

Outcome markers for clinical trials in cerebral amyloid angiopathy



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Efforts are underway for early-phase trials of candidate treatments for cerebral amyloid angiopathy, an untreatable cause of haemorrhagic stroke and vascular cognitive impairment. A major barrier to these trials is the absence of consensus on measurement of treatment effectiveness. A range of potential outcome markers for cerebral amyloid angiopathy can be measured against the ideal criteria of being clinically meaningful, closely representative of biological progression, efficient for small or short trials, reliably measurable, and cost effective. In practice, outcomes tend either to have high clinical salience but low statistical efficiency, and thus more applicability for late-phase studies, or greater statistical efficiency but more limited clinical meaning. The most statistically efficient markers might be those that are potentially reversible with treatment, although their clinical significance remains unproven. Many of the candidate outcomes for cerebral amyloid angiopathy trials are probably applicable also to other small-vessel brain diseases.

Introduction

Cerebrovascular deposition of amyloid (cerebral amyloid angiopathy) is a major cause of spontaneous intracerebral haemorrhage in elderly people and an important contributor to age-related cognitive decline.¹ Cerebral amyloid angiopathy is increasingly diagnosed during life by detection of vascular amyloid in pathological samples or detection of lobar haemorrhagic lesions by neuroimaging according to the validated Boston criteria.² There are many plausible approaches to prevention or treatment of cerebral amyloid angiopathy (eg, inhibition of β -amyloid peptide production, enhancement of β -amyloid clearance, or protection of vessels from the toxic effects of β -amyloid), and a phase 2 monoclonal antibody study (NCT01821118) has been recently initiated, but as yet there are no large-scale clinical trials.

A barrier to cerebral amyloid angiopathy trials is the absence of consensus regarding outcome markers for measurement of treatment effectiveness. An ideal cerebral amyloid angiopathy marker would be one that is clinically meaningful, closely representative of the disease's underlying biological progression, efficient at detecting changes in response to treatment, reliably and reproducibly measurable, and easily generalisable across many trial sites. In practice, no one marker will have all these desired features, resulting in trade-offs between efficient surrogate markers useful for early-phase studies aimed at identification of promising candidate treatments and clinically meaningful markers for pivotal studies to establish those treatments for medical use.

In this Review, which emerged from proceedings of the International Cerebral Amyloid Angiopathy Conference, Leiden, Netherlands, Oct 24–26, 2012, we discuss potential markers for clinical cerebral amyloid angiopathy trials on the basis of present understanding of the underlying biology and neurological effect of the disease. Emerging data suggest that advanced cerebral amyloid angiopathy can be measured by a wide range of markers, including clinical events (eg, symptomatic intracerebral haemorrhage or cognitive decline), structural brain

lesions (eg, microbleeds, white matter hyperintensities, or microinfarcts), alterations of vascular physiology, and direct visualisation with amyloid radioligands. Each marker comes with particular drawbacks, such as the non-specificity of structural brain lesions for cerebral amyloid angiopathy (vs other small-vessel diseases) or of amyloid radioligands for vascular β -amyloid (vs senile plaques). Nonetheless, rapidly accumulating data on in-vivo detection of the pathogenic steps involved in cerebral amyloid angiopathy offers substantial promise for future trials aimed at identifying disease-modifying treatments for this largely untreatable disease.

Candidate outcome markers

International consensus standards for describing, analysing, and reporting many of the lesion types described herein have been published recently³ and should facilitate cross-study comparisons and enhance generalisability of findings.

Haemorrhagic markers

Symptomatic intracerebral haemorrhage is an appealing outcome for clinical trials because of its relation to the severity and pathophysiology of the underlying cerebral amyloid angiopathy,⁴ apparent ease of detection, and clinical prominence. However, intracerebral haemorrhage is rare.⁵ It is somewhat more common in selected groups, such as individuals with several microbleeds,^{6,7} and is most common as a recurrent event in survivors of lobar intracerebral haemorrhage, with incidence estimates ranging from 2.5% to 14.3% per year.⁸ Although detection of macroscopic intracerebral haemorrhage by CT scan is technically straightforward, the presentation of intracerebral haemorrhage is sometimes too mild or non-specific to trigger a timely CT scan, or alternatively is, in some cases, rapidly fatal, thus precluding brain imaging.

These caveats notwithstanding, symptomatic intracerebral haemorrhage remains a reliable and clinically meaningful trial outcome in view of the high burden of

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disability associated with lobar intracerebral haemorrhage.⁹ Its major limitation is efficiency, because even recurrent lobar intracerebral haemorrhage occurs infrequently enough to need large sample sizes and long durations of follow-up. Under the optimistic assumptions that a treatment would reduce annual recurrence from 10% to 5% (ie, relative risk reduction of 50%), a randomised controlled trial with 1 year of follow-up would need an estimated 862 patients with cerebral amyloid angiopathy with previous intracerebral haemorrhage to achieve 80% statistical power, and 1154 patients for 90% power. A more conservative scenario in which annual recurrence is reduced from 10% to 8% would need 6420 patients to achieve 80% power. Restricting this calculation to patients with cerebral amyloid angiopathy deemed at high risk for intracerebral haemorrhage recurrence because of microbleed counts¹⁰ or *APOE* genotype¹¹ would reduce the sample size needed, but would also reduce the number of available study patients. These sample size estimates suggest that intracerebral haemorrhage would be most suitable for late-phase, rather than early-phase, trials.

