Vascular Cognitive Impairment Neuropathology Guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment

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Complete List of Authors:	Skrobot, Olivia; University of Bristol Attems, Johannes; Newcastle University, Institute of Neuroscience and Newcastle University Institute for Ageing, Campus for Ageing and Vitality Esiri, Margaret; University of Oxford Hortobagyi, Tibor; King's College London, Institute of Psychiatry Ironside, James; University of Edinburgh, National CJD Surveillance Unit Kalaria, Rajesh; Newcastle University, Centre for Vitality and Ageing King, Andrew; King's College Hospital, Department of Neuropathology Lammie, G A; Cardiff University, Histopathology Department Mann, David; University of Manchester, Mental Health and Neurodegeneration Neal, James; University of Wales, Department of Histopathology Ben-Shlomo, Yoav; University of Bristol, Department of Social Medicine Kehoe, Patrick; University of Bristol Love, Seth; Frenchay Hospital, Neuropathology
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Vascular Cognitive Impairment Neuropathology Guidelines (VCING) – a multi-centre study of the contribution of cerebrovascular pathology to cognitive impairment

O. A. Skrobot[1], J. Attems[2], M. Esiri[3], T. Hortobágyi[4], J. W. Ironside[5], R. N. Kalaria[2], A. King[6], G. A. Lammie[7], D. Mann[8], J. Neal[9], Y. Ben-Shlomo[10], P. G. Kehoe[1], S. Love[1]

[1]Dementia Research Group, School of Clinical Sciences, Faculty of Health Sciences, University of Bristol, Level 1, Learning & Research, Southmead Hospital, Bristol, BS10 5NB, UK; [2]Institute of Neuroscience and Newcastle Institute for Ageing, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK; [3] Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, OX3 9DU, UK; [4]Department of Neuropathology, Institute of Pathology, Faculty of Medicine, University of Debrecen, Nagyerdei krt. 98, Debrecen, 4032, Hungary & Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, SE5 8AF, UK; [5]Centre for Clinical Brain Sciences, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, Midlothian, EH4 2XU UK; [6]Department of Clinical Neuropathology, First floor, Academic Neuroscience Building, King's College Hospital, Denmark Hill, London, SE5 9RS, UK; [7]Institute of Cancer & Genetics, Cardiff University School of Medicine, Institute of Medical Genetics Building, Heath Park, Cardiff, CF14 4XN, UK; [8]Institute of Brain, Behaviour and Mental Health, Clinical and Cognitive Neuroscience Research group, University of

Manchester, A304 Clinical Sciences Building, Salford Royal Hospital, Stott Lane, Salford M6 8HD; [9] Institute of Infection & Immunity, Cardiff University School of Medicine, Henry Wellcome Building, Heath Park, Cardiff CF14 4N, UK; [10]School of Social and Community Medicine, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK.

Corresponding author: Seth Love

Dementia Research Group

School of Clinical Sciences

Faculty of Health Sciences

University of Bristol

Learning & Research level 1

Southmead Hospital

Bristol BS10 5NB

UK

seth.love@bristol.ac.uk

Abstract

There are no generally accepted protocols for post-mortem assessment in cases of suspected vascular cognitive impairment. Neuropathologists from 9 UK centres have collaborated in the development of a set of Vascular Cognitive Impairment Neuropathology Guidelines (VCING), representing a validated consensus approach to the post-mortem assessment and scoring of cerebrovascular disease in relation to vascular cognitive impairment. The development had three stages: (i) agreement on a sampling protocol and scoring criteria, through a series of Delphi-method surveys; (ii) determination of inter-rater reliability for each type of pathology in each region sampled (Gwet's AC2 coefficient); (iii) empirical testing and validation of the criteria, by blinded post-mortem assessment of brain tissue from 114 individuals (55 to 100 years) without significant neurodegenerative disease who had had formal cognitive assessments within 12 months of death. Fourteen different vessel and parenchymal pathologies were assessed in 13 brain regions. Almost perfect agreement (AC2 > 0.8) was found when the agreed criteria were used for assessment of leptomeningeal, cortical and capillary cerebral amyloid angiopathy, large infarcts, lacunar infarcts, microhaemorrhage, larger haemorrhage, fibrinoid necrosis, microaneurysms, perivascular space dilation, perivascular haemosiderin leakage, and myelin loss. There was more variability (but still reasonably good agreement) in assessment of the severity of arteriolosclerosis (0.45 – 0.91) and microinfarcts (0.52 – 0.84). Regression analyses were undertaken to identify the best predictors of cognitive impairment. Seven pathologies – leptomeningeal cerebral amyloid angiopathy, large infarcts, lacunar infarcts, microinfarcts, arteriolosclerosis, perivascular space dilation and myelin loss – predicted cognitive impairment. Multivariable logistic regression determined the best predictive models of cognitive impairment. The preferred model

included moderate/severe occipital leptomeningeal cerebral amyloid angiopathy, moderate/severe arteriolosclerosis in occipital white matter, and at least one large infarct (area under the ROC curve 77%). The presence of 0, 1, 2 or 3 of these features resulted in predicted probabilities of vascular cognitive impairment of 16%, 43%, 73% or 95% respectively. We have developed VCING criteria that are reproducible and clinically predictive. Assuming our model can be validated in an independent dataset, we believe that this will be helpful for neuropathologists in reporting a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment.

Key words: vascular cognitive impairment, vascular dementia, cerebrovascular disease, neuropathology, guidelines, cerebral infarct, arteriolosclerosis, cerebral amyloid angiopathy

Abbreviations:

Amyloid-β (Aβ)

Cerebral amyloid angiopathy (CAA)

Haematoxylin and eosin (HE)

Luxol fast blue (LFB)

Mini-mental state examination (MMSE)

Receiver operating characteristic (ROC)

Vascular cognitive impairment (VCI)

Vascular Cognitive Impairment Neuropathology Guidelines (VCING)

Introduction

The spectrum of vascular cognitive impairment (VCI) encompasses mild cognitive deficits that do not necessarily progress to dementia, and includes post-stroke dementia, vascular dementia, subcortical ischaemic vascular dementia, multi-infarct dementia and mixed dementias (i.e. co-morbid neurodegenerative and vascular pathology) (O'Brien *et al.*, 2003). VCI may be suspected if there is widespread disease of cerebral blood vessels (e.g. atherosclerosis, arteriolosclerosis or cerebral amyloid angiopathy (CAA), focal or diffuse ischaemic changes or foci of haemorrhage, particularly in the absence of an alternative pathological explanation for cognitive decline (Ferrer, 2010). However, these pathological abnormalities often occur, at least to some degree, without apparent cognitive impairment (Fernando *et al.*, 2004; Grinberg and Thal, 2010; Thal *et al.*, 2012) and become more prevalent with increased age (Jellinger and Attems, 2010). They are also very common in patients with Alzheimer's disease and other neurodegenerative dementias, and probably lower the threshold for neurodegenerative dementia (Esiri *et al.*, 1999; Schneider *et al.*, 2009; Schneider *et al.*, 2004).

Various protocols and definitions have been proposed to identify and categorise different types of cerebrovascular pathology in relation to dementia (Chalmers *et al.*, 2003; Deramecourt *et al.*, 2012; Esiri *et al.*, 1997; Kalaria *et al.*, 2004; Love, 2005; Montine *et al.*, 2012; Richardson *et al.*, 2012; Smallwood *et al.*, 2012; Strozyk *et al.*, 2010). Currently there are no widely accepted neuropathological criteria for the post-mortem diagnosis of VCI or vascular dementia. This poses a problem for prevalence estimates and comparison and collaboration of research and is in contrast to other types of dementia, such as Alzheimer's disease (Braak and Braak, 1991; Mirra *et al.*,

1991) and dementia with Lewy bodies (McKeith *et al.*, 2005). Highlighting these issues, a systematic review of neuropathological studies of cerebral microinfarcts in the context of vascular disease found large variability in characteristics of microinfarcts reported in the different studies and highlighted the obvious need for standardization of neuropathological criteria to allow comparison of findings in different centres (Brundel *et al.*, 2012). Other surveys of post-mortem neuropathological assessment in centres across the world have revealed wide differences in the definitions, sampling procedures and interpretation of vascular pathology (Alafuzoff *et al.*, 2012; Pantoni *et al.*, 2006). The importance of establishing evidence-based, objective criteria for post-mortem evaluation of the contribution of cerebrovascular disease to cognitive impairment is widely acknowledged (Alafuzoff *et al.*, 2012; Grinberg and Heinsen, 2010; Jellinger, 2008; Jellinger, 2013). The aim of the present study was to develop a set of Vascular Cognitive Impairment Neuropathology Guidelines (VCING) that represented a consensus approach to the post-mortem assessment and scoring of cerebral vascular disease in relation to VCI, and was supported by objective evidence of clinical relevance.

Materials and methods

Stage 1: Delphi study

Fourteen UK-based neuropathologists, mainly from the BDR network (http://brainsfordementiaresearch.co.uk), were invited to participate in a survey to agree on a protocol to (i) assess and (ii) report cerebrovascular disease, with a view to

(iii) analysing which types of vascular pathology that could be reliably assessed best predicted cognitive impairment. Nine neuropathologists accepted the invitation. A Delphi survey (Ferri *et al.*, 2005; Linstone, 1975) was conducted using an online survey tool (Bristol Online Surveys (https://www.onlinesurveys.ac.uk/) hosted by the University of Bristol. Survey responses were anonymous and were collated and analysed by an independent facilitator (O. A. S.). Responses informed questions for each subsequent round. The questions were presented to participants together with a summary of the previous results and comments on areas of agreement and disagreement. This process was iterated until consensus was achieved or when over half of the respondents agreed on one option amongst several. A two-thirds majority was sought for bimodal questions (percentages of respondents are provided where appropriate). Nine rounds of the survey were conducted. Rounds 1 and 2 assessed familiarity with previously published protocols (and directed participants unfamiliar with any protocols to the relevant publications) and prioritised a series of issues that should be resolved in order to formulate the VCING (Supplementary Table 1). Rounds 3 – 7 achieved agreement on definitions, terminologies and sampling procedures, based on published definitions and procedures or suggestions by the participants. The last two rounds were used to agree the final integrated protocol, after participants had an opportunity to review and comment on previous rounds of the survey.

