# Vascular Dementia:

# A state of play summary report and priorities for future research

## 1. Introduction

Vascular dementia has been highlighted as a research priority in the Stroke Association's 2014-2019 Research Strategy due to the devastating impact of the disease, the lack of treatments or preventive measures to stop the progression of the disease and the paucity of knowledge and research in this area.

Vascular dementia is of particular concern to the Stroke Association, as up to 30% of stroke survivors will develop vascular dementia. Stroke doubles the risk of dementia and there is still a dearth of knowledge around the pathology, risk factors, markers and other cross-contributory factors between stroke and dementia. The co-existence and co-development of these two conditions presents a very complex picture.

At the Stroke Association, we want to work in collaboration with researchers, other funders, patients and carers to identify the biggest issues that we can start to tackle with research. Our aim is to lead a programme of work in this area. Firstly, to identify the difficulties, priorities and next steps for research in this field, and to work in partnership with others to ensure we fund a programme that takes our knowledge and understanding forward in this research area.

The Dementia UK report for the Alzheimer's Society suggested that by 2025 there will be 250,000 people living in the UK with vascular dementia. We must act now to make some long overdue progress in the basic understanding of disease mechanisms, diagnostics, treatments and preventive measures for this devastating condition.

We convened a round table on 29 January 2015 to discuss the latest research and summarise the state of play in this field: what we know, what we don't know and the next priorities for research. Appendix 1 is the agenda from the January 29 roundtable and Appendix 2 is an attendance list from the day.

The following sections 2-6 of this report provide a brief summary of the topics covered and the current state of play in the research into vascular dementia. Recommendations for future research priorities will be highlighted during the report where relevant. The overall priorities that were concluded from this report and those identified at the round

table on 29 January 2015 are listed in section 8. Finally, we outline the next steps for this programme of work in section 9.

## 2. Overview/background of vascular dementia/stroke related dementia
(by Professor John O'Brien, University of Cambridge)

### Historical background

Up to the 1960s, "senile dementia" was thought to be due to cerebral arteriosclerosis, and was previously termed as arteriosclerotic dementia. By 1968, Alzheimer's Disease was recognised as the main cause of dementia in late life [(1)]. In 1974 the term 'Multi-infarct dementia (MID)' was coined [(2)].

In the 1980s and 1990s, MID was recognised to be just one of many causes of Vascular Dementia (VaD) and in 1993 consensus diagnostic criteria were published for VaD [(3)]. They outlined a set of criteria which emphasised: 1) the heterogeneity of vascular dementia syndromes; 2) the variability in clinical course, which may be static, remitting, or progressive; 3) specific clinical findings early in the course (e.g. gait disorder, incontinence, mood and personality changes) that support a vascular rather than a degenerative cause; 4) the need to establish a temporal relationship between stroke and dementia onset for a secure diagnosis; 5) the importance of brain imaging to support clinical findings; 6) the value of neuropsychological testing to document impairments in multiple cognitive domains; and 7) a protocol for neuropathologic evaluations and correlative studies of clinical, radiological, and neuropsychological features. These criteria were stratified by levels of certainty (definite, probable, and possible).

By 2003 the broader term Vascular Cognitive Impairment/ Disorders was preferred to dementia, including all subtypes, e.g. "vascular MCI" and vascular dementia.
Further subtypes of vascular dementia are as follows: Multi-infarct dementia (Cortical VaD); Small vessel dementia (Subcortical VaD); Strategic infarct dementia; Hypoperfusion dementia; Haemorrhagic dementia; Hereditary vascular dementia (CADASIL); Alzheimer's disease with CVD. In accord with the recent updates of the DSM V criteria, descriptions of mild and severe vascular cognitive disorder have been proposed [(4)].

A combination of mixed cases, pure Vascular Dementia and pure Alzheimer's Disease has been emerging more recently and a mixed pathology is recognised as a very

common dementia diagnosis in older people (results from the Cognitive Function and Ageing Studies).

Even so-called “pure” Alzheimer’s Disease (AD) is commonly associated with cerebrovascular pathology (white matter lesions on MRI, amyloid angiopathy up to approximately 100%), micro-infarcts approximately 35%).

## Risk Factors

Several risk factors for vascular disease are also risk factors for “pure” AD, such as hypertension, smoking, *APOE* ϵ4, IHD, raised cholesterol & homocysteine, diabetes, obesity and atrial fibrillation. Depression is a risk factor for VaD as well as for AD and for ‘all-cause’ dementia. Vascular risk factors for neurodegeneration are hypertension, diabetes, dyslipidemia, obesity, atherosclerosis, CHD, *APOE* ϵ4 and hyperhomocystenaemia.

Vascular dementia is the second most common cause of dementia (AD 60%, VaD 20%, DLB (Dementia with Lewy Bodies) 15%) and there is significant vascular pathology in 1/3 dementia cases [(5)]. Similar to AD, the rates of VaD rise with age [(6)]; age is the strongest risk factor.

Data from GWAS (Genome Wide Association Studies) is now starting to emerge to begin giving a picture of genetic predisposing factors [(7)].

Dementia after stroke occurs in approximately 15-30%. A further 20-25% will develop delayed dementia. The estimated incidence of new onset dementia after stroke is 7% after 1 year and 48% after 25 years [(8)].

