

Progress towards standardised diagnosis of vascular cognitive impairment: guidelines from the  
vascular impairment of cognition classification consensus study (VICCCS)

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## Abstract

INTRODUCTION: Progress in understanding and management of vascular cognitive impairment (VCI) has been hampered by lack of consensus on diagnosis, reflecting the use of multiple different assessment protocols. A large multinational group of clinicians and researchers participated in a two-phase Vascular Impairment of Cognition Classification Consensus study (VICCCS) to agree on principles (VICCCS-1) and protocols (VICCCS-2) for diagnosis of VCI. We present VICCCS-2.

**METHODS:** We used VICCCS-1 principles and published diagnostic guidelines as points of reference for an online Delphi survey aimed at achieving consensus on clinical diagnosis of VCI.

**RESULTS:** Over six survey rounds, each with 65-79 participants (mean of 72), we agreed on guidelines for diagnosis of VICCCS-revised Mild and Major forms of VCI and endorsed the National Institute of Neurological Disorders-Canadian Stroke Network neuropsychological assessment protocols and recommendations for imaging.

**DISCUSSION:** VICCCS consensus-based guidelines provide a framework for standardised diagnosis of VCI and for research collaboration.

## 1. Introduction

Since Hachinski et al [1] proposed the term multi-infarct dementia to describe dementia complicating ischaemic vascular disease, numerous other descriptors have been used to encompass the heterogeneous clinical and aetiological spectrum of cognitive impairment due to cerebrovascular disease (CVD). These include vascular dementia (VaD), vascular cognitive impairment (VCI), subcortical (ischaemic) vascular dementia, and vascular cognitive disorder, variably diagnosed according to multiple different guidelines or protocols [2-14], some agreed by national institutions or research networks, e.g. Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [11], International Statistical Classification of Diseases, 10th Revision (ICD-10) [15], the National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [16], and Diagnostic and Statistical Manual of Mental Disorders (DSM) fourth and fifth editions [17, 18].

Studies comparing some of these protocols have shown they are not readily interchangeable [19-21]. After the commencement of the vascular impairment of cognition classification consensus study

phase 1 (VICCCS-1), the American heart association/American stroke association (AHA/ASA) published a statement on vascular contributions to cognitive impairment and dementia [22]. This supported the use of assessment protocols previously published by NINDS-Canadian Stroke Network (CSN) [13]. There have been other recent contributions to this field from the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) [23] and in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [18]. The level of take up of these recent guidelines is still unclear. Only those published during VICCCS-1, before commencement of VICCCS-2, could be included for consideration in the present study [22, 24].

The aim of VICCCS was to achieve broad international consensus on diagnosis of VCI, through participation of a large pool of international researchers in an iterative survey using the Delphi approach. After two initial survey rounds, the study was separated into two phases: VICCCS-1, addressing key concepts in our understanding and terminology of cognitive impairment resulting from CVD [25], and VICCCS-2, focussing on the formulation of practical guidelines for diagnosis.

VICCCS-1 achieved broad consensus on concepts of VCI. It supported the use of 'mild' and 'major' subdivisions of the severity of impairment, aligning with the revised terminology in DSM-5. VICCCS-1 participants concluded that attempts to separate Mild VCI into further subtypes according to affected cognitive domains were at present premature, but agreed that this should be an area of future research. VICCCS-1 agreed that the Major forms of VCI (VaD) should be classified into 4 main subtypes: i) post-stroke dementia (PSD); ii) subcortical ischaemic vascular dementia (SIVaD); iii) multi-infarct (cortical) dementia (MID); and iv) mixed dementias (further subdivided according to additional neurodegenerative pathologies, e.g. VCI-AD, VCI-DLB) (see Figure 1, reproduced from [25]). Framed by these concepts, VICCCS-2 used the same Delphi methodology to agree diagnostic guidelines on determination of severity of VCI, and discrimination of subtypes.

