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Outcome Markers for Clinical Trials in Cerebral Amyloid Angiopathy

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Abstract

Efforts are underway for early-phase trials of candidate therapies for cerebral amyloid angiopathy (CAA), an untreatable cause of hemorrhagic stroke and vascular cognitive impairment. A major barrier to these trials is the lack of consensus on measuring treatment effectiveness. We review a range of potential outcome markers for CAA against the ideal criteria of being clinically meaningful, closely reflective of biological progression, efficient for smaller/shorter trials, reliably measurable, and cost effective. In practice, outcomes tend either to have high clinical salience but relatively low statistical efficiency and thus more applicability for later phase studies, or greater statistical efficiency but more limited clinical meaning. The most statistically efficient outcomes are those that are potentially reversible with treatment, though their clinical significance remains unproven. Many of the candidate outcomes for CAA trials are likely to be applicable to other

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small vessel brain diseases as well. Considerations emerging from this review outline a path towards rapid and efficient testing of emerging candidate therapies for CAA and other small vessel diseases.

Cerebrovascular deposition of amyloid (cerebral amyloid angiopathy, CAA) represents a major cause of spontaneous intracerebral hemorrhage (ICH) in the elderly as well as an important contributor to age-related cognitive decline.¹ CAA is increasingly diagnosed during life by pathological sample or neuroimaging detection of multiple strictly lobar hemorrhagic lesions according to the validated Boston criteria.² There are multiple plausible approaches to preventing or treating CAA (such as inhibiting β -amyloid peptide [A β] production, enhancing its clearance, or protecting vessels from its toxic effects) and a recently initiated phase 2 monoclonal antibody study,³ but as of yet no large-scale clinical trials.

A barrier to CAA trials is the lack of consensus regarding outcome markers for determining treatment effectiveness. An ideal CAA marker would be one that is clinically meaningful, closely reflective of the disease's underlying biological progression, efficient at detecting changes response to treatment, reliably and reproducibly measurable, and easily generalizable across multiple trial sites. In practice, no single marker will have all these desired features, resulting in tradeoffs between efficient surrogate markers useful for early-phase studies aimed at identifying promising candidate treatments versus clinically meaningful markers for pivotal studies to establish those treatments for medical use.

This manuscript, which emerged from proceedings of the International CAA Conference held in Leiden, the Netherlands 24-26 October 2012, reviews potential markers for clinical CAA trials based on current understanding of the disease's underlying biology and neurological impact. Emerging data suggest that advanced CAA can be measured by a wide range of markers, including clinical events (e.g. symptomatic ICH, cognitive decline), structural brain lesions (e.g. microbleeds, white matter hyperintensities, microinfarcts), alterations of vascular physiology, and direct visualization with amyloid radioligands. Each comes with particular drawbacks, such as the nonspecificity of structural brain lesions for CAA (versus other small vessel diseases) or of amyloid radio ligands for vascular A β (versus senile plaques). Rapidly accumulating data on *in vivo* detection of the pathogenic steps involved in CAA nonetheless offers substantial promise for future trials aimed at identifying disease-modifying therapies for this largely untreatable disease.

Search Strategy and Selection Criteria

References for this Review were identified by searches of Pub Med between 1969 and December, 2013, and references from relevant articles. The search terms “amyloid angiopathy,” “conophilic angiopathy,” “CAA,” “intracranial h(a)emorrhage,” “intracerebral h(a)emorrhage,” “cerebral/brain microbleed/microh(a)emorrhage,” “cerebral/cortical/brain microinfarct,” as well as a broader search strategy for ICH studies⁴ were used. 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.

Candidate Outcome Markers

A summary of candidate outcome markers for CAA and the authors' consensus ratings of their properties are provided in Table 1. International consensus standards for describing, analyzing and reporting many of the lesion types described below have been recently published⁵ and should facilitate cross-study comparisons and enhance generalizability of findings.