Stage 2: reproducibility study

Nine of the original fourteen neuropathologists agreed to participate in the next two stages of the study, which were funded by a Network Cooperation grant from Alzheimer's Research UK.

The neuropathologists assessed post-mortem brain tissue, according to VCING, blind to any previous clinical or pathological diagnoses. 113 cases (52F/61M, age 83.40 ± 8.95 (55-100)) were obtained from the Oxford brain bank and the Newcastle Brain Tissue Resource (NBTR) (Table 1 and Supplementary Table 2). All were Caucasians from the regional United Kingdom populations served by the two centres. The cohort comprised consecutively collected brains from autopsies with consent for brain donation that fulfilled the following criteria. The principal inclusion criterion was formal cognitive assessment, in most cases including MMSE, within 12 months of death, in a memory or vascular clinic. Exclusion criteria were the presence of substantial Alzheimer's disease (Braak tangle stage > III) (Braak and Braak, 1991), Lewy body pathology (Braak Lewy body stage > 3) (McKeith *et al.*, 2005) or other non-vascular neurological disease. In 4 cases we could exclude Braak tangle pathology of stage IV or higher but did not have adequate histology of the transentorhinal region and subiculum for precise staging. The cases included blocks of all of the brain regions specified in the VCING protocol. Formalin-fixed paraffin-embedded sections that were from the VCING-specified brain regions and had been stained with haematoxylin and eosin, or luxol fast blue (to assess myelin loss), or immunolabelled for Aβ with Chemicon 4G8 (to assess CAA), were circulated between the seven participating UK centres.

Inter-rater reliability was tested by calculating Gwet's AC2 coefficient (Gwet, 2008) for each pathology in each region. This method is a more appropriate alternative to

the conventional Kappa's coefficient when there are marked unbalanced marginal totals, i.e. very rare presentation of some pathologies when the majority of samples have no pathology. In these scenarios it has been shown that one can have a high level of concordance but low Kappa values as a statistical artefact (Feinstein and Cicchetti, 1990). The calculations were performed using AgreeStat 2015.2 programme (Advanced Analytics, LLC). Quadratic weights were assigned for scale scoring schemes, a coefficient of 1 indicating full agreement (exact same score by all participants). We used the benchmarks proposed by Landis and Koch (Landis and Koch, 1977) to evaluate the extent of agreement for the AC2 coefficient (> 0.4 indicating moderate, > 0.6 substantial and > 0.8 almost perfect agreement). Due to small numbers, scoring schemes with more than 2 levels of severity were dichotomised to produce more robust parameter estimates maximise for stage 3.

Stage 3: validation study

Multivariable logistic regression analysis was undertaken to assess the contribution of vascular pathologies to cognitive impairment (STATA 14 - StataCorp LP, Texas, USA). The primary outcome variable was a clinical diagnosis of dementia or mild cognitive impairment (henceforth collectively termed 'cognitive impairment'). As a sensitivity analysis, we also ran analyses using a cut-off of MMSE <27 (Pendlebury *et al.*, 2012). We calculated the median vascular scores (both region-specific and global) across raters for each type of pathology and brain region. Any cases with fewer than 4 raters per pathology/area were excluded.

We used a two-stage modelling process. We assessed which pathologies in which brain regions were associated with both outcomes, initially by univariable regression analysis. If multiple brain regions were significantly associated for a particular pathology and not highly co-linear, as tested by chi-square analysis, we used a stepwise multivariable model to identify in which region(s) the particular pathology best predicted cognitive impairment. Bimodal variables were also created for the presence of a particular pathology in at least one of the brain regions (termed 'global' variables). Because of the small sample size, with some cells having zero observations, we used exact (exlogistic command in Stata) rather than conventional logistic regression. This method uses the conditional distribution of the parameter-sufficient statistics and the conditional maximum likelihood estimates as an alternative to maximum likelihood estimation, which can perform poorly for small sample sizes. In addition, where the outcome variable is completed determined by the exposure, exlogistic computes the median unbiased estimate, the regression estimate that places the observed sufficient statistic at the median of the conditional distribution.

In the second stage, the best predictors from stage 1 were entered into a stepwise multivariable regression model with cognitive impairment as the dependent variable. The best combined model was used to calculate diagnostic utilities, area under the ROC curve and predicted probabilities using the presence and absence of the key pathological features. This was then repeated with the secondary outcome (MMSE < 27). Finally as a post-hoc exploratory analysis, we wanted to see if the predictive value of the best model differed by age of the subjects and we tested for age and pathology interactions, having dichotomised age at the median.

Results

Stage 1: Delphi study

In the first survey, we presented previously published protocols for neuropathological assessment in suspected vascular dementia, identified by literature review, to the participants. Participants were asked to state their familiarity and use of these protocols and to critique their utility. Results from Round 1 were presented to the participants in the subsequent round. After review of these results, respondents selected the best papers upon which to base discussions in order to formulate VCING. The 5 most supported (≥ 75%) papers were: Esiri *et al.*, 1997; Strozyk *et al.*, 2010; Deramecourt *et al.*, 2012; Montine *et al.*, 2012; and Smallwood *et al.*, 2012. Other papers that had been considered were those by Chui *et al.*, 1992; Roman *et al.*, 1993; Vinters *et al.*, 2000; Halliday *et al.*, 2002; White *et al.*, 2002; Kalaria *et al.*, 2004; Love, 2005; Hachinski *et al.*, 2006; Gold *et al.*, 2007; and the NACC Neuropathology Diagnosis Coding Guidebook of the ADC Clinical Task Force and the National Alzheimer's Coordinating Center (ADC Clinical Task Force and the National Alzheimer's Coordinating Center, 2008). Respondents suggested additions or amendments to improve the usefulness of the protocols in the selected papers. The consensus was that there should be assessment of vessel wall pathology, separate from and additional to assessment of presumed ischaemic tissue damage; both large and small vessel disease; haemorrhagic lesions as well as presumed ischaemic ones; and that there should be separate scoring systems for quantifying severity of vessel wall pathology and tissue damage.

In round 2 participants were also asked to prioritise the immediate and longer term objectives of VCING. The immediate objectives selected by ≥ 75% of respondents became the focus for Rounds 3-7 (Supplementary Table 1). The topics and key points covered in each round are summarised in Supplementary Fig. 1.

Definitions

Three of the top five immediate objectives were to develop consensus definitions. Agreed definitions are presented in Table 2. Greater discussion was required as to the distinction between arteriosclerosis and arteriolosclerosis. This was prompted by the definition presented in Deramecourt *et al.*, 2012. Although supported by a majority (75%) in Round 3, the definition was noted by one participant to relate to arteriolosclerosis rather than arteriosclerosis. Another respondent suggested that it was sufficient to identify hyaline thickening of the vessel wall with loss of tunica media even in the absence of obvious narrowing of the lumen to diagnose arteriosclerosis. After review of this feedback, consensus support (67%) was received for the definition 'hyaline thickening of walls of vessels < 150 μm in diameter, not associated with lipid vacuole-containing cells in the tunica media'. Two respondents suggested additions to the agreed definition of arteriolosclerosis that were presented to the participants in the following round. A majority (62.5%) of Round 6 respondents were in favour of including one of the suggestions: 'Diagnosis requires the absence of inflammation, amyloid or fibrinoid necrosis'.

Separate designation of microinfarcts and microhaemorrhages

All Round 3 respondents stated that they could usually distinguish between microinfarcts and microhaemorrhages. However, opinion was split (50%) as to whether they should all be co-designated as microvascular lesions, as proposed by Montine *et al.*, 2012, as this would prevent later determination of the separate contribution of these individual types of lesion to cognitive dysfunction. After subsequent feedback in Round 4, all respondents agreed that microinfarcts and microhaemorrhages should be separately recorded. Microhaemorrhage was distinguished from perivascular haemosiderin leakage by the accumulation of haemosiderin in the brain parenchyma.

Sampling procedures

The majority of Round 3 respondents (88%) supported the sampling of a specified set of blocks from one hemisphere but with additional sampling of macroscopic lesions. All respondents agreed on the utility of staining with HE and LFB. Only 25% of respondents supported the additional use of silver impregnation for axons (Bielschowsky/Bodian/Palmgren). In addition to the stains listed, immunolabelling of Aβ or staining of sections with Congo red was suggested. 86% of Round 4 respondents thought that sections should routinely be immunolabelled for Aβ and 57% of respondents suggested the use of Chemicon Clone 4G8 for this. After feedback of these results, all respondents in Round 5 agreed to the use of Chemicon clone 4G8 for immunolabelling of Aβ.

A wide range of possible brain regions to be sampled were considered for inclusion in VCING. Those supported by a majority (≥ 63%) are listed in Table 3. The subsequent

round elicited additional comments concerned the sampling of cerebral white matter regions. 86% of respondents felt that temporal and occipital white matter should be adequately represented in the blocks sampled, 86% agreed that the internal capsule should be sampled, and 71% agreed that white matter regions should routinely be sampled bilaterally in VCING.

Assessing and quantifying vessel wall pathology

In Round 3 it was agreed that atheroma of the circle of Willis (88%), arteriosclerosis (including arteriolosclerosis) (88%) and CAA (100%) should be assessed. Respondents in Round 4 indicated which published methods for assessing and quantifying these vessel wall pathologies they preferred and/or provided alternative suggestions or comments. All Round 4 respondents supported the use of the method of Esiri *et al.*, 1997 for scoring atheroma of circle of Willis. All respondents thought that the scoring of arteriolosclerosis should be based on the method of Deramecourt *et al.*, 2012, that arteriosclerosis and arteriolosclerosis should be scored together (62.5% support) and that fibrinoid necrosis and microaneurysms as complications of arteriolosclerosis should be separately scored simply as present (1) or absent (0) (75% agreement).