Cerebral microbleeds¹² are an alternative haemorrhagic marker of cerebral amyloid angiopathy. Their primary advantage as an outcome marker relative to symptomatic intracerebral haemorrhage is their substantially higher prevalence and incidence. Strictly lobar cerebral microbleeds seem to be indicative of vasculopathy related to cerebral amyloid angiopathy, but also frequently occur among presumably healthy people, possibly as a result of clinically silent cerebral amyloid angiopathy.^{13,14} Appearance of new lobar cerebral microbleeds (figure 1A) was reported in 6·1% of 831 elderly individuals in the general population who were rescanned a mean of 3·4 years after baseline MRI,¹⁴ in 17·5% of the subset with one or more strictly lobar microbleeds at baseline,¹⁴ and in 50% of 34 patients with probable cerebral amyloid angiopathy–intracerebral haemorrhage (median of three new microbleeds in patients with at least one incident lesion) rescanned after a mean of 15·8 months.¹⁰ Although more data are needed to estimate sample sizes accurately, the greater incidence of new cerebral microbleeds compared with symptomatic intracerebral haemorrhage (in terms of both the proportion of patients affected and the numerical count of incident lesions) offers substantially increased efficiency in showing any given relative reduction in incident events.

The major drawbacks of cerebral microbleeds as a study outcome are their limited relevance as a clinically meaningful outcome, their imperfect specificity for cerebral amyloid angiopathy, and technical issues in their detection. These lesions have less effect on neurological function than symptomatic intracerebral haemorrhage, although the presence of five or more strictly lobar cerebral microbleeds in the general elderly population¹⁶ or any strictly lobar cerebral microbleeds in patients with ischaemic stroke¹⁷ have been independently linked to detectable cognitive

dysfunction. Cerebral microbleeds also have clinical value as markers of increased risk of future symptomatic intracerebral haemorrhage.^{10,18} Although cerebral microbleeds are not specific for cerebral amyloid angiopathy,¹⁹ the pattern of lesions restricted to lobar brain regions seems to be associated with genetic risk factors for sporadic^{13,14,20} or familial²¹ cerebral amyloid angiopathy, suggesting that this distribution might be sufficiently specific to be used as an outcome measure. Finally, variations in detection of cerebral microbleeds across different MRI sequence parameters,²² field strengths,²³ and raters^{24–26} show the need for standardised methods in applying this marker across centres, as is done in the ongoing multicentre Restart or Stop Antithrombotics Randomised Trial (RESTART) and the Clinical Relevance Of Microbleeds In Stroke 2 (CROMIS-2) study. Microbleeds thus seem best suited to serve as an early-phase marker of treatments aimed at reducing haemorrhagic events related to cerebral amyloid angiopathy, but careful methods are needed for standardised detection and interpretation.

Recent data have implicated acute or chronic haemorrhage within or adjacent to the cortical sulci (often described as superficial siderosis when chronic or as convexity subarachnoid haemorrhage when acute) as another form of bleeding associated with cerebral amyloid angiopathy. Superficial siderosis is common in cerebral amyloid angiopathy (23 of 38 neuropathologically examined brains vs 0 of 22 brains with intracerebral haemorrhage not related to cerebral amyloid angiopathy)²⁷ and is often distant from sites of lobar haemorrhage,^{27–29} suggesting that it is a separate bleeding event related to cerebral amyloid angiopathy. Siderosis seems to also have clinical meaning in cerebral amyloid angiopathy as a trigger of transient focal neurological symptoms²⁸ and a possible marker of increased risk for future intracerebral haemorrhage.^{30,31} Progression of superficial siderosis (figure 1B) presumably represents a new bleeding event and thus is a candidate cerebral amyloid angiopathy marker, but has not yet been systematically studied or measured by standardised methods.

Non-haemorrhagic markers

White matter hyperintensities of presumed vascular origin, visualised on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI sequences, are a ubiquitous phenomenon of ageing, but occur with much greater volume in individuals diagnosed with cerebral amyloid angiopathy than in those with healthy ageing, Alzheimer's disease, or mild cognitive impairment.³² Although the precise pathophysiology of white matter hyperintensities remains ill defined (and probably heterogeneous), a vascular basis is suggested by the association with cerebral small-vessel diseases such as cerebral amyloid angiopathy and with vascular risk factors. The volume of white matter hyperintensities can be

assessed visually by ordinal rating scales or by volumetric methods, which are usually semi-automated. Progression of white matter hyperintensities between scans (figure 1C) can be measured by qualitative scales³³ or quantitative methods.³⁴ Findings from a study³⁵ in 26 patients (mean age 69.1 years) with probable or possible cerebral amyloid angiopathy scanned 1–2 years apart showed a median growth in white matter hyperintensities of 0.5 mL per year (IQR 0.1–2.8 mL per year). This pace of progression is rapid relative to population-based estimates in people with healthy ageing³⁶ and similar to that in the subset of

individuals with early confluent or confluent white matter hyperintensities at baseline in the population-based Austrian Stroke Prevention Study.³⁷