## Update on Diagnostic Criteria

Several sets of diagnostic criteria have been published for VaD since the 1960s. The continuing ambiguity in diagnostic criteria warranted a critical re-examination. The Vas-Cog study group began to address this and a broader, more inclusive set of changes/criteria have been established as diagnostic criteria, although this is still yet to be validated in large cohorts.

Imaging changes proposed as consistent with VaD on MRI/CT:

1) One large vessel infarct is sufficient for Mild VCD, and 2 or more large vessel infarcts are generally necessary for VaD (or Major VCD)

2) An extensive or strategically placed single infarct, typically in the thalamus or basal ganglia may be sufficient for VaD (or Major VCD)
3) Multiple lacunar infarcts (2) outside the brainstem; 1-2 lacunes may be sufficient if strategically placed or in combination with extensive white matter lesions
4) Extensive and confluent white matter lesions
5) Strategically placed intracerebral haemorrhage or 2 or more intracerebral haemorrhages
6) A combination of the above.

Cognitive Changes in VaD:

- Variable, especially for MID and strategic infarct dementia
- Major deficits are usually in attention, information processing and executive function
- Tests such as verbal fluency, trails/maze, clock drawing, reverse digits
- Memory, language and praxis variably affected
- Predominantly subserved by fronto-striato-thalamic circuits

In conclusion, the clinical diagnostic criteria are still debated and still need further refinement and validation. However, they are robust enough for clinical studies/ trials to proceed, and AD markers also have the potential to identify mixed cases.

**Management strategies of Vascular Dementia to date**

The main strategy so far has been to use drugs developed for Alzheimer's disease. However, recent trials have shown that these are largely ineffective, the translation of AD treatments to VaD on the basis of shared neurochemical mechanisms has failed.

Other therapies have been used: Cerebrolysin; Antiplatelet agents; BP lowering; Lipid lowering; Calcium channel blockers. Trials with these will be mentioned further in section 4.

There is limited clinical research to date on VaD, and virtually none on non-cognitive features. Some drug trials have taken place and have failed to identify any treatment options, these are summarised in section 4. We need trials of the best treatment strategies to inform the best clinical management of patients. The UK can and should do more to address this and develop an improved strategy for treatment of VaD.

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## 3. Pathophysiology and Classification of Vascular Dementia

(by Professor Raj Kalaria from University of Newcastle)

VaD assumes a clinically diagnosed dementia syndrome comprising subtypes with predominant ischaemic and haemorrhagic pathologies. Current understanding of the pathophysiology of VaD is guided by knowledge of vascular disease risk factors (see above). These may affect both the systemic (extracranial) and cerebral vasculature. Degrees of cerebrovascular pathology may be influenced by demographic, atherosclerotic, stroke-related including metabolic syndrome, poor cerebral perfusion and genetic factors. In addition to these, other medical problems, including depression, may be associated with vascular changes.

Recent advances in neuroimaging and systematic neuropathological examination have enabled better definitions of clinically diagnosed cerebrovascular disorders, which cause cognitive impairment and result in VaD. Like AD, the definitive diagnosis of VaD requires neuropathological examination. The systematic evaluation of potentially relevant clinical or phenotypic features with particular attention to timing of events is important. However, it is often difficult to define which neuropathological changes are relevant and to what degree these contribute to VaD. This challenge arises because of the heterogeneous localisation of lesions and the co-existence of other pathologies including neurodegenerative changes, particularly those characteristic of AD. The origin and type of vascular occlusion, presence of haemorrhage, distribution of arterial territories, and the size of vessels involved will define vascular dementia. Thus, many brain regions including the territories of the anterior, posterior and middle cerebral arteries, the angular gyrus, caudate and medial thalamus in the dominant hemisphere, the amygdala and hippocampus as well as the hippocampus have been implicated in VaD.

Clinicopathological correlation studies have enabled recognition of subtypes of VaD. Factors that define subtypes of VaD include multiplicity, size, anatomical location, laterality and age of the lesions besides genetic influences and previous existence of systemic vascular disease. Subtypes of pathologically defined VaD can conveniently be divided into three major types defined by the origin of vascular disease, infarct site or size of the vasculature. Large vessel disease often related to cardiac atherothromboembolic events could involve atherosclerosis, plaque rupture, intraplaque hemorrhage, thrombotic occlusion, embolism, arterial dissection and dolichoectasia. Dementia resulting from large vessel obstruction or disease includes multiple infarcts (MID is a type of VaD). Main clinical features include lateralized sensorimotor changes and aphasia depending on the location of infarction. Cerebral small vessel disease may entail degrees of pathological changes, mostly subcortical infarcts or lacunes and diffuse white matter disease, leading to subcortical ischaemic VaD. Vascular changes include arteriolosclerosis, fibrinoid necrosis, microaneurysms, microatheromas, cerebral amyloid angiopathy and segmental arterial disorganization. Subcortical ischaemic VaD involving predominantly the subcortical (below the cortex) structures is the most significant subtype of VaD and is most frequent in elderly people who survive long periods. Small vessel disease is seen with more subtle signs, including extrapyramidal signs. However, there can also be considerable overlap between the subtypes. For example, cerebral microinfarcts are apparent in both large and small vessel disease. VaD may often have a combination of cortical and subcortical lesions, thereby may be called cortico-subcortical VaD. It is rare for vascular lesions to be exclusively cortical. Strategic infarct dementia or strategic VaD

e.g. strokes occurring in thalamic or brainstem regions occurs less frequently and may involve small and large lesions. Irrespective, a definitive diagnosis of VaD should be supported by a burden relevant cerebrovascular pathology incorporating microvascular and parenchymal (tissue) changes. There should be sufficient pathology attributed to vascular changes in the general absence of neurofibrillary or neurodegenerative pathology to explain the change in cognition [(1)].