## 2. Methods

Participants in VICCCS-1 [25] were invited to participate in VICCCS-2 (supplementary figure 1). While 149 initially agreed to participate, only approximately half were active and committed respondents in three or more rounds, with low attrition and little variation in participation through the six rounds (65-79 participants in each round, a mean of 72). Of the active participants, 63-75% (mean 68%) were clinicians with direct involvement in clinical assessment. The remainder were non-clinical researchers. Continental representation across the study was: Europe 65%, North America 16%, South America 5%, Asia 10%, Africa 4%, Australia 0% (individual round representation is provided in Supplementary table 1).

### 2.1 Data collection

We used the Delphi method, an iterative, multi-staged series of structured questionnaires with feedback of anonymised responses, and progressive refinement of questions to reach consensus [26]. The process was co-ordinated by a non-participating researcher (O.A.S). Anonymisation of responses facilitated free expression of opinion throughout the study. The feedback of summary responses after each round informed subsequent questions and allowed unbiased evolution of group judgement. A threshold of two-thirds agreement was chosen to signify consensus [27] for issues refined iteratively through multiple rounds, as in VICCCS-1 [25]. For issues where this threshold was not reached we present the summary data including the view that was most strongly supported. A summary of topics covered in each Delphi round is presented in Figure 2. The first two rounds were used to select from previous publications those diagnostic criteria deemed most valuable as a basis for further discussion. These provided main themes addressed in the four subsequent rounds (November 2012 – September 2013). Consensus views from topics addressed in VICCCS-1 were utilised in discussions.

### 3. Results

#### 3.1 VICCCS foundation rounds and VICCCS-2 rounds 1 & 2

In the two foundation rounds of VICCCS the consensus view (94% of respondents) was that none of the current diagnostic protocols were fully fit for purpose and that formulation of improved assessment criteria for VCI was a priority. Data from the foundation rounds, including the researcher-led [2, 6, 7, 11-14, 16, 28-30] and organisation-based diagnostic criteria/protocols that were critiqued by the participants, are provided as supplementary material.

Participants selected their preferred criteria of the six presented (4 chosen in VICCCS foundation rounds [6, 12, 13, 31] and 2 that were published during VICCCS-1 and could therefore be accommodated in VICCCS-2 [22, 24]). These criteria were collectively thought to serve as the best starting points from which to agree diagnostic guidelines for VCI. Of these six, the AHA/ASA Scientific Statement: vascular contributions to cognitive impairment and dementia [22], henceforth referred to as AHA/ASA, was the first preference of the highest proportion of respondents (41%), followed by NINDS-CSN [13] (25%). The AHA/ASA does not itself provide assessment protocols but refers to the recommendations made in the NINDS-CSN. These guidelines provided the basis for further discussion and elaboration.

In keeping with the views of the majority of participants (65%), VICCCS-2 aimed to agree a single set of diagnostic guidelines for clinical and research use. The agreed objectives were to develop a clear and efficient protocol that was simple to use and yielded readily interpretable results, allowing discrimination of VCI subtypes and severity.

#### 3.2 VICCCS-2 rounds 3-6

##### 3.2.1 Measure of severity - differentiating between Mild and Major VCI

In VICCCS-1 round 4 participants considered the cognitive domains that needed assessment to measure the severity of VCI. These were reviewed in VICCCS-2 round 3, in which 94% agreed that the core domains for assessment should be executive function, attention, memory, language, and visuospatial function. The domains of learning, neuropsychiatry, and social cognition should be treated as optional, outside of the core assessment, unless and until there is stronger evidence for their inclusion. No other domains (including abstraction, agnosia, emotionality, praxis, and processing or psychomotor speed) were supported as core domains; for some respondents thought there were insufficient tools for assessment (e.g. apraxia, that features in NINDS-CSN, 80% of respondents).