The association between white matter hyperintensities and cognitive impairment before stroke in cerebral amyloid angiopathy,³⁸ and the presence of cognitive impairment, disability, and future decline in other groups of patients,^{39–43} suggest that assessment of white matter hyperintensities could be a means to measure a clinically meaningful aspect of small-vessel-related brain injury. However, large follow-up studies in cerebral amyloid

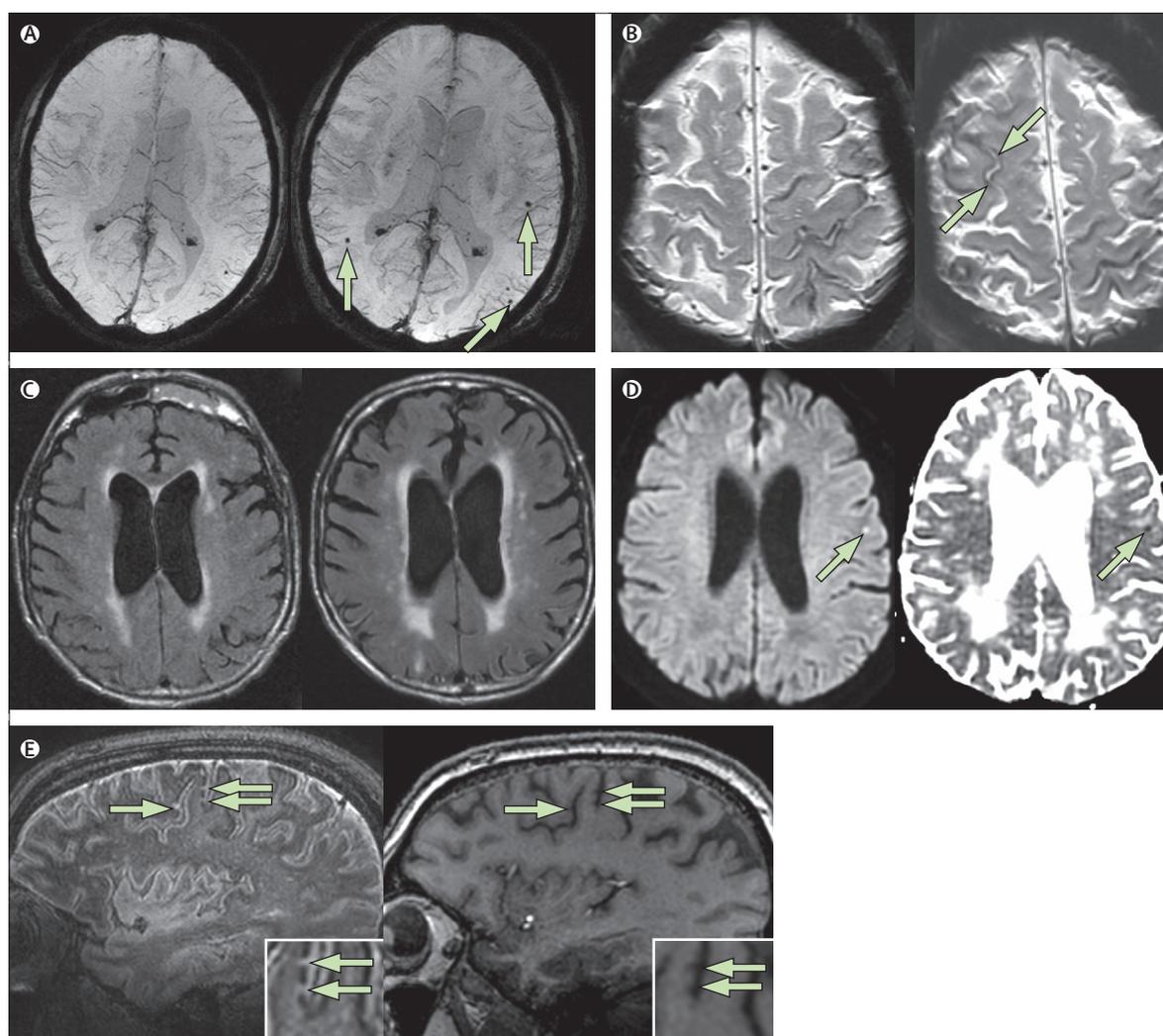


Figure 1: Examples of MRI markers

(A) 74-year-old man with six strictly lobar microbleeds on baseline T2*-weighted MRI (left-hand image shows one of these) and five incident strictly lobar microbleeds on follow-up done 3.4 years later (right-hand image shows three of the incident lesions, arrows). (B) Superficial siderosis on T2*-weighted MRI in a 69-year-old man with probable cerebral amyloid angiopathy and predominantly left hemispheric siderosis at baseline (left) and incident right superior frontal siderosis on follow-up 1.5 years later (right, arrows). (C) Growth of white matter hyperintensities on FLAIR images between baseline (left) and follow-up at 5 years (right) in an 89-year-old man with probable cerebral amyloid angiopathy, old right occipital intracerebral haemorrhage, and progressive impairment of executive function but no intracerebral haemorrhage during the inter-scan interval. Volumes of white matter hyperintensities in the left (non-intracerebral haemorrhage) hemisphere were 18.5 mL at baseline and 23.9 mL at follow-up. (D) Left frontal cortex focus of restricted diffusion (diffusion-weighted image on left, absolute diffusion coefficient map on right) consistent with a small acute infarct in a 74-year-old man with probable cerebral amyloid angiopathy and no other known vascular disease. (E) Sagittal FLAIR (left) and T1 (right) images obtained by 7T MRI¹⁵ of a 62-year-old man with mild cognitive impairment. The lesions suggestive of cortical microinfarcts are hyperintense on FLAIR and hypointense on T1 (arrows and insets for enlargement). FLAIR=fluid-attenuated inversion recovery.

angiopathy to link longitudinal change in white matter hyperintensities with longitudinal decline on cognitive testing or conversion to dementia have not yet been done. The feasibility of measuring progression of white matter hyperintensities in multicentre studies has been shown by the incorporation of this measurement in various randomised controlled trials.^{44–48} The reliability of volumetric methods for measurement of progression of white matter hyperintensities seems to be high,⁴⁹ but whether reliability is affected by inter-site variables, such as scanner manufacturer, field strength, sequence type (eg, T2-weighted vs FLAIR), or scan resolution, is largely unknown. The variability introduced by these factors might be mitigated by harmonisation of scanning parameters (particularly voxel size) across sites, use of the same scanner or sequence at baseline and follow-up, and a within-participant analysis design. Because nearly all patients with cerebral amyloid angiopathy seem to show at least some growth of white matter hyperintensities over 1–2 years,³⁵ white matter hyperintensities probably have equal or greater ability than cerebral microbleed count to detect treatment effects. Data from the only published study³⁵ on progression