Vascular cognitive impairment (VCI) is sometimes regarded as the prodromal stage of VaD. It incorporates conditions in any cognitive domain that has a vascular origin or impaired brain perfusion. Therefore, early or mild neuropathological changes such as small vessel disease or white matter rarefaction that can be linked to relevant cognitive domains e.g. executive dysfunction, slower processing speed or working memory deficits would constitute VCI or mild vascular cognitive disorder [(2)]. Relatively few prospective studies have validated clinical criteria for VaD by assessing the same cases at post-mortem. The Oxford Project to Investigate Memory and Ageing (OPTIMA) study has shown that the severity of SVD pathology was inversely related to cognitive scores and 43% of the cases with high SVD scores were designated to be demented [(3)]. It was also proposed that arteriolosclerosis is the first change occurring in VaD and most severe VaD, i.e. stage VI, can bear multiple lesions including diffuse white matter changes [(4)].

Strokes or brain infarction may lead to VaD. Many stroke patients who are treated acutely e.g. with thrombolysis, or those who have surgical interventions e.g. endarterectomy or other restorative management, may survive long enough to eventually develop dementia more than their counterparts who have not had stroke or vascular interventions. Subjects with cerebral small vessel disease may also survive long periods eventually to succumb to VaD. Incident dementia or post-stroke dementia (PSD) may occur immediately after the stroke, or be delayed after a stabilisation period of a year or longer. In such cases, dementia can have a complex aetiology with varying combinations of large and small vessel disease, as well as non-vascular pathology. The pooled prevalence estimates of PSD less than one year after the stroke were calculated to range from 7 % in population-based studies to 41 % in hospital-based studies of recurrent stroke. Multiple lesions over time and the characteristics and complications of the stroke are found to be most strongly associated with PSD. In the Newcastle COGFAST study [(5)], after a mean follow up period of 3.8 years, 24% of elderly stroke survivors developed dementia and 76% remained alive without dementia or had died without dementia. Neuroimaging studies show that the volume and site of infarcts, extent and location of WM lesions as well as brain atrophy including medial temporal atrophy, were important determinants of PSD.

Pathological examinations in this study, which is the only study of its kind, showed that >75% of PSD cases were classified as VaD. Therefore, most of the dementia that develops in stroke survivors is VaD. A key pathological change that is important in VaD is microinfarction. Microinfarcts are widely accepted to be small lesions visible only upon microscopy and may or may not involve a small vessel at its centre but are foci with pallor, neuronal loss, axonal damage (WM) and gliosis [(6)]. They are estimated to occur in thousands in severely demented cases. The neurochemistry of VaD is less clear. Various cellular signalling and regulatory mechanisms including apoptosis, autophagy, oxidative stress and inflammation are associated with VaD by virtue of their involvement in cerebral ischaemia or oligaemia. Selective transmitter specific changes have also been described. Choline acetyltransferase activity is reduced in MID and CADASIL. Other studies have reported deficits in monoamines including dopamine and 5-hydroxytryptamine (5HT) in the basal ganglia and neocortex in VaD. To compensate for the loss, 5-HT(1A) and 5-HT(2A) receptors are apparently increased in temporal cortex in MID but not subcortical VaD. Glutamatergic synapses, assessed by vesicular glutamate transporter 1, are reduced in the temporal cortex but not in the frontal lobe.

Medial temporal lobe atrophy is also associated with VaD in the general absence of neurodegenerative pathology. Even in small vessel disease the atrophy can be almost similar to that in AD. At the cellular level, atrophy of hippocampal pyramidal neurons (in CA1 and CA2) and of the dorsolateral prefrontal cortex, irrespective of the presence of any neurodegenerative pathology, are seen as important substrates of PSD and VaD [(7)]. Thus, selective hippocampal neuronal shrinkage is also an important substrate for VaD. There is a clear vascular basis for hippocampal neurodegeneration and this concurs with the neuroimaging observations of hippocampal atrophy, even in population-based incident VaD. The simplest mechanistic explanation for the atrophy is that the neuronal or dendritic arbour results in subsequent loss in connectivity, which contributes to brain structural and functional changes.

In conclusion, current evidence from pathophysiological studies of VaD indicates that small vessel disease is common to VaD and that dementia after stroke is mostly VaD. Pathological diagnosis of VaD is consistent with high burden of vascular changes and sparse or mild amount of neurodegenerative pathology. Hereditary cerebral microangiopathies such as cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL) and the retinal vascular cerebral leukoencephalopathies (RVCLs) are good models of VaD and small vessel disease dementia. Besides lacunar infarcts and severe diffuse white matter disease, microinfarction (cortical lobes and subcortical structures) is recognised as an important substrate of dementia. The deep white matter changes primarily reflecting myelin loss

may impact on axons, synapses and neuronal connections. Age-related changes in cellular mechanisms that impact on the integrity of the blood brain barrier, microvascular function and the neurovascular unit, are also likely contribute to dementia.