In Round 4, participants were asked to rate three published CAA scoring systems. Preference was expressed for the Love *et al.*, 2014 (first choice preference) and Esiri *et al.*, 1997 protocols, the latter receiving a higher combined first and second choice preference. However, most respondents wanted to take separate account of CAA in

the cortex and meninges, and to assess capillary CAA separately from arteriolar CAA, and these preferences were incorporated into a composite CAA scoring system.

Assessing and quantifying tissue damage caused by/associated with vessel disease

Most participants thought that all of the types of putatively 'vascular' tissue damage presented in Round 3 should be assessed (≥ 75%). In Round 4, participants were asked to rank their preference for the three published systems for scoring tissue damage caused by or associated with vessel disease. Deramecourt *et al.*, 2012 was the first choice of 71% of respondents. After feedback of these results, this choice was endorsed by all Round 5 respondents. However, as the respondents had previously agreed on the assessment of lacunar infarcts, larger haemorrhages and microhaemorrhages, which are not part of the Deramecourt et al., 2012 protocol, the protocol was modified to include these elements and agreed by consensus in the next round (Table 3).

The aim of Round 8 was to review and agree on the final assessment protocol. Summary results from Rounds 1-7 were presented and questions posed to confirm support or highlight points that still need clarification. The only amendments agreed in Round 9 were that CAA should be assessed separately in all 4 lobes of the cerebrum and separately in the hippocampus and the other parts of the temporal lobe, and that the abnormalities that constituted CAA vasculopathy were agreed to be concentric splitting of the vessel wall ('double barrelling'), perivascular haemorrhage, fibrinoid necrosis, and thrombosis with recanalisation. The final Delphi consensus

VCING are presented in Table 3. The form that was circulated to assessors is available as a supplementary file (Supplementary VCING validation assessment form).

Stage 2: reproducibility study

Inter-rater reliability

Table 4 shows the Gwet's AC2 coefficients for the vascular pathologies assessed after collapsing the scoring schemes based on clinical relevance. In general, analysis showed the VCING criteria to be reproducible, most achieving > 0.8, indicating almost perfect agreement. There was variability in assessment of the severity of arteriolosclerosis: agreement was high in most brain regions (almost perfect in six, substantial in three) but moderate in four brain regions. Reliability in assessing microinfarcts also varied: almost perfect in the frontal gyrus, occipital cortex, and internal capsule, substantial in seven regions and moderate in three brain regions.

Stage 3: validation study

The number and percentage of cases with vascular pathologies are detailed in Supplementary Table 3. Most pathologies were evident in under 10% of cases in the majority of brain regions. Large infarcts were rare (0-4%), as were lacunar infarcts except in the putamen (19%). No cases were agreed to have haemorrhage, fibrinoid necrosis or microaneurysms. More prevalent pathologies were: arteriolosclerosis (19-46%) in half of the brain areas assessed; leptomeningeal CAA (25-43%) in four out of

six brain areas assessed; and myelin loss in the occipital (24%) and frontal (40%) regions.

Contribution of vascular pathologies to cognitive impairment

Univariable regression analysis showed seven pathologies − arteriolosclerosis, perivascular space dilation, leptomeningeal CAA, myelin loss, microinfarcts, lacunar infarcts and large infarcts – to be predictive of cognitive impairment (Table 5) and unlikely to be due to chance. Age, gender, *APOE*, Braak stage were not associated with cognitive impairment.

The best individual predictors were entered into a multivariable regression model to identify the best combination of predictors of cognitive impairment. The best combination model (model 1) included: at least one large infarct (OR = 6.46, 95% CI 1.50-27.8, p=0.01) moderate/severe occipital leptomeningeal CAA (OR = 5.49, 95% CI 2.17-13.9, p <0.001) and moderate/severe myelin loss in at least one brain region (OR = 4.06, 95% CI 1.61-10.2, p <0.001). The model correctly classified 77.9% cases as cognitively impaired, but was more specific (92.3%) than sensitive (58.3%) with an area under the ROC curve of 78.5%. Predicted probabilities of VCI went from 11%, 38%, 75% to 95% depending whether there were 0, 1, 2 or 3 of these findings (the probabilities for individual combinations are shown in Table 6).

Replacing myelin loss in model 1 with occipital white matter arteriolosclerosis (a more specific indicator of vascular disease) for model 2 was only slightly worse in predicting correctly 72.6% cases, but with both reduced sensitivity (54.2%) and specificity (86.2%) (area under the ROC curve of 77.4%): at least one large infarct

(OR = 8.97 95% CI 2.16-37.3, p=0.003), moderate/severe occipital leptomeningeal CAA (OR = 4.24, 95% CI 1.77-10.1, p=0.001) and moderate/severe arteriolosclerosis in occipital white matter (OR= 2.70, 95% CI 1.14-6.40, p=0.02). In model 2, the predicted probabilities of VCI went from 16%, 43%, 73% to 95% depending whether there were 0, 1, 2 or 3 of these findings (see probabilities for individual combinations in Table 6).

The validated VCING are listed in Supplementary Table 4. Secondary analysis showed the same pathologies (apart from large infarcts) to be associated with MMSE < 27; however, there were differences as to the brain region in which the pathologies best predicted this outcome (Supplementary Table 5). Large infarcts globally did not quite reach significance (p = 0.08). Therefore model 1 determinants with MMSE as the dependent variable did not perform as well: 69% overall accuracy and 74.2% area under the ROC curve. Performance of model 2 was comparable: 68% cases were correctly classified cognitively impaired, with an improved sensitivity of 61.5% but reduced specificity 75 (area under ROC curve 72.3%). However, only moderate/severe arteriolosclerosis in occipital white matter was a determinant of MMSE < 27 (OR = 3.97, 95% CI 1.62-9.70, p = 0.001), with neither global large infarcts nor occipital leptomeningeal CAA reaching conventional levels of statistical significance.

For model 1 we found evidence for a modest age interaction with moderate/severe occipital leptomeningeal CAA (p=0.03) so that the odds ratio was stronger for subjects with an age ≥ 85 years than those < 85 years (OR 8.37 versus 3.52). For model 2, we found this age interaction to be even stronger with moderate/severe occipital leptomeningeal CAA (p = 0.006) (OR 11.4 versus 2.13) and there was a

similar interaction with occipital white matter arteriolosclerosis (p = 0.02) (OR 6.40 versus 1.93).

Discussion

Although multiple consensus guidelines have been produced on the post-mortem assessment of brain tissue for different diseases that cause dementia, most of the diagnostic criteria embedded in those guidelines have been based on *a priori* assumptions as to the most relevant lesions. Those assumptions can be tested in subsequent studies, as can the reliability with which the lesions can be assessed, but such post hoc studies may not address biases in sampling or assessment that are intrinsic to the initial guidelines. Our aim in the present study was to develop evidence-based practical guidelines for assessing the contribution of vascular pathology to cognitive impairment with reduced sampling bias and good reproducibility. We achieved this through several steps. The first involved the cooperation of a broad group of neuropathologists with expertise in dementia, in agreeing on clearly defined, comprehensive sampling and assessment guidelines, without making assumptions as to which types of vessel wall abnormality, ischaemic and haemorrhagic parenchymal lesion were more or less likely to be associated with dementia. We used Delphi-based methods to develop the VCING, with consensus definitions, staining procedures and assessment scoring protocols. Next we performed a blinded assessment of the inter-rater reliability of the scoring protocols and used the results to refine and simplify the assessments to achieve a high degree of reproducibility. Lastly, we applied the refined assessment procedures to a series of brains from people with varying degrees of vascular pathology and cognitive

impairment in the absence of significant neurodegenerative disease, to develop a simple model for determining the probable contribution of cerebrovascular disease to cognitive impairment.

Several of our findings are in keeping with previous studies of vascular cognitive impairment. We found significant associations of cognitive impairment with microinfarcts, lacunar infarcts, large infarcts, arteriolosclerosis, perivascular space dilation, myelin loss and leptomeningeal CAA. Strozyk et al., 2010 found leukoencephalopathy, large infarcts, lacunar infarcts and higher vascular burden (combined macroscopic score) to be associated with vascular dementia. In another study, vascular dementia was associated with brain infarcts in 66% of cases (Thal et al., 2012). Subcortical macroscopic infarcts (Schneider et al., 2009) and lacunar infarcts in the thalamus were previously shown to be important predictors of cognitive impairment (Gold et al., 2005). Microinfarcts were found in all brain regions assessed in VCING – in agreement with a recent systematic review (Brundel et al., 2012). Those in the parietal cortex and putamen were predictive of cognitive impairment. Previous studies found associations between microinfarcts and dementia or cognitive dysfunction (Arvanitakis et al., 2011; Brayne et al., 2009; Esiri et al., 1997; Gold et al., 2005; Kovari et al., 2004; Sonnen et al., 2007; Troncoso et al., 2008; White et al., 2002). Cognitive impairment was also reported to be associated with diffuse white matter demyelination (Esiri et al., 1997), periventricular demyelination (Kovari et al., 2004) and arteriolosclerotic small vessel disease (Ighodaro *et al.*, 2016; Smallwood *et al.*, 2012), and several studies found CAA to be associated with cognitive impairment, independent of its association with Alzheimer's disease (Greenberg et al., 2004; Keage et al., 2009; Neuropathology Group. Medical Research Council Cognitive and Aging, 2001; Pfeifer et al., 2002), as shown here.