81% of VICCCS-1 respondents felt the differentiation between Mild VCI and Major VCI (VaD) should be based on the number of domains affected and that both IADL and ADL were necessary determinants. In VICCCS-2 round 3, a consensus (85%) definition was achieved for *Mild VCI*: *impairment in at least one cognitive domain, and mild to no impairment in ADL (independent of the motor/sensory sequelae of the vascular event)*. In rounds 3 and 4 several definitions were considered for Major VCI (VaD) but no overall majority was achieved for any one option. On further examination of the various choices, 71% had chosen a definition that included the word “severe” and 73% had chosen an option with “at least ONE cognitive domain” (rather than “at least TWO cognitive domains”). These observations were presented to the participants in round 5, and they were asked to choose from between three most favoured definitions from the previous round. There was 60% support for the definition: severe deficits in at least ONE cognitive domain (other deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event). Consensus-level (67%) support was obtained for a definition requiring deficits in one rather than two cognitive domains and for inclusion of the descriptor “severe”. Those who did not support the mandatory inclusion of the descriptor “severe” highlighted the important issue of people with moderate cognitive impairment, and suggested the use of the

term “significant” to allow greater clinical discretion and flexibility. The scenario of a “... the case of the very bright patient whose functioning is severely compromised but still does ok on rudimentary cognitive assessment” was given as an illustrative example.

On feedback of the results of round 5, participants were asked to consider an amendment of the definition of Major VCI by substitution of “severe” by “significant”, i.e. clinically significant deficits in at least one cognitive domain (other deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event). 52% were in favour, and support for the most popular definition in round 5 – severe deficits in at least one cognitive domain (other deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event) - had dropped to 34%. Although our pre-defined consensus level (67%) was not reached for any definition in either round, it was clear that some qualification of the severity of deficit in at least one cognitive domain was preferred. Therefore, the proposed definition (representing the majority view) for *Major VCI* is: *clinically significant deficits in at least one cognitive domain (other deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event)*.

### 3.2.2 Clinical evaluation and time-frame for assessment

Recommendations of the NINDS-CSN abbreviated clinical evaluation of VCI were strongly supported by round 3 respondents (86%). However, NINDS-CSN recommendations differ for research and clinical settings, and most round 2 respondents (77%) thought the priority should be to agree a core of assessments for both research and clinical use, with the option of additional assessments for local use in either a clinical or research context.



It was agreed that a neuropsychological assessment protocol for use in a typical clinical diagnostic setting, noting time pressures and patient group capabilities, should take 60 minutes at most, although optional assessments could take additional time. The inclusion of all core items in the NINDS-CSN 60-minute protocol was supported by most round 3 respondents. Only the MMSE supplementary test was supported by most respondents (71%). Other supplemental tests -- Rey-Osterrieth Complex, Boston Naming and Digit Symbol-Coding Incidental Learning – did not achieve consensus support for inclusion. All core and supplementary items in the NINDS-CSN 30-minute protocol were also supported (Table 1).

### 3.2.3 The role of aphasia in diagnosis of VCI

VICCCS-2 round 2 respondents agreed (72%) with the AHA/ASA statement on aphasia: "Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g. annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD/VaMCI." [22]. In round 4, respondents agreed (96%) on the qualifying sentence "that the assessment of ADL should be made where possible". 68% of round 4 participants felt that "probable Mild VCI or probable Major VCI" was the appropriate classification of cases with aphasia when imaging was available, and "possible" used in for cases of aphasia when imaging was not available (90%).

### 3.2.4 Those at risk of VCI

One of the agreed 'principles' in VICCCS-1 [25] was: "The new VCI construct recognises the importance of people who are at risk of VCI, however, their consideration should be contingent upon the presentation of a sustained level of impairment even if in a very mild form as opposed to impairment that can be transient or revert to normal levels". Respondents agreed (96%) on the recommendation that the diagnosis in people at risk of VCI should be given greater consideration if

they present with at least 6 months of sustained impairment. It was also agreed (88%) that in those at risk of VCI, other potential causes of sustained impairment (e.g. depression or vitamin D deficiency), in addition to the already agreed exclusions from diagnosis (i.e. drug/alcohol abuse/dependence within 3 last months of first recognition of impairment or delirium) should have been excluded. Caregiver reporting (88%) and clinical observation (73%) were supported mechanisms to collect this information. Screening-type assessment (49%) and more detailed formal assessment (43%) were not supported by the majority.