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## 4. Clinical Trials for Treatment of VaD

(by Professor Peter Passmore, Queen's University Belfast)

### Treatment approaches in VaD

To date, intervention trials have usually focused on VaD as an overarching diagnosis. However, given its marked heterogeneity it is particularly important to distinguish between different types of VaD when considering treatment trials. Subcortical

ischaemic VaD (SIVD) is the most common form of VaD, and has an additional advantage of homogeneity in assumed underlying pathology. There are trials which have evaluated the prevention of post-stroke dementia but there are no intervention studies for established SIVD. There are no studies of non-pharmacological interventions in established SIVD.

**Licensed treatments for AD and use of other agents**

Considering acetylcholinesterase inhibitors, a recent study showed that loss of cholinergic function is only evident in VaD patients with concurrent AD [(1)]. Studies have specifically evaluated the value of donepezil, galantamine and rivastigmine [(2,3,4,5)], and a meta-analysis [(6)] included all of the trials with donepezil, galantamine, rivastigmine and memantine compared to placebo in VaD. However the authors comment "The clinical heterogeneity of VaD patients limits generalisability of the trials' outcomes because the effect of treatment on specific patients or subgroups cannot be defined". The conclusion was that cholinesterase inhibitors and memantine produce small benefits in cognition of uncertain clinical significance in patients with mild to moderate VaD. Data are therefore insufficient to support widespread use of these drugs in VaD, although further investigations are needed to identify whether there are subgroups that might benefit. One RCT of donepezil in patients with CADASIL, a genetically inherited form of severe SIVD, showed no benefit in overall cognition in comparison to placebo [(7)] but there are no specific RCTs of cholinesterase inhibitors in patients with sporadic SIVD. Other studies have also examined hydergine, nicergoline, nimodipine and Ginkgo biloba [(8,9,10,11)]. A recent updated Cochrane review also concluded that Ginkgo biloba was not effective[(12)]. Most of the interest has focused on calcium channel blockers which is reviewed in the next section.

**Calcium Channel Blockers**

There has been a longstanding interest in the potential value of CCBs in dementia. Despite the theoretical rationale, the literature is modest albeit encouraging and most clinical studies have involved only small numbers of patients. Treatment with nicardipine reduced incidence of dementia, mostly of the Alzheimer type, in the Syst-Eur Study [(13)]. Nimodipine has also been shown to have some short term benefits in VaD[(14)]. A Cochrane review identified 15 studies examining the benefit conferred by CCBs in dementia, including AD, VaD and non-specific dementia types. Of these studies, ten specifically examined VaD [(14)], the majority of which were very small and did not use operationalised diagnostic criteria to recruit participants. However, the review highlighted three studies that involved more than 50 people with VaD according

to operationalised criteria. Of these, two studies of 12 weeks duration included 67 and 62 participants respectively, and showed benefits in cognitive function and global clinical outcome [15,16]. The largest reported study, which included 259 people over six months found no significant benefit in cognitive outcomes in the overall study population of people with VaD [10]. However, a post-hoc subgroup analysis of 92 people with SIVD from this study showed significant improvement in both cognitive and functional outcome measures, contrary to the lack of effect seen in a subgroup of people with multi-infarct dementia. The authors highlighted the need for a larger a priori trial of CCBs specifically in people with SIVD [10].

In a more recent study of older people with hypertension presenting with subjective memory complaints (but without dementia), CCB use was significantly associated with better memory performance. This was independent of blood pressure level and microvascular or macrovascular alterations, suggesting a specific neuroprotective effect of this pharmacological class, which further supports the need for controlled trials to determine the potential benefits of CCB as a treatment for SIVD [17].

It could be implied that a reduction in cerebrovascular outcomes would mean that there is a positive effect on VaD. Considering cerebrovascular outcomes, in an analysis of 12 trials including 94,338 patients [18], amlodipine provided more protection against stroke and myocardial infarction than other antihypertensive drugs, including angiotensin receptor blockers (-19%, P<0.0001 and -7%, P=0.03) and placebo (-37%, P=0.06 and -29%, P=0.04). In an updated meta-analysis of 147 studies [19] to determine the quantitative efficacy of different classes of blood pressure lowering drugs in preventing coronary heart disease (CHD) and stroke, and who should receive treatment, the five main classes of blood pressure lowering drugs (thiazides, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and CCB) were similarly effective (within a few percentage points) in preventing CHD events and strokes, with the exception that CCB had a greater preventive effect on stroke (relative risk 0.92, 95% CI 0.85 to 0.98). The benefits of amlodipine based regimens on stroke have also been reported in individual trials [20].

The available evidence highlights the need to strictly define the diagnostic criteria for any trial cohort.

Additional agents have been proposed as potential treatments for VaD or SIVD. Treatment with aspirin is known to reduce the risk of vascular events including stroke, raising the possibility that aspirin could also reduce risk of VaD, or even provide an effective treatment [21]. However, the evidence for this is limited. A number of

community-based, prospective studies and one cross-sectional study indicate benefits in episodic memory or global cognitive function whilst further studies in older adults have not shown benefit [22]. B vitamin therapy has also been suggested as a treatment for VaD through reducing homocysteine levels. However, the evidence from the homocysteine lowering trials has been negative to date.