Hemorrhagic Markers

Symptomatic ICH is an appealing outcome for clinical trials because of its relationship to underlying CAA severity and pathophysiology,⁶ apparent ease of detection, and importance to patients. ICH is a relatively rare event, however.⁷ It is somewhat more common in selected groups such as individuals with multiple microbleeds,^{8, 9} and most common as a recurrent event in survivors of lobar ICH, with incidence estimates ranging from 2.5% to 14.3% per year.⁴ Although detection of “macroscopic” ICH by CT scan is technically straightforward, it should be noted that the presentation of ICH may also be too mild or nonspecific to trigger a timely CT scan, or alternatively may be rapidly fatal precluding brain imaging.

These caveats notwithstanding, symptomatic ICH remains a reliable and clinically meaningful trial outcome given the high burden of disability associated with lobar ICH.¹⁰ Its major limitation is efficiency, as even recurrent lobar ICH occurs infrequently enough to require large sample sizes and long durations of follow-up. Under the optimistic assumptions that a treatment would reduce annual recurrence from 10% to 5% (i.e. relative risk reduction of 50%), a randomized controlled trial with one year follow-up would be estimated to require 862 CAA subjects with prior ICH to achieve 80% statistical power and 1154 subjects for 90% power. A more conservative scenario in which annual recurrence was reduced from 10% to 8% would require 6420 subjects to achieve 80% power. Restricting to CAA patients deemed at higher risk for ICH recurrence because of microbleed counts¹¹ or apolipoprotein E genotype¹² would reduce the required sample size, but also reduce the number of available study subjects. These sample size estimates suggest that ICH would be most suitable for late- rather than early-phase trials.

*Cerebral microbleeds*¹³ (CMB) represent an alternative hemorrhagic marker of CAA. Their primary advantage as an outcome marker relative to symptomatic ICH is substantially higher prevalence and incidence. Strictly lobar CMB appear to be indicative of CAA-related vasculopathy, but also frequently occur among presumably healthy persons, possibly a result of clinically silent CAA pathology.^{14, 15} Appearance of new lobar CMB (Fig. 1A) has been reported in 6.1% of 831 older individuals in the general population rescanned after a mean 3.4 years,¹⁵ 17.5% of the subset with one or more strictly lobar microbleeds at baseline,¹⁵ and in 50% of 34 probable CAA-ICH patients (median of 3 new microbleeds in positive subjects) rescanned after mean 15.8 months.¹¹ Although more data are required to estimate sample sizes accurately, the greater incidence of new CMB relative to symptomatic ICH (in

terms of both the proportion of subjects affected and the numerical count of incident lesions) offers substantial efficiencies in demonstrating any given relative reduction in incident events.

The major drawbacks of CMB as study outcome are their somewhat limited relevance as a clinically meaningful outcome, their imperfect specificity for CAA, and technical issues in their detection. These lesions clearly have less impact on neurologic function than symptomatic ICH, though the presence of many (5 or more) strictly lobar CMB in the general elderly¹⁶ or any strictly lobar CMB in ischemic stroke patients¹⁷ have been independently linked to detectable cognitive dysfunction. CMB also have clinical impact as markers of increased risk of future symptomatic ICH.^{11, 18} CMB are not specific for CAA,¹⁹ but the pattern of lesions restricted to lobar brain regions appears to associate with genetic risk factors for sporadic^{14, 15, 20} or familial²¹ CAA suggesting that this distribution might be sufficiently specific to be used as an outcome measure. Finally, variations in CMB detection across different MRI sequence parameters,²² field strengths,²³ and raters²⁴⁻²⁶ demonstrate the need for standardized methods in applying this marker across centers, as in the ongoing multicenter RESTART and CROMIS-2 studies. Microbleeds thus appear best suited to serve as an early phase marker of therapies aimed at reducing CAA-related hemorrhagic events, but require careful methods for standardized detection and interpretation.