### 3.2.5 Possible and Probable terms in VCI and 'Mixed dementias' subgroup

In the AHA/ASA, which served as a starting point to discuss the use of the terms 'possible' and 'probable' in VCI, only the categories of 'possible' VaD or VaMCI allowed the inclusion of other phenotypes (e.g. evidence of other neurodegenerative disorders). The AHA/ASA also does not provide separate diagnosis or allow delineation of further subgroups of patients (e.g. the co-morbidities present in mixed dementias). In VICCCS-1 the consensus was that VCI should contain a standalone 'umbrella-like' subgroup termed "mixed dementias". VICCCS-1 participants also agreed that this subgroup could comprise further subgroups that included patients with specific combinations of phenotypes, each of which would be specifically named where possible (e.g. VCI-AD if there is evidence of both VCI and AD). Furthermore, it was agreed that the order of the descriptive phenotypic terms relevant to patients should attempt to reflect the relative contribution of phenotypes present, i.e. AD-VCI, or VCI-AD, to the extent that discrimination was possible.

On consideration of differences between the AHA/ASA and VICCCS-1, VICCCS-2 round 2 respondents agreed (92%) that the diagnostic guidelines should attempt to incorporate the VICCCS-proposed "mixed dementias" as a separate distinct diagnostic subgroup of Major VCI and 'probable' or 'possible' are to be used to differentiate the level of diagnostic evidence to help classify patients for both Major VCI (VaD) subgroups (81%) and Mild VCI (70%).

### 3.2.6 Incorporating temporal relationships in VCI diagnosis

In AHA/ASA a clear temporal relationship between a vascular event and onset of cognitive deficits is required for a 'probable' diagnosis. In VICCCS-1, the definition of PSD – an agreed subgroup of major VCI (VaD), required that cognitive decline develop within 6 months of stroke. However, temporal relationships were not discussed for other subtypes of VCI. In VICCCS-2, respondents thought that a clear temporal relationship between a vascular event and onset of cognitive deficits should not be an essential component for diagnosis of Mild VCI (77%), (SIVaD) (88%), mixed dementias (85%) or MID (74%).

### 3.2.7 The role of imaging in VCI diagnosis

In VICCCS-2 round 3, the consensus was that imaging evidence of CVD was essential for diagnosis of Major VCI (VaD) (86%) and Mild VCI (79%). In round 4, although most respondents felt the NINDS-CSN recommendations were possible/appropriate in the respondents' clinical settings (75% MRI / 81% CT), 93% thought that the "acceptable MRI measures" proposed in NINDS-CSN should be the core recommendation for imaging in clinical settings, and the "recommended MRI measures" supported as additional measures for use in either clinical or research contexts (Table 2 and 3).

Several respondents stated that CT might be insensitive or insufficient to detect small vessel diseases or evaluate vascular status. The limitations of CT for VCI are also highlighted in NINDS-CSN. In round 4, respondents agreed (93%) that MRI should be the gold standard imaging for VCI and 90% agreed that CT should be used only if MRI were not available or deemed too costly. A consensus (68%) was reached on the use of the term "possible" Mild VCI or Major VCI if neither MRI nor CT imaging were available. Yet 89% felt that "probable" was the appropriate diagnostic category if only CT imaging were available.

Majority support (67%) was not reached for any of the other "future" imaging methods described in NINDS-CSN, and the consensus was that none of these is was ready for inclusion in clinical diagnosis.

A summary of VICCCS diagnosis guidelines are provided in Panel 1.