of white matter hyperintensities in cerebral amyloid angiopathy suggest that 238 patients (119 per group) would be needed to detect a 50% reduction in progression of white matter hyperintensities with 80% power, or fewer patients if trials were restricted to those with the most extensive baseline white matter hyperintensities. Thus, progression of white matter hyperintensities seems to represent another promising outcome marker for early-phase trials and is a reasonably well-validated marker for cognitive disability. Its major limitations are absence of specificity for cerebral amyloid angiopathy, the loose association between white matter hyperintensities and haemorrhagic manifestations of cerebral amyloid angiopathy (raising the possibility that drugs that block progression of white matter hyperintensities might not also block bleeding), and the cost and labour needed for serial MRI scans and volumetric measurements.

Microinfarcts, defined as areas of infarction only visible on histopathological examination (ie, up to about 1–2 mm)⁵⁰ have long been associated with advanced cerebral amyloid angiopathy.^{51,52} Although individually small, accumulating evidence suggests that these lesions might collectively have important independent effects on cognition.^{50,53} Substantial efforts have focused on visualising microinfarcts *in vivo*—a prerequisite to regarding these lesions as potential outcome markers. Two emerging candidate approaches are detection of clinically silent foci of restricted diffusion by diffusion-weighted imaging (DWI)^{54–57} and structural imaging of the mature lesions with ultra-high-field MRI.¹⁵ DWI lesions (figure 1D), typically several millimetres in diameter on MRI, are postulated (but without neuropathological confirmation) to represent acute microinfarcts at the large end of the microinfarct size spectrum. Such lesions

have been reported in about 10–20% of patients with cerebral amyloid angiopathy imaged either at the time of intracerebral haemorrhage or in the chronic post-intracerebral haemorrhage period,^{54–57} suggesting that they might represent a marker of ongoing brain injury related to cerebral amyloid angiopathy. Recently, structural imaging at 7 T has revealed small FLAIR hyperintense and T1 hypointense lesions (figure 1E), with MRI-histopathological correlation at post mortem, confirming this appearance as bona-fide microinfarcts.¹⁵ A key limitation of both approaches is their ability to detect lesions only at the upper limit of microinfarct size, leaving most microinfarcts (with an estimated mean diameter of about 0.3 mm)⁵⁸ undetectable with present neuroimaging. Other remaining challenges are the still undefined association between DWI and 7 T FLAIR lesions, the temporal limitations of DWI (hyperintensities are typically visible only 1–2 weeks after infarction), and the generalisability of these methods across centres. The clinical effect of microinfarcts on cognitive function and future haemorrhagic or ischaemic stroke risk in patients with cerebral amyloid angiopathy also remains to be identified. Data suggest that both the overall lesion burden⁵⁸ and incidence of new lesions^{54,55} are greater for microinfarcts than for cerebral microbleeds, thus highlighting their potential for high statistical efficiency as an outcome if they could be sensitively detected.