Recent data have implicated acute or chronic hemorrhage within or adjacent to the cortical sulci (often described as *superficial siderosis* when chronic or *convexity subarachnoid hemorrhage* when acute) as another form of CAA-associated bleeding. Superficial siderosis is common in CAA (23 of 38 neuropathologically examined brains versus 0 of 22 brains with non-CAA related ICH²⁷), often distant from sites of lobar hemorrhage²⁷⁻²⁹ suggesting that it is a separate CAA-related bleeding event. Siderosis may also have clinical meaning in CAA as a trigger of transient focal neurological symptoms²⁸ and a possible marker of increased risk for future ICH.^{30, 31} Progression of superficial siderosis (Fig 1B) presumably represents a new bleeding event and thus a candidate CAA marker, but has not yet been systematically studied or measured by standardized methods.

Nonhemorrhagic Markers

White matter hyperintensities (WMH) of presumed vascular origin, visualized on T2-weighted or FLAIR MRI sequences, are a ubiquitous phenomenon of aging, but occur at much greater volume in individuals diagnosed with CAA than in healthy aging or Alzheimer disease (AD)/mild cognitive impairment.³² Although the precise pathophysiology of WMH remains ill-defined (and may indeed be heterogeneous), a vascular basis is suggested by its association with cerebral small vessel diseases such as CAA and with vascular risk factors. WMH *volume* can be assessed visually using ordinal rating scales or by volumetric methods, usually semi-automated. WMH *progression* between scans (Fig. 1C) can be measured by qualitative scales³³ or quantitative methods.³⁴ A study in 26 patients (mean age 69.1) with probable or possible CAA scanned 1-2 years apart found median WMH growth of 0.5 mL per year (interquartile range 0.1-2.8 mL per year),³⁵ a rapid pace of progression relative to population-based estimates in normal aging subjects³⁶ and similar to that in the subset of

individuals with baseline early confluent or confluent WMH in the population-based Austrian Stroke Prevention Study.³⁷

The association between WMH and pre-stroke cognitive impairment in CAA,³⁸ and with multiple markers of cognitive impairment, disability, and future decline in non-CAA subjects³⁹⁻⁴³ suggest that WMH may measure a clinically meaningful aspect of small vessel-related brain injury. Larger follow-up studies in CAA have not yet been done to link longitudinal change in WMH with longitudinal decline in cognitive testing or conversion to dementia, however. The feasibility of measuring WMH progression in multicenter studies has been demonstrated by its incorporation in a range of reported randomized controlled trials,⁴⁴⁻⁴⁸ supporting its feasibility. The reliability of volumetric methods for measuring WMH progression appears to be high,⁴⁹ but it is largely unknown if reliability is affected by inter-site variables such as scanner manufacturer, field strength, sequence type (e.g. T2-weighted vs. FLAIR), or scan resolution. The variability introduced by these factors might be mitigated by harmonization of scanning parameters (particularly voxel size) across sites, use of the same scanner/sequence at baseline and follow-up, and a within-subject analysis design. As nearly all CAA subjects appear to show at least some WMH growth over 1-2 years,³⁵ WMH may have equal or greater ability as CMB count to detect treatment effects. Data from the single published study on WMH progression in CAA indicate that 238 subjects (119 per arm) would be needed to detect a 50% reduction in WMH progression with 80% power, or fewer subjects if trials are restricted to those with more extensive baseline WMH. WMH progression thus appears to represent another promising outcome marker for early phase trials as well as a reasonably well-validated marker for cognitive disability. Its major limitations are its lack of specificity for CAA, the relatively loose connection between WMH and CAA's hemorrhagic manifestations (raising the possibility that agents that block WMH progression might not also block bleeding), and the cost/labor required for serial MRI scans and volumetric measurements.