#### 4. Discussion

VICCCS-2 has provided new consensus-based guidelines for diagnosis of Mild and Major VCI as previously defined [25], with AHA/ASA and NINDS-CSN guidelines as reference points for discussions. Clinical evaluation and neuropsychological protocols in the NINDS-CSN were supported for use by VICCCS respondents. The "acceptable MRI measures" outlined in NINDS-CSN should be the core recommendation for imaging in clinical settings. In terms of assessing severity, VICCCS diagnosis guidelines specify deficits in at least 1 domain, with clinically significant cognitive deficits of sufficient severity (moderate to severe) and severe deficits in ADL differentiating Major from Mild forms. Patients with PSD, SIVaD and MID and mixed dementias should also be subcategorised and any comorbid neurodegenerative disease recorded.

##### 4.1 Comparison of VICCCS with recently published guidelines

VICCCS was conducted between 2010 and 2013, which coincided with the development of DSM-5 and VASCOG criteria for Vascular Cognitive Disorders (VCD) [23]. VICCCS participants provided collective feedback on draft DSM-5 proposals that were made available prior to their finalisation, through a tailored survey developed (by O.A.S), in consultation with P.S. acting on behalf of the DSM-5 Neurocognitive Disorders Work Group. VICCCS respondents agreed that the Mild and Major terminologies proposed in DSM-5 were helpful and should be adopted in VICCCS. The VASCOG criteria are also aligned with DSM-5 [23].

In terms of assessing severity, both AHA/ASA and VICCCS specify the same core domains for assessment. In VASCOG, visuoconstructional-perceptual ability, praxis-gnosis-body schema and social cognition are additionally tested. The definitions of Mild VCI are comparable; however, they are not sub-categorised in VICCCS as respondents felt more evidence was needed. The definition of major forms of VCI in VICCCS and VASCOG requires deficits in at least 1 domain, rather than 2 domains as specified in AHA/ASA. Loss of independence in IADL is the threshold in VASCOG and DSM-5. In VICCCS-1 IADL and ADL were both deemed necessary factors to determine severity. Patients with PSD, SIVaD and MID are also subcategorised in VICCCS but not specified in AHA/ASA, although subtypes in VASCOG include cortical-subcortical and subcortical ischaemic. The AHA/ASA category of "Unstable VaMCI", for cases which revert to normal from VaMCI, was not supported by VICCCS respondents.

One of the main differences between VICCCS and AHA/ASA is the VICCCS subcategorisation of patients with comorbid pathologies under the umbrella term "mixed dementias" but with the types of pathologies specified. Diagnostic categorisation of these patients was seen to be important. Improvements in the accuracy of this would be an important goal of any future operational diagnostic protocols and research in biomarkers may be helpful. VASCOG criteria encompass categories of multiple causation, including VCD with concomitant AD (Major or Mild) and VCD with additional pathology: e.g. Lewy body disease. AHA/ASA does not delineate these subgroups of patients, with only the categories of 'possible' VaD or VaMCI allowing the inclusion of other phenotypes (e.g. evidence of other neurodegenerative disorders).

In VICCCS the use of probable and possible terms are reserved for the strength of evidence to support diagnosis. One such line of supportive evidence is a clear temporal relationship between a vascular event and onset of cognitive deficits in PSD, which is differentiated from other forms of VCI by the onset of symptoms within six months of stroke. Another is the imaging of CVD. VICCCS respondents concluded that MRI is the gold standard for imaging; if CT were the only means

available, only a 'probable' diagnosis could be made, and only a diagnosis of 'possible' if no imaging were available. The recent STRIVE imaging criteria [33] most likely warrant consideration in the context of VICCCS-2, however they were published after the completion of our study. VICCCS supports and expands on the AHA/ASA guidance on patients with aphasia, in whom assessment of ADL should be done when possible, allowing a diagnosis of 'probable' with imaging evidence or 'possible' without it.