Individual pathologies predicted cognitive impairment with 60-65% accuracy (univariable analysis). Combining the best predictors from three pathologies improved this accuracy to 78%: moderate/severe occipital leptomeningeal CAA, at least one large (> 10-mm diameter) infarct, and moderate/severe myelin loss in at least one brain region (model 1). The predictive probabilities of VCI for this model ranged from 11%-95%, depending on which combinations of pathologies were present. Our second model, with slightly lower predictive accuracy (77%), combined moderate/severe occipital leptomeningeal CAA, at least one large infarct, and moderate/severe arteriolosclerosis in the occipital white matter. We interpret the CAA and arteriolosclerosis as proxy measures of white matter damage leading to cognitive impairment, in agreement with previous findings (Esiri *et al.*, 1997; Greenberg *et al.*, 2004). Both models in the present study were derived from cases without significant neurodegenerative pathology. As myelin loss is not specific for cerebral ischaemia and may result from neurodegenerative changes in overlying cerebral cortex (Agosta *et al.*, 2011; Coleman, 2005; Leys *et al.*, 1991; McAleese *et al.*, 2015; Tosto *et al.*, 2015), we favour the second model as all three determinants are specific measures of cerebrovascular pathology. Although empirically its performance was slightly worse, it was comparable with regard to the area under the ROC curve (77.4% compared with 78.5% in the first model) and the probability of cognitive impairment ranged from 16% to 95%, depending on the combination of key pathological abnormalities present. Interestingly, we observed that the strength of association of some of the pathological findings with cognitive impairment may differ in an older as compared to younger brain. Our interaction tests were done *post hoc* and must therefore be treated with caution as they may simply reflect a type I error. However, the findings are of potential interest and are in keeping with other neuropathological data

suggesting that vascular disease plays an increasingly important role in the development of dementia in the very old (Brayne *et al.*, 2009).

Strengths and limitations: Delphi study

Our initial expectation was that we could use previously published protocols for neuropathological assessment in suspected vascular dementia as the basis for the present study. However, our literature review indicated that no single published protocol covered the full range of relevant pathologies, supporting the need for this study. Indeed, even with reference to five different published guidelines, we had insufficient detail on definitions of some terms and scoring schemes. The scoring protocol for assessing and quantifying tissue damage caused or associated with vessel disease by Deramecourt *et al.*, 2012 was adopted for assessment of several of the vascular pathologies but participants devised further criteria for scoring lacunar infarcts, larger haemorrhage and microhaemorrhages. All respondents supported the scoring method of Esiri *et al* (Esiri *et al.*, 1997) for atheroma of circle of Willis. We extended Deramecourt *et al.*, 2012 for arteriolosclerosis with additional scoring of the associated complications of fibrinoid necrosis and microaneurysms. scoring schemes (Esiri *et al.*, 1997; Love *et al.*, 2014) were adapted for assessment of CAA.

The underlying principle of the Delphi method is that decisions made through iterative review by a group are more likely to be valid than those made by individuals. The iterative process was particularly important to reconcile differences in the definitions and terminology used by the neuropathologists. However, the participants

held similar views on most topics without the need for repeated rounds of questions, for example with reference to which brain regions and pathologies should be assessed.

Strengths and limitations: reproducibility and validation studies

Strengths of the study were the relatively large number of neuropathologists and the combination of cohorts from two UK brain banks, providing cases with a broad range of vascular pathology and cognitive performance. Our primary outcome measure was cognitive impairment. Although MMSE scores were available for most cases, this test is relatively insensitive to the progressive decline and loss of executive function typically seen in VCI (Ihara *et al.*, 2013; Pendlebury *et al.*, 2010; Pendlebury *et al.*, 2012) and we therefore used MMSE scores in secondary analysis.

Large haemorrhages, microhaemorrhages, fibrinoid necrosis and microaneurysms were either rare or not present in this cohort. In consequence, these elements of the protocol could not be validated, although is quite possible that some of the rarer pathologies may also predict cognitive impairment. High inter-rater reliability for these pathologies simply reflected agreement amongst the assessors for the absence of pathology in the majority of cases. Modelling and diagnostic predictions could not be fully realised due to insufficient numbers for some pathologies in regional analysis; however, global measures were employed to overcome this limitation. The models presented in the present study are limited by the cohort size and composition of the cohort. It will be important to assess the reproducibility of these models in a much larger cohort, ideally with standardised prospective collection of clinical and cognitive data.

A final limitation of the present study was its reliance solely on morphological assessment of vascular pathology. Recent studies have shown that biochemical assessments can provide additional information of potential relevance to vascular cognitive impairment. Examples include measurement of the concentration of both vascular endothelial growth factor and the ratio of myelin-associated glycoprotein to proteolipid protein-1 to assess cerebral perfusion (Barker *et al.*, 2014; Love and Miners, 2015a; Love and Miners, 2015b; Miners *et al.*, 2015; Thomas *et al.*, 2015), and measurement of von Willebrand factor as a marker of microvascular density (Miners *et al.*, 2014; Thomas *et al.*, 2015). It is possible that the inclusion of these and other biochemical assays, e.g. of vesicular glutamate transporter and choline acetyltransferase activity (Kirvell *et al.*, 2010; Sharp *et al.*, 2009) or of vasoconstrictors such as endothelin-1 or angiotensin II (Ashby *et al.*, 2016; Barker *et al.*, 2014) might enhance neuropathological assessment of the determination of the contribution of cerebral vascular disease to cognitive impairment.

Conclusion

This study has used consensus VCING to evaluate which vascular pathologies, amongst a broad range, best predict cognitive impairment. Our findings suggest that neuropathologists can use a combination of the three main determinants – moderate/severe occipital leptomeningeal CAA, at least one large infarct, and moderate/severe arteriolosclerosis in the occipital white matter – to assign a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment in an individual case (Fig. 1). Further validation of the VCING in a larger clinical cohort is encouraged.

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Legends for figures

Fig. 1: VCING model estimating the likelihood that cerebrovascular disease contributed to cognitive impairment. Combinations of the three main determinants − at least one large (> 10-mm diameter) infarct, moderate/severe occipital leptomeningeal CAA, and moderate/severe arteriolosclerosis in the occipital white matter − are used to assign a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment in an individual case. The bars in the upper, middle and lower photomicrographs represent 1 mm, 250 μm and 100 μm respectively.

Supplementary Fig. 1: Topics covered in each round of the Delphi survey.

Table 1: Cohort details: mean age, gender and clinical diagnosis. MMSE score, Braak tangle stage and *APOE* allele frequencies were available for most cases (figures shown).

Cohort details	**N=114**
Mean age ± SD (range)	83.29 ± 8.99 (55-100)
Gender (M/F)	61/ 53
Clinical diagnosis 'cognitive impairment':	**49:**
Stroke with dementia (11) / Stroke with mild dementia (2)	13
Dementia	9
VaD (3) /probable VaD (3)	6
Probable AD (2) / Possible AD (3)	5
Multi-infarct dementia (MID)	1
Possible dementia with white matter disease	1
Possible DLB	1
~~Possible frontal lobe dementia~~	~~1~~
Mild dementia with parkinsonism or AD or DLB	1
History schizophrenia/depression, dementia in last 4 years	1
Depression/dementia	2
Mild cognitive impairment	1
Subjective memory problems	4
Cognitive impairment/ Orthostatic hypotension	3
Clinical diagnosis 'normal':	**65:**
Cognitively normal	31
Almost blind	1
Stroke, no dementia	16
Cardiac disease	1
Heart failure	1
High alcohol intake	2
Epilepsy	1
Carcinoma	1
Parkinsonism	1
Parkinsons aphasia	1
Depression (4) / Depression, TIAs (1)	5
Some psychiatric symptoms	1
Schizo-affective disorder	1
Mental lethargy	1
Progressive mental confusion – delirium	1
MMSE score mean ± SD (range) (n = 100)	23.03 ± 7.05 (0-30)
MMSE score <27/ ≥27	48/ 52
Braak stage: 0	8
I-II	76
III-IV	26
Genotype data (n = 77)	
APOE ε4 allele frequency	0.14
APOE ε2 allele frequency	0.06

Table 2: Delphi study agreed definitions. Definitions were developed amongst respondents through multiple survey rounds, apart from those denoted * that were taken from Strozyk *et al.* (Strozyk *et al.*, 2010).

Agreed definitions	
Atherosclerosis/atheroma	Disease of medium-sized to large arteries at the base of the brain, characterised by formation of plaques showing varying degrees of destruction of the vessel wall and accumulation of lymphocytes and macrophages; in later stages plaques may contain necrotic core, cholesterol clefts and foci of calcification.
Arteriolosclerosis	Hyaline thickening of walls of vessels <150μm in diameter, not associated with lipid-containing cells replacing the tunica media. Diagnosis requires an absence of intramural inflammation, amyloid or fibrinoid necrosis.
Large infarct	Maximum diameter >1 cm*.
Lacunar infarct	Cystic lesion visible to the naked eye but <1 cm in diameter*.
Microinfarct	Ischaemic lesion found on microscopic examination but not visible to the naked eye*.
Large haemorrhage	Haemorrhagic lesion visible to the naked eye which is easily identifiable on macroscopic examination.
Microhaemorrhage	Haemorrhagic lesion (with parenchymal involvement) found on microscopic examination which is not visible to the naked eye.
White matter pallor	A reduction in myelin staining in white matter in Luxol fast blue stained sections.
White matter rarefaction	Weakly stained/pale and loose appearance of myelinated fibres.

Table 3: Pathologies and brain areas agreed for assessment after Delphi process.

Pathology	Brain areas assessed
Arteriolosclerosis (0-3)*	All four lobes of cerebrum (frontal and occipital white matter scored separately) Hippocampus (anterior and posterior scored separately) Basal ganglia (caudate, globus pallidus, internal capsule and putamen scored separately) Thalamus
Fibrinoid necrosis (0/1)	
Microaneurysms (0/1)	
Perivascular space dilation (0-3)*	
Perivascular haemosiderin leakage (0-3)*	
Microinfarcts (0/1)*	
Lacunar infarcts (0-3)	
Large infarcts (0/1)*	
Microhaemorrhage (0/1)	
Larger haemorrhage (0/1)	
CAA[#]; **leptomeningeal (0-4)** **cortical (0-4)** **capillary (0/1)**	All four lobes of cerebrum, with separate scores for hippocampus and temporal neocortex
Myelin loss (0-3)*	Internal capsule, frontal white matter and occipital white matter
Atheroma of circle of Willis[$]	

Samples are taken from the specified regions in one hemisphere with additional sampling of macroscopic lesions. Temporal and occipital white matter should be adequately represented in the blocks sampled. Scoring schemes for arteriolosclerosis, dilatation of perivascular spaces, and infarcts were adapted from Deramecourt *et al* (Deramecourt *et al.*, 2012)*; for CAA from Esiri *et al* 1997 (Esiri *et al.*, 1997) and (Love *et al.*, 2014)[#], with CAA-associated vasculopathic changes given a score of 4; for assessment of atheroma of circle of Willis from Esiri, Wilcock and Morris (Esiri *et al.*, 1997)[$].