## Recent and Ongoing trials

There are some prevention trials that are targeted against established cardiovascular risk factors and in which dementia or cognitive impairment is an end point. The SBP intervention trial (SPRINT) is a study of intensive blood pressure reduction with cognition as a secondary endpoint (expected 2018). ASPREE (Aspirin in reducing events in the Elderly) has a primary end point of death from any cause or incident dementia or persistent physical disability (expected 2016). The secondary prevention of small subcortical strokes trial (SPS3) had cognitive decline as a secondary outcome measure but was negative in terms of any effect on cognition. NICE (Efficacy and safety study of nimodipine to prevent mild cognitive impairment after acute ischemic strokes) is different in that it has cognitive function as the primary and VaD as a secondary end point. PODCAST (Prevention Of Decline in Cognition After Stroke Trial) was a pilot study and had cognitive decline as a primary outcome and dementia as a secondary outcome but recruitment was lower than expected and the results were negative. These are prevention trials and it is disappointing that cognition remains a secondary endpoint in most studies of this nature. While the results may be informative about prevention they will not resolve the problem of therapeutic intervention in established VaD.

## Upcoming Trials

There are some further trials in the pipeline which will be starting imminently:

Prevent-SVD trial (or LACI-1, Lacunar Intervention 1) is a phase 2 trial in patients with lacunar stroke testing cilostazol and/or isosorbide mononitrate dose escalation, safety and intermediary effect on cerebrovascular reactivity with the aim of preventing progression of small vessel disease (recurrent stroke, cognitive decline, dependency, death).

LACI-2 (Lacunar Intervention Trial 2) is an early phase 3 trial of the same drugs in patients with lacunar stroke testing trial feasibility prior to progressing to large scale phase 3 trial with the same clinical outcomes as in LACI-1 above.

PRESERVE is a clinical trial which will determine whether intensive versus standard, treatment of blood pressure in hypertensive individuals with SVD and radiological leukoaraiosis is associated with reduced cognitive decline.

## Conclusion

A priority for future research must be to introduce a cognitive measure as an endpoint in all trials. At the very least, this should be a secondary endpoint for trials which do not have a focus on the assessment of vascular cognitive impairment or dementia.

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## 5. Pre-clinical models of vascular dementia

(by Dr Stuart Allan, University of Manchester and Dr Atticus Hainsworth, St George's University of London)

### Summary

Vascular cognitive impairment/dementia (VCID) in humans reflects a multitude of clinical pathological states[1-3]. These range from pure genetic small vessel arteriopathy (CADASIL, CARASIL, COL4A1/2 mutations) to post-stroke dementia following a large artery ischaemic event[1;3;4]. The most common source of VCID is diffuse white matter

pathology with focal lacunar lesions due to small artery disease ("small vessel disease")[1;3;5]. At present no experimental model replicates all salient features of VCID[2;6]. Systematic reviews of the experimental animal literature have concluded that existing animal models of VCID are far from ideal, in that they do not typically reflect the underlying clinical pathology[6-8]. In order to be useful (i.e. translational), an experimental model should faithfully reflect at least one of the pathological processes involved in human cognitive disease[9]. This would be useful for: i) prospective studies of the temporal and spatial development of the disease and identification of molecular and cellular mechanisms involved; ii) preclinical testing of drugs and other interventions. In a robust model of VCID we would expect to measure the following types of data: radiological, behavioural, cognitive, histopathological, gene/protein expression and other molecular profiling.

A recent US-based roundtable concluded: "*the need for new model systems with metabolic similarity to humans, such as animal models with white matter vascular injury, animal models of hypertension or the potential utility of stem cell/induced pluripotent models are in need of further exploration.*"[2]

## Experimental systems

Rodents, primarily rats and mice, have the advantage of availability, cost, and well-established procedures for genetic modification. Also, we have a wealth of prior experience and data with respect to vascular lesions and behaviour in rodents. It would be advantageous to increase our knowledge and experience in larger species with more abundant white matter and human-like (i.e. gyrencephalic) brain anatomy. This is especially important given the central role of white matter lesions in human VCID[4;5].

Primate experiments remain highly informative[10;11], although restricted to relatively few centres worldwide. Other large mammalian species may be considered, including dogs[6;12], pigs[13] and sheep[14;15]. There may also be benefit from non-mammalian species (zebrafish, *Drosophila* and *C. elegans*) in terms of screening platforms, though any findings in such systems would need to be confirmed in higher species. *In vitro* systems may also contribute for this purpose. It is clear that *in vivo* models cannot be replaced for stroke research, due to the complexities of the systems and mechanisms involved.

