for anticoagulation (especially atrial fibrillation). However, there are certain clinical scenarios where it is more clear that avoiding or discontinuing antithrombotic drugs (based on the presence of CMBs) may be beneficial for the patient. For example, in an elderly patient with suspected CAA (due to lobar ICH) and vascular risk factors, and where cognitive effects are also present, the finding of multiple lobar microbleeds on MRI will possibly tip the balance away from antithrombotic use (because the risk of bleeding may be determined to be greater than the risk of thromboembolic disease). Routinely imaging the brain using more sensitive techniques for CMB detection (e.g., SWI) may lead to even earlier diagnosis of patients with CAA and better inform decisions regarding antithrombotic treatments [148].

Future research in the field will hopefully help to develop and validate a reliable risk model, incorporating the most promising neuroimaging and blood markers of bleeding risk (including CMBs), in order to aid anticoagulation decisions in stroke populations who may have the highest risk of ICH. Further prospective studies are required to definitively establish how CMBs relate to future ICH risk on oral anticoagulants. One large, prospective, UK-wide, inception cohort study of patients with acute cardioembolic stroke or transient ischemic stroke due to atrial fibrillation is curently underway (Clinical Relevance of Microbleeds in Stroke [CROMIS]-2).

With regard to antiplatelet drugs, the evidence regarding any ICH risk associated with CMBs is even more limited. In a case–control study, lobar CMBs (suggesting possible CAA) were found to be risk factors for aspirin-related ICH [149], expanding the results of a previous report [150]. In the recent pooled analysis by Lovelock *et al.*, a weak association was found between CMBs and ICH in antiplatelet users versus nonusers (OR: 1.7; 95% CI: 1.3–2.3; $p < 0.001$) [147]. It is possible that when antiplatelet drugs are given for primary prevention (for which no data are available) the risk:benefit ratio is less favorable for patients with multiple CMBs compared with the setting of secondary prevention, where the benefit of antiplatelet medication has been proven in large randomized controlled trials [48,151].

CMBs in the setting of other treatments

Thrombolysis

Another relevant question is whether there is an increased risk of ICH after thrombolysis of patients with ischemic stroke when CMBs are present. Some studies that explored the association between CMBs and the risk of hemorrhagic transformation following intravenous tissue plasminogen activator in patients who have had ischemic stroke have indicated possible links [143,152], while more recent studies have questioned these findings [153,154]. The BRASIL study (the largest prospective, multicenter study to date), which included 570 ischemic stroke patients, found that symptomatic ICH occurred in 5.8% of patients with CMBs versus 2.7% of patients without CMBs ($p = 0.170$) [153]. However, all of the studies were underpowered to provide reliable data of such an effect [6,155] and leave unanswered the questions of the role of strictly lobar microbleeds (reflecting underlying CAA pathology) and multiple CMBs on the shaping of the risk [49].

Statins

Some neurologists have raised concerns over the use of statins in patients with CMBs. In the Rotterdam study, low serum cholesterol levels were found to be strongly associated with the presence of strictly lobar microbleeds [56]. However, this association was not replicated in the recent update of the study [85]. Lee and colleagues also found a relationship between low cholesterol concentrations and higher microbleed burden in the 172 patients they studied [156]. In a more recent retrospective analysis of 349 patients with acute ischemic stroke or transient ischemic attack, previous statin therapy was not associated with either the prevalence or the degree of CMBs [157]. The role of statins and low serum cholesterol in patients with microbleeds needs further exploration, particularly in light of the results of a randomized controlled trial of atorvastatin in patients with stroke, which showed a small increase in the incidence of ICH among patients receiving high doses of the drug [158]. The increased risk of ICH may be due to pleiotropic effects of statins other than the lipid-lowering effects [159].

Conclusion & future perspective

Despite a growing body of research that has provided significant insights into the understanding of the risk factors, pathophysiology and neurological sequelae of CMBs, many basic and clinical questions still remain unsettled. As MRI techniques become more sensitive, CMBs will be increasingly detected in various patient populations and healthy elderly people, raising even more clinical dilemmas.