Microinfarcts, defined as areas of infarction not visible by eye but seen on histopathological examination (i.e. up to about 1 to 2 millimeters)⁵⁰ have long been noted in association with advanced CAA^{51, 52} Although individually tiny, accumulating evidence indicates that these lesions may collectively have important independent effects on cognition.^{50, 53} Substantial efforts have focused on visualizing microinfarcts *in vivo*, a prerequisite for considering 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 ultrahigh field MRI.⁵⁸ DWI lesions (Fig. 1D), typically several millimeters in diameter on MRI, are postulated (still without neuropathological confirmation) to represent acute microinfarcts at the large end of the microinfarct size spectrum. Such lesions have been reported in approximately 10-20% of CAA patients imaged either at the time of ICH or in the chronic post-ICH period, suggesting they may represent a marker of ongoing CAA-related brain injury. More recently, structural imaging at 7 Tesla has revealed small FLAIR hyperintense and T1 hypointense lesions (Fig. 1E) with post-mortem MRI-histopathologic correlation confirming this appearance as bona fide microinfarcts.⁵⁸ A key limitation of both approaches is their ability to detect lesions only at the upper limit of microinfarct size, leaving the majority of microinfarcts (with an

estimated mean diameter of approximately 0.3 mm⁵⁹) invisible to current neuroimaging. Other remaining challenges are the still undefined relationship between the DWI and 7T FLAIR lesions, the temporal limitations of DWI (hyperintensities are typically visible only 1-2 weeks following infarction), and the generalizability of either method across centers. The clinical impact of microinfarcts on cognitive function and future hemorrhagic or ischemic stroke risk in CAA patients also remains to be determined. Current data suggest that both the overall lesion burden⁵⁹ and incidence of new lesions^{54, 55} is much greater for microinfarcts than cerebral microbleeds, highlighting their potential for extremely high statistical efficiency as an outcome if they could be sensitively detected.

Diffusion tensor imaging (DTI) obtained from multidirectional MRI diffusion gradients allows measurement of the amount (mean diffusivity, MD) and directional bias (fractional anisotropy, FA) of water diffusion throughout the brain. A small study of 11 participants with CAA-related ICH and 13 matched healthy controls found reduced FA in the temporal white matter (inferior longitudinal and occipital fasciculi, 17% reduction) and splenium of the corpus callosum (15% reduction) as well as increased FA of lower magnitude in deep grey matter structures.⁶⁰ The changes were bilateral and did not appear to be influenced by the hemisphere of cerebral hemorrhage. Another study of global MD in 49 CAA subjects found higher values among those with pre-ICH cognitive impairment compared to those without.⁶¹ These data suggest that white matter microstructure is abnormal in CAA and can be measured using DTI. They require further validation, however, in particular to determine whether clinically relevant changes can be detected over time as has been suggested for other small vessel disease.⁶² Standardized DTI appears to be feasible across scanners and sites. Standardized DTI across scanners and sites has not been extensively studied, but may be feasible.⁶³ Other techniques developed to probe the microstructure of cerebral white matter, such as *magnetization transfer imaging*, *MR spectroscopy*, and *quantitative mapping of MR parameters* (e.g. proton density, T1, T2, T2*), have yet to be applied or validated in the context of CAA, but hold promise based on reports in aging or ischemic small vessel disease.⁶⁴

Enlarged *perivascular spaces* (PVS, also termed Virchow-Robin spaces), the potential spaces surrounding small parenchymal blood vessels, represent another candidate nonhemorrhagic marker visible on MRI. Enlarged or dilated PVS, presumed to reflect the accumulation of interstitial fluid, have been linked to the presence and severity of cerebral small vessel disease.^{65, 66} CAA appears to be preferentially associated with high numbers of visible PVS in the centrum semiovale,^{67, 68} consistent with the known localization of CAA to the superficial cortical vessels. As with other emerging markers, enlarged PVS will require analysis for incident appearance over time, standardization across sites, and correlation with clinical status for it to be evaluated as a potential outcome marker.