## The current state of play

Vascular brain injury models are well-represented at expert centres within the UK. Acute, focal ischemic lesions are induced by middle cerebral artery (MCA) occlusion in mice and rats[16-19]. Behavioural data are routinely recorded, usually as a measure of motor deficit rather than cognitive impairment. Stereotaxic injection of the potent vasoconstrictor endothelin-1[20] yields a small, precisely-targeted ischaemic lesion. This has been used to produce pure white matter micro-infarct[20]. Global hypoperfusion models include bilateral carotid artery occlusion (2VO) in rats[21], and bilateral carotid stenosis using wire coils in mice[22;23]. A refinement of the 2VO protocol employs constrictor cuffs to give a gradual arterial occlusion over ~1-2 days[21]. These global models produce ischemic white matter lesions, reflecting the low baseline perfusion of white matter. Other pathologies are also common, including hippocampal cell death, small haemorrhages and vascular amyloid deposition.

Genetic alterations include inbred strains (e.g. SHRSP) or transgenic manipulations (e.g. Tg2576 mice, Notch3 mutant). These may be combined with risk factors such as age, hypertension, diabetes mellitus, hyperhomocysteinemia or high-fat diet[9]. A large number of transgenic mouse strains are now available worldwide, and commercial breeders can produce new transgenic strains cost-effectively.

There has, however, been some concern raised by researchers that rodents have a relative lack of white matter compared with humans, which may bring into question the relevance of these models for studying vascular cognitive impairment.

**What will success look like?**

1. Preclinical models offer pathological information on specific steps in a disease process. For example, MCA occlusion informs on the sequence of cellular lesions as acute ischaemic penumbra develops, progresses and becomes infarct, and mutant APP-expressing Tg2576 mice inform on the process of amyloid plaque growth. For a given pathological process a representative model informs on the timescale and the sequence of events, and the molecular details. We stress that an *in vivo* model cannot be expected to explain the initiating pathogenic changes that lead to the human disease.

2. Preclinical models allow us to test the effectiveness of possible therapies and to ask whether drugs or other interventions alter the pathological process. They also allow us to validate possible clinical biomarkers and endpoints, such as radiological or biochemical signatures. A good translational model allows us to test whether these markers relate to known molecular and cellular pathology.

## Future priorities

1. Define guidelines and criteria for pre-clinical models relevant to VCID.

   What would be required?

   a) Reproducibility between operators and labs.
   b) 3Rs compliant
   c) mimic a pathological process known to be relevant in VCID, and at least one behavioural or imaging endpoint known to be relevant in VCID.

2. Make progress with larger animal models with abundant white matter and gyrencephalic brain, e.g. sheep, pigs and dogs.

3. Re-engage Pharma industry involvement. Pharma companies have huge rodent datasets, also primate and large mammal data relevant to VCID. Pharma colleagues also offer useful translational perspective.

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## 6. Biomarkers

### 6.1 **Existing inflammatory and cardiovascular biomarkers for validation studies in VaD**

During the discussions at the January 2015 round table, it was highlighted that there is much to be done in terms of existing biomarkers and validation. Areas highlighted as potential avenues for future priority research were as follows:

- Validate cerebrospinal fluid (CSF) and blood biomarkers as well as identifying them.
- Use a big data approach to go back and look at inflammatory markers (N.B. stroke survivors who have pre- or post-stroke infection do worse and progress faster to dementia or death) and cardiovascular markers which may be useful – make full use of existing datasets e.g. Dementia Platform UK and UK Biobank can help here.
- MRI is useful but it is very important to include clinical and patient-relevant outcomes like disability and dementia.
- Develop an approach to compare MRI and biomarkers together as indicators of risk or prognosis (potential biomarkers to include: serum BDNF, elevated VEGF, nitrate, nitrites).
- Mechanistic and transcriptional/translational studies are needed to identify pathways to target. There is a need for pre-clinical or experimental medicine approaches to understand the relevant pathways and mechanisms behind disease development.

- Evaluate other possible markers, for example: coagulation; fibrinolytic, inflammation, in order to measure endothelial function. However, we must ensure to make efficient use of existing data before embarking on new studies.
- Use proteomics and metabolomics approaches to identify relevant changes and molecular signatures related to specific clinical phenotypes or outcomes, and thus identify potential new biomarkers; this is already being done in cardiology.
- We must develop ways to stratify patients to identify those at most risk and to improve methods for clinical trials.

## 6.2 **MRI Biomarkers**

(by Professor Hugh Markus, University of Cambridge)

Conventional MRI is very sensitive to the pathological features of cerebral small vessel disease which include lacunar infarcts, more diffuse regions of white matter hyperintensity, microbleeds, and atrophy [1,2]. A number of studies, primarily of cross sectional case control design, have consistently shown that lacunar infarcts, diffuse white matter damage measured using diffusion tensor imaging (DTI), and atrophy correlate with cognitive impairment [1]. More advanced image analysis techniques such as network analysis suggests that lacunar infarcts and white matter damage cause cognitive impairment via disconnection of complex cortical-subcortical circuits [3]. The changes in MRI parameters, particularly DTI and lacunar infarcts, can be detected in longitudinal studies [4]. This sensitivity to change and correlation with cognition, has led to suggestion that MRI may be a useful surrogate marker for clinical trials [1,5]. It has been shown that it is much easier to detect change using these MRI parameters than it is with cognitive testing which appears relatively insensitive to change.

It may also be worth considering combinations of imaging features as this may better represent the total burden of brain damage than do the individual features. Some studies have shown it is possible to miss risk factors when looking just at the individual feature [6].