Thus, there is an urgent need to understand the underlying cellular and molecular mechanisms of CMBs, which are key to understanding how vascular amyloid (CAA) and hypertensive small-vessel diseases interact and affect

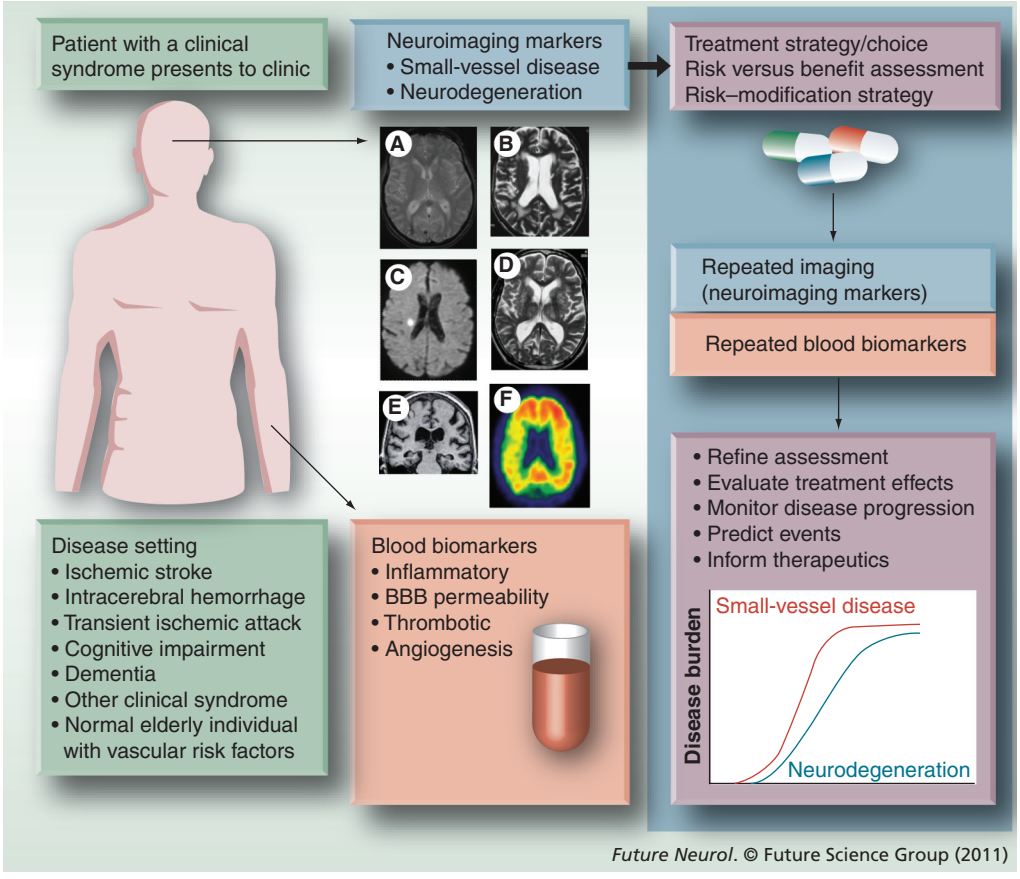

Figure 10. A potential new clinical paradigm of the future role of imaging markers (including cerebral microbleeds) and blood biomarkers to guide treatment decisions, evaluate treatment effects and monitor disease progression in cerebrovascular and other neurological disorders. Neuroimaging modalities and findings with potential clinical implications include: **(A)** cerebral microbleeds on axial T2*-weighed gradient-recalled echo; **(B)** white matter changes on axial T2-weighted MRI; **(C)** silent acute ischemic lesions on axial diffusion-weighted images; **(D)** enlarged perivascular spaces on axial T2 images; **(E)** medial temporal atrophy and white matter lesions on coronal FLAIR images; and **(F)** amyloid-β load on PET images using radioligands (e.g., Pittsburgh compound B).

the brain, particularly with regard to ICH risk and cognitive function. Future research should investigate CMBs together with other imaging markers of small-vessel disease (e.g., WMCs, microinfarcts and lacunes) and neurodegeneration (e.g., focal or global atrophy) in combination with histopathological validation wherever possible.

Over the coming years, the methodology used to detect and identify CMBs will improve. Standardization of MRI parameters, clarification of the role of SWI (as a more sensitive method compared with T2*-GRE) and the development of automated detection techniques [160] will facilitate side-to-side comparisons and pooling of data from different studies.

Clinical expectations will focus on CMBs and other MRI findings as markers for the diagnosis of small-vessel arteriopathies, and as prognostic biomarkers for predicting an individual's risk of neurologic deterioration and cerebrovascular events (particularly ICH), facilitating individually tailored antithrombotic or disease-modifying treatments. The available evidence suggests that microbleeds in specific locations may be helpful in diagnosing the underlying cause of ICH, thereby differentiating the specific microangiopathic pathology (hypertensive small-vessel damage or CAA) *in vivo*. Since CMB burden can be considered to be an intermediate phenotype (or endophenotype) between risk factors, underlying small-vessel pathology and cerebral 'end-organ' damage and clinical impairment, it might be a useful surrogate marker for identifying individuals at the highest risk to target with aggressive treatments and increasing the power of trials to detect treatment effects.