Diffusion tensor imaging (DTI) obtained from multi-directional MRI diffusion gradients allows measurement of the amount (mean diffusivity) and directional bias (fractional anisotropy [FA]) of water diffusion throughout the brain. In a study of 11 participants with intracerebral haemorrhage related to cerebral amyloid angiopathy and 13 matched healthy control individuals, reduced FA was found in the temporal white matter (inferior longitudinal and occipital fasciculi, 17% reduction) and splenium of the corpus callosum (15% reduction) and increased FA of lower magnitude was found in deep grey matter structures.⁵⁹ The changes were bilateral and did not seem to be affected by the hemisphere in which the cerebral haemorrhage was located. In another study of global mean diffusivity in 49 patients with cerebral amyloid angiopathy, higher values were seen among patients with pre-intracerebral haemorrhage cognitive impairment than among those without.⁶⁰ These data suggest that the white matter microstructure is abnormal in cerebral amyloid angiopathy and can be measured with DTI. However, further validation is needed, in particular to identify whether clinically relevant changes can be detected over time, as has been suggested for other small-vessel diseases.⁶¹ Standardised DTI seems to be feasible across scanners and sites.⁶² Other techniques developed to probe the microstructure of cerebral white matter, such as magnetisation transfer imaging, MR spectroscopy, and quantitative mapping of magnetic resonance parameters (eg, proton density, T1, T2, and T2*), have yet to be applied or validated in the context of cerebral amyloid

angiopathy, but hold promise on the basis of reports on ageing and ischaemic small-vessel disease.⁶³

Enlarged perivascular spaces (also termed Virchow-Robin spaces), the potential spaces surrounding small parenchymal blood vessels, represent another candidate non-haemorrhagic marker visible on MRI. Enlarged or dilated perivascular spaces, presumed to be due to the accumulation of interstitial fluid, have been linked to the presence and severity of cerebral small-vessel disease.^{64,65} Cerebral amyloid angiopathy seems to be preferentially associated with high numbers of visible perivascular spaces in the centrum semiovale,^{66,67} which is consistent with the known localisation of cerebral amyloid angiopathy to the superficial cortical vessels. Enlarged perivascular spaces will need analysis for incident appearance over time, standardisation across sites, and correlation with clinical status if they are to be assessed as a potential outcome marker.

Cognitive function markers

Along with symptomatic intracerebral haemorrhage, cognitive decline is the most clinically salient manifestation of cerebral amyloid angiopathy. Findings from several studies have shown the association of cerebral amyloid angiopathy with cognitive impairment across cohorts, institutions, and countries.⁶⁸⁻⁷⁴ In the Religious Orders Study,⁷⁴ individuals with moderate-to-very-severe cerebral amyloid angiopathy pathological abnormalities at autopsy (18.9% of the 404 study participants) showed worse perceptual speed and episodic memory than those with none-to-minimum cerebral amyloid angiopathy; this difference was independent of Alzheimer's disease pathology, cerebral infarcts, Lewy bodies, age at death, sex, and education in a multivariable analysis. The precise mechanism by which advanced cerebral amyloid angiopathy gives rise to cognitive impairment remains undefined and could represent the cumulative effects of the various haemorrhagic and non-haemorrhagic tissue injuries discussed earlier as well as the contribution from coexistent Alzheimer's disease pathology. Vascular amyloid itself might also trigger reactive changes and neuronal degeneration in surrounding tissue.⁷⁵

Prevention of cognitive decline, like prevention of symptomatic intracerebral haemorrhage, represents a clinically meaningful outcome appropriate for late-phase trials, although it is inefficient for early-phase studies. One theoretical advantage of cognition as an outcome is that it might be sensitive to cumulative changes across many haemorrhagic and non-haemorrhagic lesion types, potentially showing a sum of treatment effects too small to be detected individually. Cognitive testing also has the advantages of using methods that are well accepted by academic and industrial organisations (although primarily developed for Alzheimer's disease rather than vascular cognitive impairment), validated across examiners and institutions, cost-effective, time efficient, quantitative, and

measurable longitudinally. These advantages are offset by the non-specificity of any cognitive test battery for cerebral amyloid angiopathy and the absence so far of a sensitive and specific cognitive profile to discriminate cerebral amyloid angiopathy from other age-related disorders, because episodic memory and perceptual speed⁷⁴ overlap with domains affected in Alzheimer's disease and other common dementias. Moreover, the absence of a clear link between cognitive functioning and any injury type related to cerebral amyloid angiopathy also limits the ability of these measures to provide specific pathophysiological information on the biological effects of candidate treatments. Finally, cognitive impairment related to cerebral amyloid angiopathy probably represents brain injury that is largely irreversible and thus trials of sufficient size and duration are needed for substantial progression to occur in untreated participants. No information is yet available on the rate of cognitive decline in cerebral amyloid angiopathy.