However, further work is required before these MRI markers can be widely adopted in clinical practice. In particular this includes:

1. Longitudinal studies to show that MRI parameters, and change in MRI parameters over time, can **predict** which patients will progress to cognitive decline and dementia.
2. Studies using longitudinally acquired data to determine which MRI markers, or combination of markers, are both most sensitive to change and also correlate best with clinical endpoints.
3. Clinical trials in which MRI parameters are used to determine whether they provide similar information (but in smaller sample sizes) to that obtained using clinical endpoints.

## 7. Other key areas to focus on

1. Determining optimal clinical endpoints for clinical studies. Some studies, such as SPS3, have shown that change in cognition is insensitive to detecting the effects of different treatment. In the SPS3 trial, in patients randomised between normal and intensive blood pressure lowering, there was no difference between the two groups primarily because there was no cognitive change in either group [(7)]. This inability to detect cognitive change in patients with cerebral small vessel disease has been described in other studies. It is likely to reflect a number of phenomena including measurement error in the cognitive techniques used, learning effects, and importantly drop out of patients with more severe disease who therefore do not attend for the follow-up cognitive testing.

2. Work is required to work out which endpoints would be most useful to assess efficacy in clinical trials. This could include surrogate endpoints such as MRI (see MRI section) or other clinical endpoints. For example; measuring progression to disability or dementia may prove more sensitive and allow inclusion of patients with more rapid progression who cannot attend for follow-up cognition. Work in prospective longitudinal datasets is required to determine the sensitivity of different outcome measures, and to allow planning of realistic sample sizes for future clinical trials.

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## 8. Research Priorities

The key research priorities highlighted in the writing of this report have been organised into 6 overall research priorities as follows:

i) Clinical diagnostic criteria need further refinement and larger scale validation.

ii) Rigorous naturalistic studies and trials of best strategies are required to inform optimal management. The UK should do more to develop an improved strategy for clinical management of VaD.

iii) Define guidelines and criteria for pre-clinical models relevant to VCID.

The following would be required:

a. Reproducibility between operators and labs.

b. 3Rs compliant

c. Mimic a pathological process known to be relevant in VCID, and at least one behavioural or imaging endpoint known to be relevant in VCID.

d. Make progress with larger animal models with abundant white matter and gyrencephalic brain, e.g. sheep, pigs and dogs.

e. Re-engage Pharma involvement. Pharma companies have huge rodent datasets, also primate and large mammal data relevant to VCID. Pharma colleagues also offer useful translational perspective.

iv) Identify and validate a range of relevant biomarkers, including MRI and combinations of MRI and other biomarkers, as follows:

a. Validate cerebrospinal fluid (CSF) and blood biomarkers as well as identifying them.

b. Use a big data approach to go back and look at inflammatory markers (N.B. stroke survivors who have pre- or post-stroke infection do worse and progress faster to dementia or death) and cardiovascular markers which may be useful – make full use of existing datasets e.g. Dementia Platform UK and UK Biobank can help here.

c. Develop an approach to compare MRI and biomarkers together as indicators of risk or prognosis (potential biomarkers to include: serum BDNF, elevated VEGF, nitrate, nitrites).

d. Longitudinal studies to determine which MRI markers, or combination of markers, are both most sensitive to change and also correlate best with clinical endpoints. Change in MRI parameters over time can be used to predict which patients will progress to cognitive decline and dementia.

e. Evaluate other possible markers, for example: coagulation; fibrinolytic, inflammation, in order to measure endothelial function. However, we must ensure to make efficient use of existing data before embarking on new studies.

f. Use proteomics and metabolomics approaches to identify relevant changes and molecular signatures related to specific clinical phenotypes or outcomes, and thus identify potential new biomarkers; this is already being done in cardiology.

v) Mechanistic and transcriptional/translational studies are needed to identify pathways to target. There is a need for pre-clinical or experimental medicine approaches to understand the relevant pathways and mechanisms behind disease development.

vi) We must develop ways to stratify patients to identify those at most risk and to improve methods for clinical trials. This includes:

a. Perform clinical trials in which MRI parameters are used to determine whether they provide similar information (but in smaller sample sizes) to that obtained using clinical endpoints.

b. Determine optimal clinical endpoints for clinical studies and include patient-relevant outcomes like disability and dementia.

c. Establish which endpoints would be most useful to assess efficacy in clinical trials. This could include surrogate endpoints such as MRI (see MRI section) or other clinical endpoints. For example, measuring progression to disability or dementia may prove more sensitive and allow inclusion of patients with more rapid progression who cannot attend for follow-up cognition.

d. Work in prospective longitudinal datasets is required to determine the sensitivity of different outcome measures, and allow planning of realistic sample sizes for future clinical trials.

The 6 key research priorities from the January 2015 workshop on vascular dementia following discussion of all the above topics were:

i) Basic science is needed to understand the neuropathology, mechanisms of disease and pathways involved; additionally we need discovery science to look for novel drug targets.

ii) Stratification of vascular disease is necessary to help stratify patients and identify those most at risk.

iii) Clinical trials could potentially be used to address repurposing of existing drugs or testing novel lipid lowering agents.

iv) Identify and validate biomarkers: Make use of existing data on inflammatory and cardiovascular markers; perform MRI and biomarker comparison studies.

v) Validate pre-clinical models of VaD.

vi) Large-scale validation of classification systems previously developed.