Cognitive Performance

Along with symptomatic ICH, cognitive decline is the most clinically salient manifestation of CAA. Multiple studies have demonstrated the association of CAA and cognitive impairment across cohorts, institutions, and countries.⁶⁹⁻⁷⁵ In the Religious Orders Study, individuals with moderate-to-very severe CAA pathology at autopsy (representing 18.9% of

the 404 study subjects) demonstrated worse perceptual speed and episodic memory than those with no-to-minimal CAA, remaining independent of AD pathology, cerebral infarcts, Lewy bodies, age at death, sex, and education in multivariable analysis.⁷⁵ The precise mechanism by which advanced CAA gives rise to cognitive impairment remains undefined, and could represent the cumulative effects of the various hemorrhagic and nonhemorrhagic tissue injuries discussed above as well as contribution from coexistent AD pathology. Vascular amyloid itself may also trigger reactive changes and neuronal degeneration in surrounding tissue.⁷⁶

Prevention of cognitive decline, like prevention of symptomatic ICH, represents a clinically meaningful outcome appropriate for late-phase trials, though is relatively inefficient for early-phase studies. One theoretical advantage of cognition as an outcome is that it might be sensitive to cumulative changes across multiple hemorrhagic and nonhemorrhagic lesion types, potentially demonstrating the sum of treatment effects too small to be detected individually. Cognitive testing also has the advantages of utilizing tools that are well accepted by academia and industry (though primarily developed for AD rather than vascular cognitive impairment), validated across examiners and institutions, cost effective, relatively time efficient, quantitative, and measurable longitudinally. These advantages are offset by the nonspecificity of any cognitive test battery for CAA and the absence thus far of a sensitive and specific cognitive profile to discriminate CAA from other age-related conditions, as episodic memory and perceptual speed⁷⁵ overlap with domains affected in AD and other common dementias. Moreover, The absence of a clear link between cognitive performance and any single CAA-related injury type also limits the ability of these measures to provide specific pathophysiologic information on the biological effects of candidate treatments. Finally, CAA-related cognitive impairment likely represents largely irreversible brain injury and thus requires trials of sufficient size and duration for substantial progression to occur in untreated subjects. No information is yet available on rate of cognitive decline in CAA.

Vascular pathology and physiology

The hemorrhagic and nonhemorrhagic structural lesions and cognitive measures considered above are believed to reflect vascular-mediated injury to the brain rather than abnormalities of the vessels themselves. They may thus measure relatively late and irreversible steps in the postulated pathways leading from vascular dysfunction to brain injury and clinical dysfunction. An effective therapy 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 subjects. Direct markers of vessel pathology and physiology, conversely, might not only be blocked from worsening, but also actually improved by an effective treatment. A marker that is reversible might provide the highest level of statistical efficiency, allowing the possibility of smaller/shorter studies of candidate therapies.

Vascular amyloid can be detected and quantified by PET scanning with the amyloid radioligand [11C]-Pittsburgh Compound B (PiB). Although this agent was initially developed to detect senile plaque A β in AD, multiple studies have demonstrated increases in both global and occipital lobe PiB retention in nondemented sporadic^{77, 78} and familial⁷⁹

CAA subjects and at foci of past⁸⁰ and future⁸¹ CAA-related hemorrhagic lesions. Higher PiB retention is also independently associated with greater WMH burden in CAA but not AD or healthy elderly subjects,³² suggesting a link with CAA-related nonhemorrhagic as well as hemorrhagic brain injury.

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 demonstrate reduction of PiB retention in AD subjects⁸² and clearance of CAA in a transgenic mouse model.⁸³ It is unknown, however, whether reduction of vascular amyloid burden in CAA patients will have beneficial clinical effects; such benefits have not yet been demonstrated with amyloid clearance in AD.⁸⁴ Among other hurdles to be overcome in applying amyloid imaging to CAA trials are the specialized facilities and high cost required for production of radiolabeled amyloid ligands, the nonspecificity of current agents for vascular versus plaque amyloid, and the absence of natural history data on rate of vascular amyloid progression. Fluorine-18-tagged amyloid ligands such as florbetapir F 18,⁸⁵ longer-lived and therefore less expensive and logistically demanding than carbon-11 compounds, have been developed for AD, though not yet tested in CAA. It is also notable that methods for performing and analyzing PiB-PET across multiple sites have been developed by the Alzheimer Disease Neuroimaging Initiative⁸⁶ and other multicenter collaborations.