Markers of vascular pathophysiology

The haemorrhagic and non-haemorrhagic structural lesions and cognitive measures discussed seem to represent vascular-mediated injury to the brain rather than abnormalities of the vessels themselves. Thus, they probably measure late and irreversible steps in the postulated pathways leading from vascular dysfunction to brain injury and clinical dysfunction. An effective treatment might prevent future changes in these markers, but studies to detect this effect need to be large and long enough for sufficient new injuries to occur in the untreated participants. Conversely, direct markers of pathological and physiological vessel abnormalities might not only be blocked from worsening, but might also be improved by an effective treatment. A marker that is reversible might provide the highest level of statistical efficiency, allowing the possibility of smaller and shorter studies of candidate therapies.

Vascular amyloid can be detected and quantified by PET scanning with the amyloid radioligand C¹¹-labelled Pittsburgh Compound B (PiB). Although this compound was initially developed to detect β -amyloid deposits in Alzheimer's disease, several studies have shown increases in both global and occipital lobe PiB retention in patients with non-demented sporadic^{76,77} and familial⁷⁸ cerebral amyloid angiopathy and at foci of past⁷⁹ and future⁸⁰ haemorrhagic lesions related to cerebral amyloid angiopathy. Higher PiB retention is also independently associated with greater burden of white matter hyperintensities in patients with cerebral amyloid angiopathy but not in those with Alzheimer's disease or in healthy elderly participants,³² suggesting a link with non-haemorrhagic as well as haemorrhagic brain injury related to cerebral amyloid angiopathy.

Amyloid load could potentially serve as an outcome marker for early-phase studies aimed at reversing or preventing vascular amyloid deposition. This approach

has been used in conjunction with anti-amyloid antibody infusion to show reduction of PiB retention in patients with Alzheimer's disease⁸¹ and clearance of cerebral amyloid angiopathy in a transgenic mouse model.⁸² However, whether reduction of vascular amyloid burden in patients with cerebral amyloid angiopathy will have beneficial clinical effects is unknown; such benefits have not yet been shown with amyloid clearance in Alzheimer's disease.⁸³ Among other hurdles to be overcome in applying amyloid imaging to cerebral amyloid angiopathy trials are the specialised facilities needed and the high cost of production of radiolabelled amyloid ligands, the non-specificity of present radiolabelled ligands for vascular versus plaque amyloid, and the absence of natural history data on rate of vascular amyloid progression. Fluorine-18-labelled amyloid ligands such as ¹⁸F-florbetapir,⁸⁴ which have longer half-lives and are therefore less expensive and logistically demanding than carbon-11 compounds, have been developed for Alzheimer's disease, although these have not yet been tested in cerebral amyloid angiopathy. Also, methods for undertaking and analysing PiB-PET across several sites have been developed by the Alzheimer's Disease Neuroimaging Initiative⁸⁵ and other multicentre collaborations.

Cerebral amyloid angiopathy is also associated with altered vascular reactivity to physiological stimulation. Findings from studies measuring the functional MRI (fMRI) blood oxygen level-dependent (BOLD) response to visual stimulation (figure 2) showed that patients with cerebral amyloid angiopathy had 27–28% reduced peak amplitude,^{86,87} 73% longer time to peak, and 42% longer time to return to baseline⁸⁶ compared with control participants matched for age. Altered BOLD response might represent either vascular or neuronal dysfunction, but the findings that patients with cerebral amyloid angiopathy and control individuals had similar visual-evoked response potentials⁸⁷ and that similar results occurred in analyses restricted to responding voxels only⁸⁶ suggest that the differences are due to the effects of cerebral amyloid angiopathy on the vessels themselves. The fMRI response to visual stimulation seems to be associated with markers of the severity of cerebral amyloid angiopathy, such as microbleed count and volume of white matter hyperintensities,^{86,87} suggesting that these parameters might mark the underlying extent of disease and represent a potentially important mechanism for its pathogenesis. Like vascular amyloid deposition, impaired vascular reactivity is at least partly reversible in transgenic mouse