The core principles of any research we fund should consider the following (following January 2015 roundtable discussions):

- Use a big data approach: make use of brain banks and existing datasets, including high throughput data from pharma industry, and in particular, incorporate use of DPUK (Dementias Platform UK) and/or UKBiobank.

- Bring expertise in proteomics, metabolomics and new technologies into the field.

- Capacity building in this field is essential, need to bring in fresh talent with new skills, technologies and fresh perspective (e.g. from other fields)

- Multi-disciplinary research teams are essential to bring expertise and understanding of both stroke and dementia and bring multiple and fresh perspectives into the field.

## 9. Next Steps

The Stroke Association will use this report to engage service users in discussion about where they think priorities should be in this field. To do this, we will first develop a lay summary version and secondly we will convene a workshop of stroke survivors, family members and carers with experience of vascular dementia to discuss what they think the priorities should be. We will also invite research experts and other funders to participate in this second meeting relating to our priorities in this field. We will hold this research priority setting workshop on vascular dementia on 4 September 2015.

The Stroke Association will develop a call for proposals in the field of vascular dementia after convening a funders meeting on this topic to find areas where we may have mutual interests and priorities. We will arrange this meeting for autumn 2015, and if strategic alignment and agreement to co-fund can be achieved with one or more collaborator funders in this field, we plan to go ahead with a call for proposals in early 2016, with the intention to fund new research in this area around autumn 2016.

The below table outlines the approximate timeframe for planned activities:

| **Timeframe** | **Activity** |
|---|---|
| **May-July 2015** | **State of Play Review Writing** |
| **August 2015** | **Publish State of Play Review on website (accompanied by a lay summary for service users)** |
| **Sept 4 2015** | **Priority setting workshop with service users** |

| | |
|---|---|
| **Oct 2015 (date tbc)** | **Funders meeting to discuss priorities and areas of alignment and mutual interest** |
| **Oct-Dec 2015** | **Develop Call for Proposals** |
| **Jan/Feb 2016** | **Launch Call for Proposals** |
| **July 2016** | **Application Deadline** |
| **November 2016** | **Awards Panel Meeting** |
| **December 2016** | **Council of Trustees ratify funding awards**<br><br>**Awards made** |

## Appendix 1: Agenda from Roundtable on Vascular Dementia 29 January 2015

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|---|---|
| **Meeting** | Research Round table on Vascular Dementia |
| **Date** | 29 January 2015 |
| **Time** | 10.45 – 16.15hrs (followed by reception until 18:00) |
| **Venue** | Council Chambers, Stroke Association House |

**Chair:** Professor Seth Love, University of Bristol

10.45-11.00 Arrival and Refreshments

11.00-11.10 Welcome and Introductions

11.10-11.20 Stroke Association Research Strategy and Introduction to the Vascular Dementia Priority Programme – Dr Kate Holmes (Stroke Association)

**Session 1: Overview**

11.20-11.40 "Vascular dementia: where are we now?" An overview by Professor John O'Brien (University of Cambridge)

11.40-12.00 "The pathophysiology of vascular dementia" by Professor Raj Kalaria (Newcastle University)

12.00-12.45 Questions and discussion of morning

12.45-13.15 Lunch

**Session 2: Clinical Trials Update**

13:15-13:30 "MRI imaging in VCI and its potential use in clinical trials" by Professor Hugh Markus (University of Cambridge)

13.30-13.45 AFFECT study: Professor Peter Passmore (Queens University Belfast)

13:45-14:00 PODCAST study: Professor Philip Bath (University of Nottingham)

14.00-14.45 Questions and discussion about current/recent research and the next priorities in vascular dementia/cognitive vascular impairment

14.45-15.00 Refreshment break

15.00-15.45 Feedback from discussions, what are the research priorities in this field?

15.45-16.15 Next steps agreed

16.15-18.00 Reception and networking

## Appendix 2: Attendance at Roundtable on 29 January 2015

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|---|---|
| Professor Philip Bath | University of Nottingham |
| Dr Giovanna Zamboni | University of Oxford |
| Professor Stuart Allan | University of Manchester |
| Professor Seth Love | University of Bristol |
| Dr Atticus Hainsworth | St George's University of London |
| Professor Peter Passmore | Queen's University, Belfast |
| Professor Martin Rossor | University College London |
| Professor Rob Stewart | King's College London |
| Professor Paul Ince | University of Sheffield |
| Professor Hugh Markus | University of Cambridge |
| Professor Joanna Wardlaw | University of Edinburgh |
| Professor John O'Brien | University of Cambridge |
| Professor Raj Kalaria | University of Newcastle |
| Dr Roxana Carare | University of Southampton |
| Dr Dale Webb | Stroke Association |
| Dr Kate Holmes | Stroke Association |
| Dr Madina Kara | Stroke Association |
| Dr Shamim Quadir | Stroke Association |
| Miss Rachael Sherrington | Stroke Association |
| Dr Shannon Amoils | British Heart Foundation |
| Professor Jeremy Pearson | British Heart Foundation |
| Dr Clare Walton | Alzheimer's Society |
| Dr Simon Ridley | Alzheimer's Research UK |
| Dr Catherine Moody | Medical Research Council |