#### 4.2 Reflection on the Delphi process

A key principle of the Delphi method is that decisions achieved through iterative consultation of a structured specialist group of individuals are likely to be more accurate than those made by individuals or without iteration. The use of online surveys in VICCCS allowed an unprecedented number of international participants to participate in a flexible manner over an extended period. The combination of anonymity with repeated group feedback facilitated contemplation and provided scope for uninhibited change in opinions, all of which promoted the generation of consensus [26, 32]. There was little participant attrition between rounds, with 90-97% of participants responding over rounds 2-6 when the guidelines were developed, reflecting engagement of a large motivated core of respondents. Although there was variation in respondent numbers in each round, the variation was small and most topics were dealt with over multiple rounds. The maintenance of a high and relatively consistent number of respondents throughout the study provides assurance that the guidelines truly reflect the considered opinion. Despite the large number of respondents and the range of clinical and research backgrounds, it is noteworthy that we achieved consensus on most topics addressed in VICCCS. Reaching consensus was most challenging for the definition of Major VCI (VaD), perhaps reflecting the sensitivities associated with this diagnosis and the implications for health and social care services. Consequently, specific thresholds of severity of impairment were not established.

## 5. Conclusions

We present a consensus-based set of guidelines for diagnosing VCI, supported by a large multinational group of researchers. These VICCCS guidelines have drawn upon, critiqued, expanded and refined previous efforts. We hope that they will be widely adopted, to improve consistency in diagnosis and standardisation in VCI research. This would allow better comparison of findings across studies and facilitate large-scale collaborative research on a group of diseases that despite modest prevalence and considerable heterogeneity have major societal impact.

## 6. Acknowledgements

### 6.1 Contributors

OAS was the study coordinator, analysed the data, formulated the questionnaires and wrote the manuscript. PGK was Chief investigator, conceived and designed the study, obtained the necessary funding, reviewed each round data, formulated the questionnaires and wrote the manuscript. YB-S, APP, SL were Co-investigators and members of the Steering Group. Other listed authors were members of the Steering Group who reviewed the content of the pilot questionnaires, draft and final manuscript and were participants in the study. Authors listed under the banner of VICCCS groups contributed to data gathering in multiple survey rounds and approved the final submitted version of the paper.

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## Legends

Figure 1: Revised conceptualisation of VCI in VICCS. Subtypes of VCI are divided according to level of VCI impairment into Mild VCI and Major VCI (VaD). Mild VCI is not further sub-divided at this time. Major VCI (VaD) is classified into 4 main subtypes as depicted. The 6 month temporal basis (denoted by the hashed box) for cognitive decline after stroke differentiates PSD from other forms of major VCI (VaD). Post stroke dementia (PSD) and Mixed dementias are further delineated if a comorbid neuropathology is present (N.B. AD and Dementia with Lewy bodies (DLB) are given as examples, with # denoting other possible combinations). Subcortical ischaemic vascular dementia or Multi-

infarct (cortical) dementia subtype cases with these specific types of dementia alone, however cases also presenting with any other neurodegenerative pathology would then be categorised as Mixed dementias (dashed arrows) according to the comorbidities present.

Key words: vascular cognitive impairment, vascular dementia, guidelines, criteria, consensus, Delphi

#### Abbreviations:

Alzheimer's disease (AD)

Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)

Instrumental activities of daily living / activities of daily living (IADL/ADL)

The American heart association/American stroke association (AHA/ASA)

Cerebrovascular disease (CVD)

Dementia with Lewy bodies (DLB)

Diagnostic and Statistical Manual of Mental Disorders (DSM)

International Statistical Classification of Diseases, 10th Revision (ICD-10)

Mild cognitive impairment (MCI)

Multi-infarct dementia (MID)

The National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)

National Institute of Neurological Disorders-Canadian Stroke Network (NINDS-CSN)

Post-stroke dementia (PSD)

Subcortical ischaemic vascular dementia (SIVaD)

Vascular dementia (VaD)

The International Society of Vascular Behavioural and Cognitive Disorders (VASCOG)

Vascular cognitive disorders (VCD)

Vascular cognitive impairment (VCI)

The Vascular Impairment of Cognition Classification Consensus Study (VICCCS)