Table 4: Inter-rater reliability in assessment of each vascular pathology in each brain region.

Brain region	Arteriolosclerosis		Fibrinoid necrosis		Microaneursyms		Perivascular space dilation		Perivascular haemosiderin leakage	
	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.
Frontal cortex	0.91	0.89 to 0.93	0.95	0.93 to 0.97	0.99	0.98 to 1	0.99	0.97 to 1	0.98	0.96 to 0.99
Frontal white matter	0.45	0.38 to 0.53	0.82	0.79 to 0.86	0.94	0.92 to 0.96	0.81	0.76 to 0.86	0.79	0.74 to 0.85
Temporal cortex	0.87	0.84 to 0.91	0.93	0.90 to 0.96	0.99	0.97 to 1	0.98	0.96 to 1	0.92	0.88 to 0.95
Occipital cortex	0.90	0.88 to 0.93	0.96	0.94 to 0.98	0.99	0.99 to 1	0.99	0.99 to 1	0.96	0.94 to 0.98
Occipital white matter	0.52	0.46 to 0.59	0.88	0.85 to 0.91	0.96	0.95 to 0.98	0.84	0.80 to 0.89	0.81	0.76 to 0.86
Parietal cortex	0.78	0.74 to 0.83	0.91	0.88 to 0.94	0.95	0.93 to 0.98	0.95	0.92 to 0.98	0.82	0.77 to 0.88
Anterior Hippocampus	0.89	0.85 to 0.93	0.92	0.87 to 0.96	0.98	0.95 to 1	0.98	0.94 to 1	0.97	0.93 to 1
Post hippocampus	0.89	0.86 to 0.93	0.91	0.88 to 0.95	0.98	0.96 to 1	0.98	0.95 to 1	0.96	0.92 to 0.99
Caudate	0.73	0.68 to 0.78	0.87	0.83 to 0.90	0.95	0.92 to 0.97	0.95	0.92 to 0.98	0.98	0.96 to 1
Putamen	0.50	0.43 to 0.57	0.80	0.75 to 0.84	0.86	0.82 to 0.90	0.81	0.76 to 0.87	0.90	0.87 to 0.93
Internal capsule	0.88	0.86 to 0.91	0.95	0.92 to 0.97	0.97	0.95 to 0.98	0.99	0.99 to 1	0.98	0.97 to 0.99
Globus pallidus	0.53	0.46 to 0.61	0.86	0.82 to 0.90	0.94	0.91 to 0.97	0.87	0.83 to 0.92	0.92	0.88 to 0.95
Thalamus	0.68	0.63 to 0.74	0.79	0.74 to 0.83	0.86	0.82 to 0.90	0.90	0.86 to 0.94	0.96	0.93 to 0.98

Brain region	Microinfarct		Large infarct		Lacunar infarct		Microhaemorrhage		Larger haemorrhage	
	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.
Frontal cortex	0.84	0.78 to 0.89	0.98	0.96 to 0.99	0.99	0.99 to 1	0.98	0.97 to 1	0.99	0.98 to 1
Frontal white matter	0.57	0.52 to 0.62	0.93	0.89 to 0.96	0.95	0.93 to 0.97	0.95	0.93 to 0.98	0.99	0.98 to 1
Temporal cortex	0.75	0.70 to 0.81	0.95	0.92 to 0.98	0.99	0.97 to 1	0.98	0.96 to 1	0.99	0.973 to 1
Occipital cortex	0.83	0.79 to 0.88	0.98	0.96 to 1	1.00	0.99 to 1	0.98	0.97 to 1	1.00	0.99 to 1
Occipital white matter	0.60	0.56 to 0.64	0.97	0.94 to 0.99	0.97	0.95 to 0.98	0.95	0.92 to 0.97	0.99	0.98 to 1
Parietal cortex	0.71	0.65 to 0.78	0.95	0.92 to 0.98	0.98	0.95 to 1	0.96	0.93 to 0.99	0.99	0.97 to 1
Anterior Hippocampus	0.64	0.58 to 0.69	0.98	0.94 to 1	0.99	0.96 to 1	0.99	0.94 to 1	1.00	0.99 to 1
Post hippocampus	0.60	0.55 to 0.65	0.97	0.94 to 1	0.99	0.98 to 1	0.99	0.97 to 1	1.00	0.99 to 1
Caudate	0.64	0.59 to 0.69	0.98	0.96 to 1	0.93	0.91 to 0.96	0.97	0.95 to 1	1.00	0.98 to 1
Putamen	0.52	0.45 to 0.59	0.91	0.87 to 0.95	0.81	0.76 to 0.86	0.96	0.95 to 0.98	1.00	0.99 to 1
Internal capsule	0.81	0.77 to 0.85	0.97	0.95 to 0.99	0.99	0.98 to 1	0.99	0.99 to 1	1.00	0.99 to 1
Globus pallidus	0.65	0.59 to 0.71	0.95	0.92 to 0.98	0.85	0.81 to 0.89	0.98	0.95 to 1	0.99	0.97 to 1
Thalamus	0.55	0.49 to 0.61	0.96	0.94 to 0.98	0.87	0.84 to 0.91	0.92	0.89 to 0.95	1.00	0.99 to 1

Brain region	Leptomeningeal CAA		Cortical CAA		Capillary CAA		Myelin loss	
	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.	Coefficient	95% C.I.
Frontal cortex	0.89	0.85 to 0.93	0.96	0.93 to 0.98	0.92	0.89 to 0.96	Not scored	
Frontal white matter	Not scored		Not scored		Not scored		0.75	0.70 to 0.80
Temporal cortex	0.91	0.87 to 0.95	0.96	0.94 to 0.99	0.92	0.87 to 0.96	Not scored	
Occipital cortex	0.84	0.78 to 0.90	0.92	0.89 to 0.96	0.84	0.79 to 0.90	Not scored	
Occipital white matter	Not scored		Not scored		Not scored		0.82	0.77 to 0.87
Parietal cortex	0.91	0.88 to 0.95	0.95	0.93 to 0.98	0.93	0.90 to 0.96	Not scored	
Anterior Hippocampus	0.95	0.90 to 0.99	0.97	0.93 to 1	0.95	0.91 to 1	Not scored	
Post hippocampus	0.93	0.88 to 0.98	0.97	0.94 to 1	0.96	0.92 to 1	Not scored	
Caudate	Not scored		Not scored		Not scored		Not scored	
Putamen	Not scored		Not scored		Not scored		Not scored	
Internal capsule							0.95	0.93 to 0.97
Globus pallidus	Not scored		Not scored		Not scored		Not scored	
Thalamus	Not scored		Not scored		Not scored		Not scored	

Gwet's AC2 coefficient (Coefficient), 95% confidence interval (CI). P-value <0.001 for all collapsed scores.

Table 5: Brain region-specific univariable logistic regression, showing significant associations with cognitive impairment.

Pathology[§]	Brain region	Normal (%) N= 65	Cognitively impaired (%) N= 48	Odds Ratio	95% C.I.	p - value
Arteriolosclerosis	Occipital white matter	18 (28)	26 (54)	3.09	1.41-6.78	0.005
	Global	45 (69)	43 (90)	3.82	1.32-11.09	0.008
Leptomeningeal CAA	Occipital	20 (31)	29 (60)	3.43	1.57-7.51	0.002
Leptomeningeal CAA[#]	Occipital	8 (12)	16 (33)	1.89	1.17-3.04	0.009
Leptomeningeal CAA	Global	27 (42)	31 (65)	2.57	1.19-5.54	0.02
Myelin loss	Occipital white matter	10 (15)	17 (35)	3.02	1.23-7.39	0.02
	Frontal white matter	20 (31)	25 (52)	2.45	1.13-5.30	0.02
	Global	23 (35)	33 (69)	4.02	1.82-8.89	0.001
Myelin loss#	Frontal white matter	2 (3)	7 (15)	5.38	1.06-27.17	0.04
Microinfarcts	Parietal cortex	2 (3)	8 (17)	6.63	1.34-32.88	0.02
	Putamen	4 (6)	11 (23)	4.53	1.35-15.28	0.02
	Global	23 (35)	27 (56)	2.35	1.09-5.04	0.03
Lacunar infarcts	Thalamus	0	6 (13)	*12.8	1.79-∞	0.008
Large infarcts	Global	3 (5)	12 (25)	6.89	1.82-26.05	0.004
Perivascular space dilation	Global	5 (8)	12 (25)	4.00	1.30-12.29	0.02

[§]Classified as present versus absent.
[#] Leptomeningeal CAA and myelin loss reclassified as severe versus none or mild.
*Exact logistic regression used to estimate the odds ratio as cells with null value.
'Global' refers to the pathology in at least one brain region.

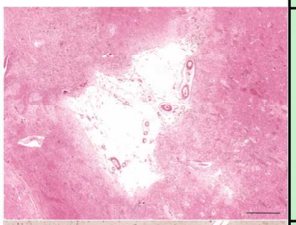
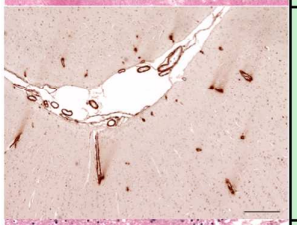
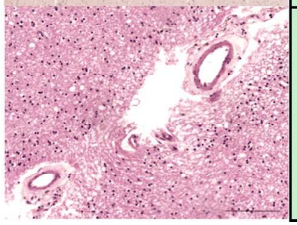
Table 6: Predictive probabilities of cognitive impairment given the presence or absence of pathology.