In the future, MRI may be combined with other predictive biomarkers in clinical risk estimation (Figure 10) in cerebrovascular and other neurological diseases. In this scenario, a combination of imaging markers – perhaps including molecular imaging of pathogenic proteins (e.g., amyloid) using PET ligands [161] and blood biomarkers could be used to assess the relative balance of risk for future cerebral infarction or hemorrhage and future physical or cognitive decline, informing therapeutic decisions as well as potentially evaluating treatment effects and monitoring disease progression (Figure 10).

Executive summary

Background

- Cerebral microbleeds (CMBs) are tiny perivascular hemorrhages seen as small, well-demarcated, hypointense, rounded lesions on MRI sequence that are sensitive to magnetic susceptibility effects.
- CMBs are increasingly recognized in patients with all forms of cerebrovascular disease, Alzheimer's disease, vascular cognitive impairment and normal elderly populations.

MRI detection & differential diagnosis

- Care must be taken to distinguish CMBs from other similar neuroimaging findings and artefacts ('mimics').
- No consensus is yet available on an optimal imaging protocol for the identification of CMBs.

Histopathology of CMBs

- These radiological lesions are due to focal accumulations of hemosiderin-laden macrophages adjacent to abnormal small vessels, being mainly affected by hypertensive small-vessel disease or cerebral amyloid angiopathy (CAA).

Risk factors & associations

- Aging, hypertension and *APOE* genotype, along with other neuroimaging correlates of cerebral small-vessel disease (e.g., lacunar infarcts and white matter changes) form the most consistent associations with CMBs.
- The risk factors for CMBs vary according to their anatomical location in the brain (deep/infratentorial vs strictly lobar), reflecting the specific, primary, underlying vascular pathological change (either hypertensive or CAA-associated, respectively).

Pathophysiology

- CMBs may provide direct evidence of microvascular leakiness.
- Endothelial/BBB derangement may play a key role in CMB formation.
- At least two pathways can lead to CMBs: CAA-mediated (degenerative) and hypertension-associated pathways.

Clinical implications

- CMBs are a marker of specific small-vessel angiopathies, and have important associations with disease-related risk factors.
- Microbleeds in specific locations may be helpful in diagnosing the underlying cause of intracerebral hemorrhage.
- Accumulation of multiple CMBs over time could have an insidious effect on the brain.
- CMBs appear to contribute to cognitive impairment.
- CMBs show promise for linking vascular and degenerative pathologies in dementia.
- CMBs may be useful surrogate markers for identifying individuals at the highest risk for targeting aggressive treatments and monitoring treatment effects (e.g., antihypertensive medication and antithrombotics).

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The activity supported the learning objectives.					
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1. Your patient is a 78-year-old white woman being evaluated for mild forgetfulness. She has a history of mild hypertension that is well controlled with a diuretic. She is about to undergo brain MRI. Based on the review by Drs Charidimou and Werring, which of the following statements regarding diagnosis of cerebral microbleeds (CMBs) in this patient is most likely correct?

- ☐ **A** CMBs are moderately large, hyperintense, rounded lesions on MRI sequences that are sensitive to magnetic susceptibility effects
- ☐ **B** There is an optimal MRI imaging protocol to identify CMBs
- ☐ **C** Deep/infratentorial CMBs most likely reflect underlying cerebral amyloid angiopathy (CAA)
- ☐ **D** Aging, hypertension and *APOE* genotype are risk factors for CMBs

2. The patient described in question 1 has a brain MRI thought to be consistent with a CMB. Based on the review by Drs Charidimou and Werring, which of the following statements about the underlying histopathology and pathophysiology is most likely correct?

- ☐ **A** CMBs reflect leaking from moderate-sized blood vessels
- ☐ **B** CMBs are caused by copper-laden macrophages
- ☐ **C** Hypertensive vasculopathy is the only pathway known to result in CMBs
- ☐ **D** Endothelial and BBB derangement may play a key role in CMB formation

3. Based on the review by Drs Charidimou and Werring, which of the following statements about the clinical implications of CMBs is most likely correct?

- ☐ **A** The location of microbleeds is not helpful in diagnosing the underlying cause of intracranial hemorrhage
- ☐ **B** The number of CMBs or their change over time is not a helpful prognostic marker
- ☐ **C** CMBs may be a possible contributor to cognitive impairment and dementia
- ☐ **D** CMBs play no role in treatment decisions or monitoring treatment response