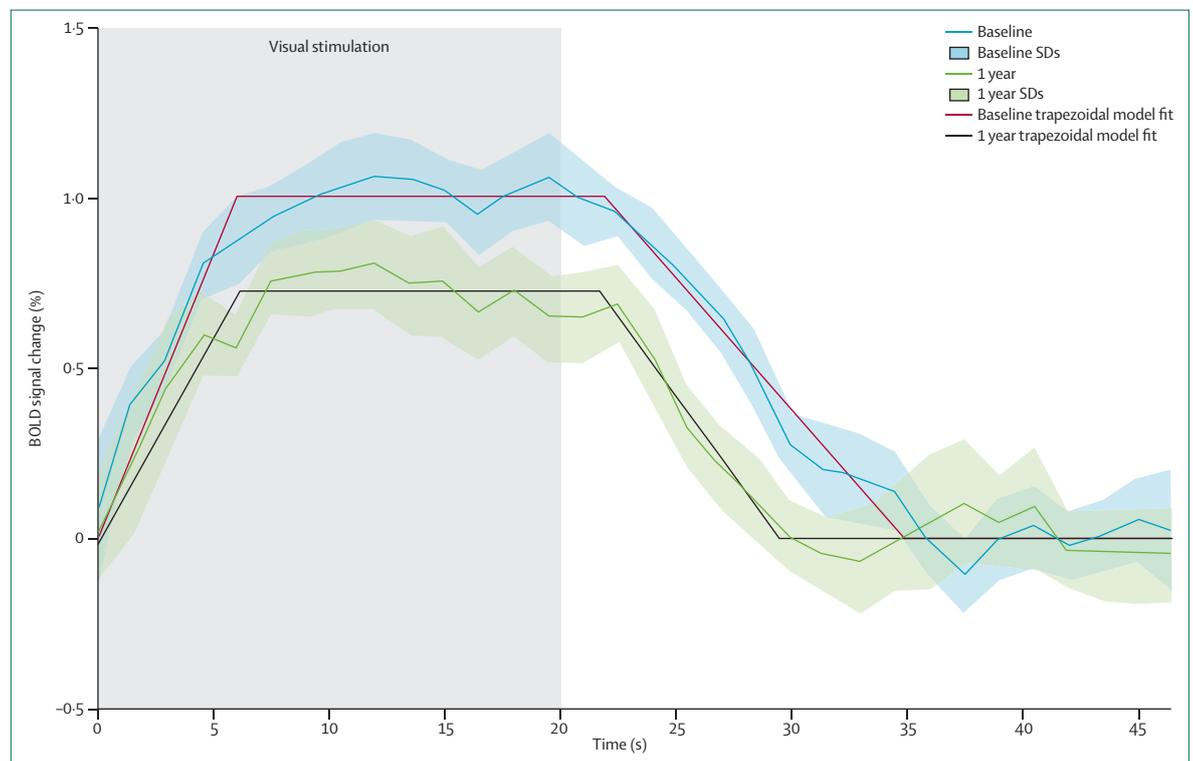


Figure 2: Serial functional MRI measurement of response to visual stimulation

Functional MRI studies are shown from an 83-year-old woman with probable cerebral amyloid angiopathy. Functional MRI with visual stimulation was done at baseline (blue line and error space) and again with the same scanner and protocol after 1 clinically asymptomatic year (green line and error space). The blue and green solid lines represent the change from baseline BOLD signal averaged over 16 cycles of visual stimulation (on 20 s, shaded region, then off 28 s), with SDs of the responses shown in blue and green spaces and the trapezoidal model fits in red and black lines, as described previously.⁸⁶ The amplitude of the modelled peak response in this participant decreased from 1.06% at baseline to 0.80% at 1 year. BOLD=blood oxygen level dependent.

models,^{88,89} raising the possibility that BOLD fMRI might serve as an efficient marker for trials aimed at reducing the effects of amyloid on vessel physiology. However, the reproducibility of this approach across several timepoints and study sites remains to be established.

Circulating biomarkers

Biomarkers in CSF or plasma offer another approach for measurement of underlying, potentially reversible aspects of cerebral amyloid angiopathy pathogenesis. Two studies^{90,91} of CSF from patients with cerebral amyloid angiopathy found reductions in β -amyloid₄₀ and β -amyloid₄₂, with phosphotau and total tau concentrations above those in elderly control individuals but lower than in patients with Alzheimer's disease. These findings are broadly consistent with the pathological abnormalities that occur in cerebral amyloid angiopathy, which entail vascular deposition of β -amyloid₄₀ and β -amyloid₄₂ and inconsistent coexistence of tau-containing lesions. The association between CSF β -amyloid and progression of cerebral amyloid angiopathy has yet to be explored; by analogy to Alzheimer's disease,⁹² one might expect the reductions in CSF β -amyloid in cerebral amyloid angiopathy to be associated inversely with, and have the same meaning as, amyloid burden in cerebral amyloid angiopathy measured by PiB-PET.

Findings from a study of plasma β -amyloid showed raised β -amyloid₄₀ and β -amyloid₄₂ concentrations in patients with probable cerebral amyloid angiopathy compared with healthy control individuals⁹³—differences not seen in an earlier analysis.⁹⁴ Another candidate family of molecules, the matrix metalloproteinases (MMPs) MMP-2 and MMP-9, are highly expressed near intracerebral haemorrhage related to cerebral amyloid angiopathy, but are not raised in plasma of patients with cerebral amyloid angiopathy.⁹⁵ These circulating biomarker studies are substantially limited by the small number of patients with cerebral amyloid angiopathy examined (fewer than 100 patients so far) and the

absence of data on reproducibility across sites and longitudinal change with disease progression.