Model 1

Group	Probability	Global large infarcts	Occipital leptomeningeal CAA	Global myelin loss
1	0.11	0	0	0
2	0.34	0	0	1
3	0.41	0	1	0
4	0.45	1	0	0
5	0.74	0	1	1
6	0.77	1	0	1
7	0.82	1	1	0
8	0.95	1	1	1

Model 2

Group	Probability	Global large infarcts	Occipital leptomeningeal CAA	Occipital white matter arteriolosclerosis
1	0.16	0	0	0
2	0.34	0	0	1
3	0.45	0	1	0
4	0.63	1	0	0
5	0.69	0	1	1
6	0.82	1	0	1
7	0.88	1	1	0
8	0.95	1	1	1

Likelihood that cerebral vascular disease contributed to cognitive impairment		Low (<50%)			Moderate (50-80%)		High (>80%)		
One or more large (> 10 mm) subcortical cerebral infarcts		-	-	-	+	-	+	+	+
Moderate or severe occipital leptomeningeal CAA		-	+	-	-	+	+	-	+
Moderate or severe occipital white matter arteriolosclerosis		-	-	+	-	+	-	+	+

Supplementary Table 1: Immediate and later objectives of Delphi study (≥ 63% support by respondents)

Immediate objectives:
Definitions of parenchymal lesions attributable to cerebrovascular or systemic vascular disease (100%)
Definitions of pathology of cerebral blood vessels (88%)
Terminology for descriptions (88%)
Terminology for diagnosis (88%)
Definitions of vascular brain lesions (88%)
Sampling procedures (75%)
Consensus nomenclatures (75%)
Definitions of cerebral vessel disorders (63%)
Staining/immunostaining procedures (63%)
Consensus assessment protocols (63%)
Later objectives:
Correlation with MRI scan/clinical findings (88%)
Validation and universal adoption (75%)
Measurement/quantification of pathology (63%)
Which neuropathological lesions are functionally significant (63%)
Thresholds for causative lesions (63%)

Supplementary Table 2: List of individual cases.

Case no	Gender	Age	*APOE*	Braak score	MMSE	Listed cause of death	Centre	Cognitive impairment
1	M	77	23	II	30	Congestive cardiac failure	Oxford	No
2	M	78	33	0	22	Acute subdural haematoma	Oxford	No
3	F	81	33	II	26	Peritoneal carcinomatosis	Oxford	No
4	F	73	33	I	30	Renal failure	Oxford	No
5	F	80	34	II	30	Post-op coronary bypass surgery	Oxford	No
6	M	77	34	II	6	Bronchopneumonia	Oxford	Yes
7	F	87	33	II	28	Multiple pulmonary emboli	Oxford	No
8	M	79	33	II	24	Urinary tract infection	Oxford	No
9	M	86	23	II	27	Bronchopneumonia	Oxford	No
10	M	86	33	II	28	Not known	Oxford	Yes
11	M	87	23	II	28	Ruptured aortic aneurysm	Oxford	No
12	F	79	33	II	30	Endometrial cardinoma, pulmonary emboli	Oxford	No
13	M	83	33	II	29	Bowel carcinoma with metastases	Oxford	No
14	M	76	33	II	28	Ischaemic heart disease	Oxford	No
15	F	71	24	II	17	Urinary tract infection	Oxford	Yes
16	F	85	n/a	II	24	Carcinomatosis	Oxford	Yes
17	F	94	33	II	23	Acute cerebral infarction	Oxford	Yes
18	F	85	33	II	13	Urinary tract infection	Oxford	No
19	M	88	33	II	28	Carcinomatosis	Oxford	No
20	M	86	33	II	15	Bronchopneumonia	Oxford	Yes
21	F	100	34	II	30	Cardiac failure	Oxford	No
22	M	92	33	II	24	Congestive cardiac failure	Oxford	No

23	M	69	n/a	II	n/a	Multi-infarct dementia	Newcastle	Yes
24	F	84	n/a	II	30	Rectal carcinoma	Oxford	No
25	M	55	n/a	0	28	Liver cancer	Newcastle	No
26	M	87	34	<VI	n/a	Bronchopneumonia, hip fracture	Newcastle	No
27	F	88	33	II	29	Bronchopneumonia	Oxford	No
28	M	83	n/a	0	n/a	Bronchopneumonia	Newcastle	Yes
29	F	87	3,4	III	16	Pulmonary emboli	Newcastle	Yes
30	F	89	n/a	III	29	Ischaemic bowel and multi organ failure	Newcastle	No
31	F	87	n/a	III	n/a	Bronchopneumonia	Newcastle	Yes
32	M	68	33	II	30	Myocardial infarction	Oxford	No
33	F	86	n/a	III	n/a	Not known	Newcastle	Yes
34	F	96	n/a	III	27	Acute subdural haematoma, atrial fibrillation	Newcastle	No
35	M	88	n/a	<VI	9	Probable brain stem infarct whilst undergoing surgery	Newcastle	Yes
36	M	77	33	II	29	Probable myocardial infarct	Newcastle	No
37	M	97	n/a	<VI	n/a	Not known	Newcastle	Yes
38	M	72	n/a	III	n/a	Stroke	Newcastle	Yes
39	M	81	n/a	I	12	Not known	Newcastle	Yes
40	M	60	n/a	II	20	Bronchopneumonia, cardiac arrest	Newcastle	Yes
41	F	91	33	I	n/a	Aspiration pneumonia	Newcastle	Yes
42	M	91	33	I	20	Chest infection	Newcastle	Yes
43	F	71	33	III	12	Probable stroke	Newcastle	Yes
44	F	97	34	II	22	Pneumonia	Newcastle	No
45	M	75	n/a	III	11	Bronchopneumonia	Newcastle	Yes

46	M	84	n/a	I	n/a	Diverticulitis with perforation	Newcastle	Yes
47	F	78	n/a	0	28	Metastatic cancer, probably ovarian	Newcastle	No
48	M	94	34	I	22	Pneumonia	Newcastle	Yes
49	F	88	33	I	16	Ischaemic heart disease, recurrent urinary tract infection	Newcastle	Yes
50	F	74	33	III	29	Bronchopneumonia	Newcastle	No
51	F	94	n/a	II	29	Left ventricular failure, ischaemic Heart Disease	Newcastle	No
52	F	92	33	II	17	Pneumonia	Newcastle	Yes
53	M	75	33	II	12	Pneumonia	Newcastle	Yes
54	F	90	33	II	19	Not known	Newcastle	Yes
55	F	82	34	III	18	Pneumonia	Newcastle	Yes
56	F	96	33	II	21	Stroke and left ventricular failure	Newcastle	Yes
57	M	84	34	III	28	Pneumonia, chronic renal failure	Newcastle	No
58	M	87	n/a	III	25	Not known	Newcastle	Yes
59	F	93	33	III	13	Cardiac arrest ischaemic heart disease	Newcastle	Yes
60	F	95	n/a	III	30	Ischaemic bowel	Newcastle	No
61	M	82	34	III	26	Cardiac arrhythmia, severe coronary artery atherosclerosis and ischaemic heart disease	Newcastle	No
62	M	88	33	II	21	Chest Infection	Newcastle	No
63	M	96	23	III	13	Frailty of old age, dementia	Newcastle	Yes
64	F	92	n/a	II	24	Cardiac arrest, severe coronary artery atherosclerosis, chronic ischaemic heart disease	Newcastle	Yes
65	F	79	n/a	0	n/a	Bronchopneumonia, cardiac arrest	Newcastle	Yes
66	F	98	33	III	17	Frailty of old age, cardiac arrest	Newcastle	Yes
67	F	95	24	II	27	Not known	Oxford	No

68	F	89	n/a	III	25	Peritonitis	Newcastle	No
69	M	83	33	II	12	Metastatic carcinoma of rectum	Newcastle	Yes
70	F	91	23	I	29	Heart failure, chest infection	Newcastle	No
71	F	74	33	I	27	Lung carcinoma	Newcastle	No
72	F	91	n/a	III	n/a	Ischaemic heart disease, coronary athersclerosis and thrombosis	Newcastle	Yes
73	M	73	n/a	II	n/a	Probable stroke	Newcastle	Yes
74	F	88	n/a	III	27	Aspiration pneumonia, anterior circulation stroke	Newcastle	No
75	M	92	33	III	28	Frailty of age	Newcastle	No
76	M	93	33	II	10	Not known	Newcastle	No
77	M	87	n/a	II	20	Strokes	Newcastle	Yes
78	M	81	n/a	III	10	Not known	Newcastle	Yes
79	M	70	n/a	0	27	Not known	Newcastle	No
80	M	88	23	II	29	Pulmonary embolus, pancreatic cance, intra-abdominal metastases	Newcastle	No
81	M	85	33	II	29	Pneumonia, renal failure	Newcastle	No
82	M	70	n/a	II	27	Pneumonia, delirium	Newcastle	No
83	M	95	33	II	15	Frailty of old age	Newcastle	Yes
84	M	81	n/a	II	29	Pneumonia,iInfective endocarditis	Newcastle	No
85	M	93	33	II	9	Congestive cardiac failure	Oxford	Yes
86	M	78	n/a	III	18	Not known	Newcastle	Yes
87	M	82	3,4	III	25	Heart failure	Newcastle	No
88	F	94	n/a	II	27	Not known	Newcastle	No
89	M	73	n/a	0	30	Peritonitis, perforated viscus	Newcastle	No
90	F	88	3,4	III	26	Respiratory failure - exacerbation of COPD	Newcastle	No