CAA is also associated with *altered vascular reactivity* to physiologic stimulation. Studies measuring the functional MRI (fMRI) blood oxygen level-dependent (BOLD) response to visual stimulation (Fig. 2) found that CAA subjects had 27 to 28% reduced peak amplitude,^{87, 88} 73% longer time till peak and 42% longer time till return to baseline⁸⁷ relative to similar aged control subjects. Altered BOLD response might represent either vascular or neuronal dysfunction, but the observations that CAA and control subjects had similar visual evoked response potentials⁸⁸ and that similar results could be obtained in analyses restricted to responding voxels only⁸⁷ argue that the differences are due to the effects of CAA on the vessels themselves. The fMRI response to visual stimulation appears to correlate with markers of CAA severity such as microbleed count and WMH volume,^{87, 88} suggesting that these parameters might reflect the underlying extent of disease and a potentially important mechanism for its pathogenesis. Like vascular amyloid deposition, impaired vascular reactivity has been demonstrated in transgenic mouse models to be at least partly reversible,^{89, 90} raising the possibility that BOLD fMRI might serve as an efficient marker for trials aimed at reducing amyloid's effects on vessel physiology. The reproducibility of this approach across multiple time points and multiple study sites remains to be determined, however.

Circulating Biomarkers

Biomarkers in cerebrospinal fluid (CSF) or plasma offer another approach for measuring underlying, potentially reversible aspects of CAA pathogenesis. Two studies of CSF from patients diagnosed with CAA found *reductions of the β -amyloid peptide A β 40 and A β 42 species*, with phospho- and total tau concentrations above those in elderly controls but lower than in AD.^{91, 92} These findings are broadly consistent with the pathology of CAA, which

entails vascular deposition of A β 40 as well as A β 42 and inconsistent coexistence of tau-containing lesions. The association between CSF A β and CAA disease progression has yet to be explored; by analogy to AD,⁹³ one might expect the reductions in CSF A β in CAA to correlate inversely with, and carry roughly the same information as, amyloid burden in CAA measured by PiB-PET.

A recent study of plasma A β reported elevated A β 40 and A β 42 concentrations in probable CAA relative to healthy controls,⁹⁴ differences not seen in an earlier analysis.⁹⁵ Another candidate family of molecules, the matrix metalloproteinases MMP-2 and MMP-9, have been found to be highly expressed near CAA-related ICH, but are not elevated in plasma of CAA patients.⁹⁶ These circulating biomarker studies are substantially limited by the very small number of CAA subjects examined (fewer than 100 published across all studies to date) and absence of data on reproducibility across sites or 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 CAA trials (see Table 1). Markers now exist for most of the postulated steps in CAA pathogenesis, ranging from vascular amyloid deposition itself to physiologic alterations, hemorrhagic and nonhemorrhagic structural damage, symptomatic hemorrhagic stroke, and cognitive dysfunction. It is thus possible to consider pilot trials for CAA in which one or more of these markers is used to demonstrate a particular biological activity of a candidate therapy, such as use of PiB-PET to demonstrate partial clearance of plaques in the phase 2 AD study of bapineuzumab.⁸² Such pilot trials might be particularly efficient when using potentially reversible markers like amyloid imaging and vascular reactivity. None of the imaging biomarkers has yet been linked closely enough to neurologic impairment, however, to serve as a true surrogate marker of clinically meaningful treatment effects. Symptomatic ICH and cognitive testing thus remain the only reasonably valid outcomes for studies aimed at demonstrating true clinical benefit.

Although the pathogenic mechanisms and data reviewed here focus specifically on CAA, many of the considerations and findings can be generalized to all forms of cerebral small vessel disease associated with vascular cognitive impairment (VCI). Despite increasing understanding of the biology of these small vessel processes, there are few established treatments for VCI prevention; control of hypertension was the only class I recommendation for patients at risk for VCI in a scientific statement from the American Heart Association/American Stroke Association.⁹⁷ Trials to establish specific therapies for common age-related small vessel pathologies, like those for CAA, would be greatly facilitated by study outcomes that are clinically and biologically meaningful, statistically efficient, and generalizable across sites. Nearly all of the measures of tissue injury and altered physiology described above are observed as well in arteriolosclerosis or chronic hypertensive vasculopathy,^{14, 56, 98-100} suggesting that these markers may represent general features of damage to the small cerebral vessels. No in vivo methods have yet emerged to measure arteriolosclerosis pathology in an analogous fashion to PiB detection of CAA, however,

highlighting the importance of achieving further progress in molecular imaging of small vessel diseases.