Conclusions and recommendations

Several lessons and plans for future studies can be drawn from this overview of outcome markers for cerebral amyloid angiopathy trials (table). Markers exist for most of the postulated steps in cerebral amyloid angiopathy pathogenesis, ranging from vascular amyloid deposition itself to physiological alterations, haemorrhagic and non-haemorrhagic structural damage, symptomatic haemorrhagic stroke, and cognitive dysfunction. Thus, pilot trials are possible for cerebral amyloid angiopathy in which one or more of these markers is used to show a particular biological activity of a candidate therapy, such as use of PiB-PET to show partial clearance of plaques in the phase 2 study of bapineuzumab in Alzheimer's disease.⁸¹ Such pilot trials might be particularly efficient when using potentially reversible markers such as amyloid imaging and vascular reactivity. However, none of the imaging biomarkers has yet been linked closely enough to neurological impairment to serve as a true surrogate marker of clinically meaningful treatment effects. Thus, symptomatic intracerebral haemorrhage and cognitive testing remain the only reasonably valid outcomes for studies aimed at showing clinical benefit.

Although the pathogenic mechanisms and data reviewed herein focus specifically on cerebral amyloid angiopathy, many of the considerations and findings can be generalised to all forms of cerebral small-vessel disease associated with vascular cognitive impairment. Despite increasing understanding of the biology of these small-vessel processes, there are few established treatments for prevention of vascular cognitive impairment; control of hypertension was the only class I recommendation for patients at risk of vascular cognitive impairment in a scientific statement from the American Heart Association/American Stroke Association.⁹⁶ Trials to establish specific therapies for common age-related small-vessel pathological abnormalities, such as those for

	Link to clinical function	Measure of cerebral amyloid angiopathy severity or progression	Statistical efficiency for small or short studies	Reproducibility across sites	Cost-effectiveness
Symptomatic intracerebral haemorrhage	+++	++	+	+++	++
Microbleeds	++	+++	++	++	+
White matter hyperintensities	++	+++	++	++	+
Microinfarcts	++	?	++	?	+
Diffusion-tensor imaging changes	++	?	++	?	+
Cognitive testing	+++	+	+	+++	+++
Amyloid imaging	?	+++	+++	++	+
Vascular reactivity	?	++	+++	?	+
CSF amyloid	?	?	+++	+++	+

+ = low. ++ = moderate. +++ = high. ? = Unknown. Ratings represent the authors' consensus based on the literature cited in the corresponding sections of the text.

Table: Overview of candidate outcome markers for human studies in cerebral amyloid angiopathy

Search strategy and selection criteria

We identified references for this Review by searches of PubMed between 1969 and December, 2013. The search terms were “amyloid angiopathy”, “conophilic angiopathy”, “CAA”, “intracranial h(a)emorrhage”, “intracerebral h(a)emorrhage”, “cerebral/brain microbleed/microh(a)emorrhage”, and “cerebral/cortical/brain microinfarct”. We also did broader searches for intracerebral haemorrhage studies. References were also identified from the bibliography of identified articles and the authors’ files. Only papers published in English or with available English translations of relevant data were reviewed. The final reference list was generated on the basis of relevance to the topics covered in this Review.

cerebral amyloid angiopathy, would be greatly facilitated by study outcomes that are clinically and biologically meaningful, statistically efficient, and generalisable across sites. Nearly all of the measures of tissue injury and altered physiology described herein also occur in arteriolosclerosis or chronic hypertensive vasculopathy,^{13,56,97–99} suggesting that these markers might represent general features of damage to the small cerebral vessels. However, no in-vivo methods have yet emerged to measure arteriolosclerosis pathology in a similar way to PiB detection of cerebral amyloid angiopathy, highlighting the importance of achieving further progress in molecular imaging of small-vessel diseases.

Data that strengthen the links between imaging biomarkers and neurological function would allow greater reliance on these more efficient surrogate markers of clinical outcome in future trials. Based on present data, the volume of white matter hyperintensities seems to have the closest association with cognition, and microbleeds the closest association with symptomatic intracerebral haemorrhage, but improved imaging modalities and larger study populations may provide stronger support for other neuroimaging markers or combinations of markers. Other key areas of need are identification of the rates of biomarker progression over time and validation of imaging methods across sites; both are prerequisites for the ultimate goal of multicentre biomarker-based interventional trials. Further growth in the range of trial outcome markers, together with improved mechanistic understanding of small-vessel degeneration, will provide a strong foundation for identifying successful disease-modifying treatments for cerebral amyloid angiopathy and related diseases.

Contributors

All authors contributed to the literature search, drafting of the manuscript, and critical revision process.

Declaration of interests

Massachusetts General Hospital, University of Calgary, Washington University and Barnes Jewish Hospital, Leiden University Medical Center, and Lille University Hospital have clinical research support agreements with Pfizer, sponsor of an ongoing trial for cerebral amyloid angiopathy. JAS has received consulting fees or sat on paid advisory

boards related to amyloid imaging for AVID Radiopharmaceuticals, Eli Lilly, and GE Healthcare. All other authors declare that they have no competing interests.

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