91	F	90	33	II	17	Bronchopneumonia	Oxford	Yes
92	F	71	33	II	13	Acute cerebral infarction	Oxford	Yes
93	F	81	33	II	24	Bronchopneumonia	Oxford	No
94	M	82	n/a	III	n/a	Bronchopneumonia, cardiac arrest	Newcastle	Yes
95	M	67	33	0	26	Carcinoma of lung	Oxford	No
96	M	65	33	II	26	Myocardial infarction	Oxford	Yes
97	F	79	33	II	30	Carcinoma of oesophagus	Oxford	No
98	M	80	33	II	29	Not known	Oxford	No
99	M	69	34	II	27	Food inhalation	Oxford	No
100	M	85	33	II	29	Ruptured aortic aneurysm	Oxford	No
101	F	92	33	II	0	Pulmonary emboli	Oxford	Yes
102	F	78	34	II	21	Myocardial infarct	Oxford	No
103	F	76	34	II	29	Ischaemic heart disease	Oxford	No
104	M	78	23	II	25	Bronchopneumonia	Oxford	No
105	F	79	44	II	30	Bronchopneumonia	Oxford	No
106	F	92	33	II	16	Old age, cerebral infarct	Oxford	Yes
107	F	99	33	II	29	Cardiac failure	Oxford	No
108	F	85	34	II	29	Carcinoma of lung	Oxford	No
109	M	80	34	II	29	Metastatic prostate carcinoma	Oxford	No
110	M	91	33	II	10	Pericarditis, congestive cardiac fauilure	Oxford	Yes
111	M	77	34	II	30	Myocardial infarction	Oxford	No
112	M	76	33	II	28	Myocardial infarction	Oxford	No
113	M	68	n/a	II	28	Complications of coronary surgery	Newcastle	No

Supplementary Table 3: Number (percentage) of cases with each vascular pathology in each brain region.

Brain region	Arteriolosclerosis	Perivascular space dilation	Perivascular haemosiderin leakage	Microinfarcts	Lacunar infarcts	Large infarcts	Leptomeningeal CAA	Cortical CAA	Capillary CAA	Myelin loss
Frontal cortex	1 (1%)	0	0	5 (4%)	0	1 (1%)	37 (33%)	16 (14%)	5 (4%)	*Not scored*
Frontal white matter	52 (46%)	6 (5%)	16 (14%)	8 (7%)	4 (4%)	3 (3%)	*Not scored*	*Not scored*	*Not scored*	45 (40%)
Temporal cortex	3 (3%)	0	1 (1%)	2 (2%)	0	3 (3%)	27 (25%)	12 (11%)	5 (5%)	*Not scored*
Occipital cortex	0	0	0	3 (3%)	0	5 (4%)	49 (43%)	17 (15%)	13 (12%)	*Not scored*
Occipital white matter	44 (39%)	4 (4%)	8 (7%)	2 (2%)	1 (1%)	5 (4%)	*Not scored*	*Not scored*	*Not scored*	27 (24%)
Parietal cortex	8 (7%)	2 (2%)	6 (5%)	10 (9%)	0	1 (1%)	29 (26%)	11 (10%)	5 (5%)	*Not scored*
Anterior hippocampus	3 (3%)	0	0	5 (5%)	0	1 (1%)	9 (9%)	2 (2%)	2 (2%)	*Not scored*
Posterior hippocampus	3 (3%)	0	0	7 (6%)	0	0	13 (12%)	5 (5%)	2 (2%)	*Not scored*
Caudate	21 (19%)	0	0	5 (4%)	3 (3%)	0	*Not scored*	*Not scored*	*Not scored*	*Not scored*
Putamen	44 (39%)	10 (9%)	5 (4%)	15 (13%)	21 (19%)	5 (4%)	*Not scored*	*Not scored*	*Not scored*	*Not scored*
Internal capsule	3 (3%)	0	0	1 (1%)	0	1 (1%)	*Not scored*	*Not scored*	*Not scored*	3 (3%)
Globus pallidus	41 (37%)	2 (2%)	5 (5%)	3 (3%)	5 (5%)	3 (3%)	*Not scored*	*Not scored*	*Not scored*	*Not scored*
Thalamus	24 (22%)	1 (1%)	2 (2%)	12 (10%)	6 (5%)	0	*Not scored*	*Not scored*	*Not scored*	*Not scored*

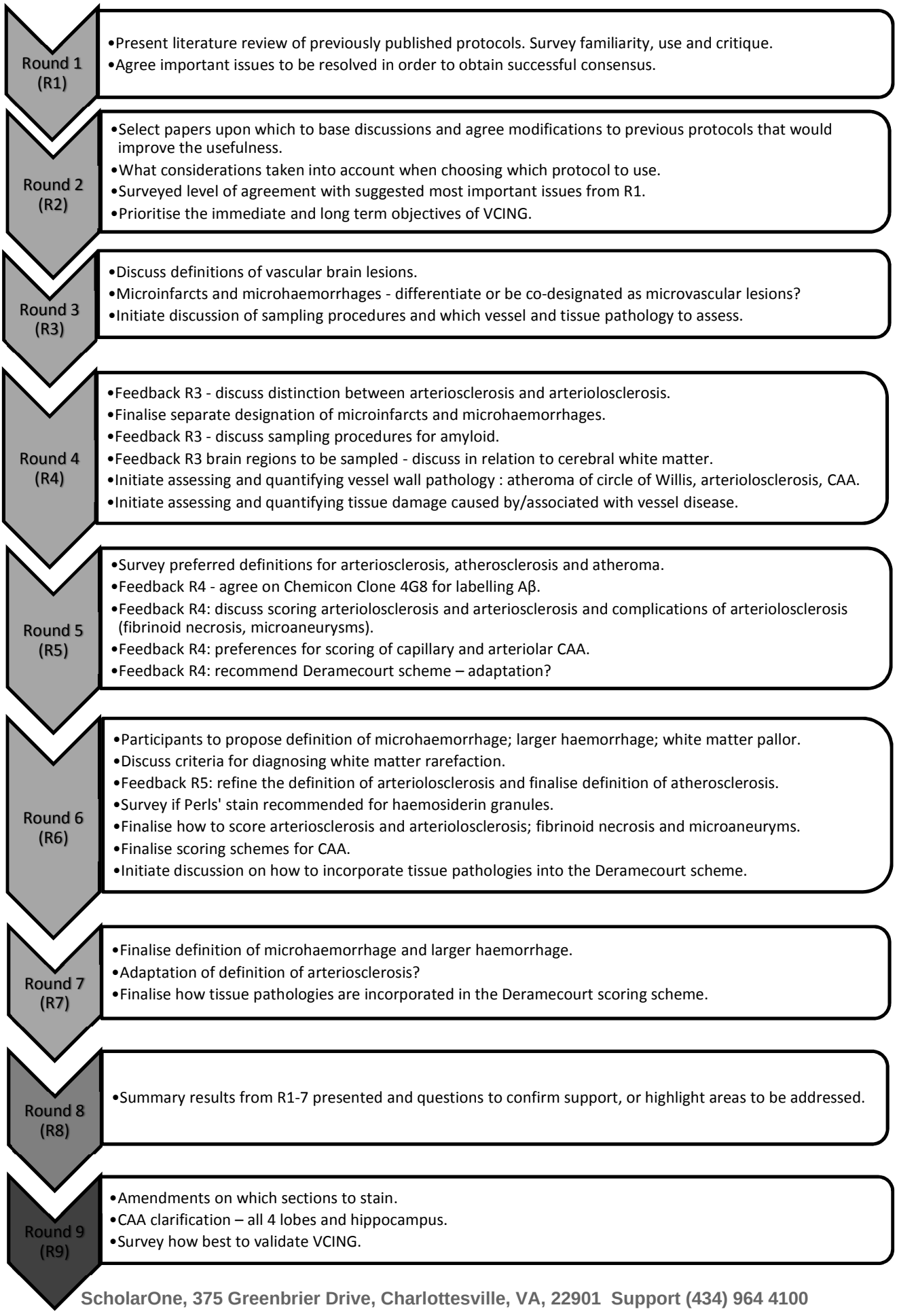
Supplementary Table 4: VCING scoring scheme used for the validation multivariable analysis.

Validated VCING scoring scheme	
Arteriosclerosis and arteriolosclerosis	0 = normal or mild thickening of the vessel media, mild fibrosis 1 = partial loss of smooth muscle cells in the media and moderate hyaline fibrosis, or complete loss of smooth muscle cells in the media with severe hyaline fibrosis and lumen stenosis
Fibrinoid necrosis and microaneurysms	0 = absent 1 = present
Perivascular space dilation	0 = minimal dilatation, or perivascular space ≥ vessel diameter for only a minority of arterioles 1 = perivascular space ≥ vessel diameter for majority of arterioles
Perivascular haemosiderin leakage	0 = absent or < 3 haemosiderin granule deposits in perivascular space 1 = ≥ 3 haemosiderin deposits in perivascular space
Microinfarcts, lacunar infarcts, large infarcts, microhaemorrhage, larger haemorrhage	0 = absent 1 = present
Leptomeningeal and cortical arteriolar CAA: **Capillary CAA:**	0 = absent, trace, or occasional vessel affected 1 = several vessels circumferentially affected, or widespread involvement of circumferentially affected vessels, or CAA with secondary changes (concentric splitting, haemorrhage, fibrinoid necrosis, recanalisation) 0 = absent 1 = present
Myelin loss:	0 = dense and homogeneous myelin staining, mild diffuse or focal myelin pallor 1 = severe focal/diffuse myelin pallor with vacuolation or tigroid appearance of white matter, or total focal/diffuse destruction of myelin, or white matter infarcts

Supplementary Table 5: Brain region-specific univariable logistic regression, showing significant associations with MMSE <27.