Data that strengthen the links between imaging biomarkers and neurologic function would allow greater reliance on these more efficient surrogate markers of clinical outcome in future trials. Based on current data, WMH volume appears to have the closest demonstrated correlation to cognition and microbleeds the closest correlation to symptomatic ICH, but improving imaging modalities and larger study populations may provide stronger support for other neuroimaging markers or combinations of markers. Other key areas of need are determination of the rates of biomarker progression over time and validation of imaging methods across sites, both prerequisites for the ultimate goal of multicenter biomarker-based interventional trials. Further growth in the armamentarium of trial outcome markers, together with improved mechanistic understanding of small vessel degeneration, will provide a strong foundation for identifying successful disease-modifying therapies for CAA and related diseases.

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A **B**

C **D**

E **Figure 1.**

Examples of MRI markers. Panels A shows a 74 year old man with a total of 6 strictly lobar microbleeds on baseline T2*-weighted MRI (left-hand panel shows 1 of these) and 5 incident strictly lobar microbleeds on follow-up performed 3.4 years later (right-hand panel shows 3 of the incident lesions, arrows). Panels B show superficial siderosis on T2*-weighted MRI in a 69 year old man with probable CAA and predominantly left hemispheric siderosis at baseline (left) and incident right superior frontal siderosis on follow-up 1.5 years later (right, arrows). Panels C show growth of WMH on FLAIR images between baseline (left) and follow-up at 5 years (right) in an 89 year old man with probable CAA, old right occipital ICH, and progressive impairment of executive function but no ICH during the inter-scan interval. WMH volumes in the left (non-ICH) hemisphere were 18.5 cc at baseline and 23.9 cc at follow-up. Panels D shows a left frontal cortex focus of restricted diffusion (DWI image on left, absolute diffusion coefficient map on right) consistent with a small acute infarct in a 74 year old man with probable CAA and no other known vascular disease. Panel E shows sagittal FLAIR (left) and T1 (right) images obtained by 7T MRI⁵⁸ of a 62 year old man with mild cognitive impairment. The lesions suggestive of cortical microinfarcts appear hyperintense on FLAIR and hypointense on T1 (arrows and insets for enlargement).

Figure 2.

Serial functional MRI measurement of response to visual stimulation. Exemplar fMRI studies are shown from a 83 year old woman with probable CAA. fMRI with visual stimulation was performed at baseline (blue line, red error space) and again using the same scanner and protocol after 1 clinically asymptomatic year (green line, yellow error space). The blue and green solid lines represent the change from baseline BOLD signal averaged over 16 cycles of visual stimulation (on 20 sec, shaded region, then off 28 sec), with standard deviations of the response shown in red and yellow spaces and the trapezoidal model fits in solid and dashed black lines as described.⁸⁷ The amplitude of the modeled peak response in this subject decreased from 1.06% at baseline to 0.80% at 1 year.

Table 1

Overview of Outcome Markers for Human Studies in CAA

Outcome Marker	Link to Clinical Function	Measure of CAA Severity/Progression	Statistical Efficiency for Smaller/Shorter Studies	Reproducibility Across Sites	Cost Effectiveness
Symptomatic ICH	+++	++	+	+++	++
Microbleeds	++	+++	++	++	+
WMH	++	+++	++	++	+
Microinfarcts	++	?	++	?	+
DTI 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.

ICH = Intracerebral hemorrhage WMH = White matter hyperintensities DTI = Diffusion-tensor imaging CSF = Cerebrospinal fluid