Pathology[§]	Brain region	Normal (%) N=52	Cognitive impairment (%) N=48	Odds Ratio	95% C.I.	p - value
Arteriolosclerosis	Frontal white matter	16 (33)	31 (60)	2.95	1.31-6.68	0.009
	Occipital white matter	11 (23)	30 (58)	4.59	1.92 -10.94	0.001
	Putamen	12 (25)	24 (46)	2.57	1.10-6.02	0.03
	Thalamus	5 (10)	16 (31)	3.82	1.28-11.45	0.02
	Global	30 (62)	46 (89)	4.60	1.64-12.91	0.004
Leptomeningeal CAA#	Occipital	6 (13)	15 (29)	1.69	1-2.84	0.05
Myelin loss	Frontal white matter	10 (21)	29 (56)	4.79	1.98-11.62	0.001
	Global	13 (27)	33 (64)	4.68	2-11	<0.001
Microinfarct	Putamen	3 (6)	12 (23)	4.50	1.18-17.10	0.027
	Global	14 (29)	30 (58)	3.32	1.44-7.60	0.005
Lacunar infarcts	Thalamus	0	5 (10)	6.65	0.88-∞	0.07
Perivascular space dilation	Putamen	1 (2)	8 (15)	8.55	1.03-71.13	0.047
	Global	3 (6)	11 (21)	4.02	1.05-15.45	0.042

[§]Classified as present versus absent
[#] Leptomeningeal CAA reclassified as severe versus none or mild.
*Exact logistic regression used to estimate the odds ratio.
'Global' refers to the pathology in at least one brain region.


Round 1 (R1)
•Present literature review of previously published protocols. Survey familiarity, use and critique.
•Agree important issues to be resolved in order to obtain successful consensus.
Round 2 (R2)
•Select papers upon which to base discussions and agree modifications to previous protocols that would improve the usefulness.
•What considerations taken into account when choosing which protocol to use.
•Surveyed level of agreement with suggested most important issues from R1.
•Prioritise the immediate and long term objectives of VCING.
Round 3 (R3)
•Discuss definitions of vascular brain lesions.
•Microinfarcts and microhaemorrhages - differentiate or be co-designated as microvascular lesions?
•Initiate discussion of sampling procedures and which vessel and tissue pathology to assess.
Round 4 (R4)
•Feedback R3 - discuss distinction between arteriosclerosis and arteriolosclerosis.
•Finalise separate designation of microinfarcts and microhaemorrhages.
•Feedback R3 - discuss sampling procedures for amyloid.
•Feedback R3 brain regions to be sampled - discuss in relation to cerebral white matter.
•Initiate assessing and quantifying vessel wall pathology : atheroma of circle of Willis, arteriolosclerosis, CAA.
•Initiate assessing and quantifying tissue damage caused by/associated with vessel disease.
Round 5 (R5)
•Survey preferred definitions for arteriosclerosis, atherosclerosis and atheroma.
•Feedback R4 - agree on Chemicon Clone 4G8 for labelling Aβ.
•Feedback R4: discuss scoring arteriolosclerosis and arteriosclerosis and complications of arteriolosclerosis (fibrinoid necrosis, microaneurysms).
•Feedback R4: preferences for scoring of capillary and arteriolar CAA.
•Feedback R4: recommend Deramecourt scheme – adaptation?
Round 6 (R6)
•Participants to propose definition of microhaemorrhage; larger haemorrhage; white matter pallor.
•Discuss criteria for diagnosing white matter rarefaction.
•Feedback R5: refine the definition of arteriolosclerosis and finalise definition of atherosclerosis.
•Survey if Perls' stain recommended for haemosiderin granules.
•Finalise how to score arteriosclerosis and arteriolosclerosis; fibrinoid necrosis and microaneuryms.
•Finalise scoring schemes for CAA.
•Initiate discussion on how to incorporate tissue pathologies into the Deramecourt scheme.
Round 7 (R7)
•Finalise definition of microhaemorrhage and larger haemorrhage.
•Adaptation of definition of arteriosclerosis?
•Finalise how tissue pathologies are incorporated in the Deramecourt scoring scheme.
Round 8 (R8)
•Summary results from R1-7 presented and questions to confirm support, or highlight areas to be addressed.
Round 9 (R9)
•Amendments on which sections to stain.
•CAA clarification – all 4 lobes and hippocampus.
•Survey how best to validate VCING.

VCING assessment form

Assessing and quantifying vessel wall pathology

Please refer to the VCING Delphi protocol agreed definitions:
Arteriolosclerosis = Hyaline thickening of walls of vessels <150μm in diameter, not associated with lipid-containing cells replacing the tunica media. Diagnosis requires an absence of intramural inflammation, amyloid or fibrinoid necrosis.
Atherosclerosis/atheroma = Disease of medium-sized to large arteries at the base of the brain, characterised by formation of plaques showing varying degrees of destruction of the vessel wall and accumulation of lymphocytes and macrophages; in later stages plaques may contain necrotic core, cholesterol clefts and foci of calcification.

Scoring key for respective vessel wall pathology:

Arteriolosclerosis/arteriosclerosis *(Deramecourt 2011 adapted):*
0= Normal
1= Mild thickening of the vessel media, mild fibrosis
2= Partial loss of smooth muscle cells in the media, moderate hyaline fibrosis
3= Complete loss of smooth muscle cells in the media, severe hyaline fibrosis, lumen stenosis

Please base your score upon the overall impression in the section rather than the worst vessel

Fibrinoid necrosis and microaneurysms (as complications of arteriolosclerosis):
0= absent
1= present

Cerebral amyloid angiopathy (CAA)
These assessments are to be made in all 4 main lobes and hippocampus. Separate assessment of leptomeningeal and cortical vessels on a 4 point scale, as well as recording of presence or absence of capillary CAA:
0= absent
1= trace or occasional vessel affected
2= one or a few vessels circumferentially affected
3= widespread involvement of circumferentially affected vessels
4= as 3, with secondary changes

Please use the key provided to make the assessments

N.B. Please use the N/A option for when the assessment is not applicable for that brain area, or in the few cases where there is not a slide for that brain area.

Please record the identification number of the case you are assessing and your name at the top of the form

Brain

	Arteriolosclerosis 0-3	Fibrinoid necrosis 0/1	Microaneurysms 0/1	Leptomeningeal CAA 0-4	Cortical CAA 0-4	Capillary CAA 0/1	Comments
Superior & middle frontal gyri	score	score	score	score	score	score	
Superior & middle temporal gyri	score	score	score	score	score	score	
Anterior Hippocampus & entorhinal cortex	score	score	score	score	score	score	
Posterior hippocampus	score	score	score	score	score	score	
Occipital cortex inc. Calcarine cortex (BA17 & 18)	score	score	score	score	score	score	
Inferior parietal lobule	score	score	score	score	score	score	
Frontal white matter	score	score	score				
Caudate nucleus	score	score	score				
Globus pallidus	score	score	score				
Internal capsule	score	score	score				
Putamen	score	score	score				
Thalamus	score	score	score				
Occipital white matter	score	score	score				

Assessing and quantifying tissue damage caused by/associated with vessel disease

Please refer to the VCING Delphi protocol agreed definitions:
Large infarct (also called macroinfarct) = Maximum diameter >1 cm (Strozyk 2010)
Lacunar infarct = Cystic lesion visible to the naked eye but <1 cm in diameter (Strozyk 2010)
Microinfarct = Ischaemic lesion found on microscopic examination but not visible to the naked eye (Strozyk 2010)
Microhaemorrhage = Haemorrhagic lesion found on microscopic examination which is not visible to the naked eye
Larger haemorrhage = Haemorrhagic lesion visible to the naked eye which is easily identifiable on macroscopic examination
White matter pallor = A reduction in myelin staining in white matter in Luxol fast blue stained sections
White matter rarefaction = weakly stained/pale and loose appearance of myelinated fibres

Scoring Key - VCING adaptation of the Staging of cerebrovascular pathology in dementia (Deramecourt 2011)

Perivascular space dilatation
0= Absent
1= The perivascular space is < the artery diameter in all sections
2= The perivascular space is ≥ the artery diameter in a minority of sections
3= The perivascular space is ≥ the artery diameter in the majority of sections

Perivascular haemosiderin leakage
0= Absent
1= <3 haemosiderin granule deposits in the perivascular space
2= 3 to 5 haemosiderin granule deposits in the perivascular space
3= >5 haemosiderin granule deposits in the perivascular space

Myelin loss *(LFB staining)*
0= Dense and homogeneous myelin staining
1= Mild diffuse or focal myelin pallor
2= Severe focal/diffuse myelin pallor with vacuolation or tigroid appearance of the white matter
3= Total focal/diffuse destruction of the myelin, or white matter infarcts

Microinfarcts
0= absent
1= present

Large infarcts
0= absent
1= present

Lacunar infarcts
0= absent
1= solitary
2= 2-4
3= 5 or more

Microhaemorrhage
0= absent
1= present

Larger haemorrhage
0= absent
1= present

Please use the key provided to make the assessments

N.B. Please use the N/A option for when the assessment is not applicable for that brain area, or in the few cases where there is not a slide for that brain area.

Please record the identification number of the case you are assessing and your name at the top of the form

	Perivascular space dilation 0-3	Perivascular haemosiderin leakage 0-3	Myelin loss 0-3	Microinfarcts 0/1	Large infarcts 0/1	Lacunar infarcts 0-3	Microhaemorrhage 0/1	Larger haemorrhage 0/1	Comments
Superior & middle frontal gyri	score	score		score	score	score	score	score	
Superior and middle temporal gyri	score	score		score	score	score	score	score	
Anterior Hippocampus & entorhinal cortex	score	score		score	score	score	score	score	
Posterior hippocampus	score	score		score	score	score	score	score	
Occipital cortex including Calcarine cortex (BA17 & 18)	score	score		score	score	score	score	score	
Inferior parietal lobule	score	score		score	score	score	score	score	
Frontal white matter	score	score	score	score	score	score	score	score	
Caudate nucleus	score	score		score	score	score	score	score	
Globus pallidus	score	score		score	score	score	score	score	
Internal capsule	score	score	score	score	score	score	score	score	
Putamen	score	score		score	score	score	score	score	
Thalamus	score	score		score	score	score	score	score	
Occipital white matter	score	score	score	score	score	score	score	score	