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Journal of the Neurological Sciences 252 (2007) 106–112

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Disease progression in vascular cognitive impairment: Cognitive, functional and behavioural outcomes in the Consortium to Investigate Vascular Impairment of Cognition (CIVIC) cohort study

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Received 13 July 2006; received in revised form 6 October 2006; accepted 30 October 2006
Available online 26 December 2006

Abstract

Background and purpose: Empirical studies to clarify the outcomes in Vascular Cognitive Impairment (VCI) are needed. We compared cognitive, functional, and behavioural outcomes in patients with VCI to patients with no cognitive impairment (NCI), and Alzheimer's disease (AD).

Methods: Secondary analysis of the Consortium to Investigate Vascular Impairment of Cognition (CIVIC), a multi-centre Canadian memory clinic 30-month cohort study.

Results: Of 1347 patients, 938 were eligible for follow-up, of whom 239 (24.5%) were lost and 29 (3%) had died. Of the remaining 697 patients, 125 had NCI, 229 had VCI, and 343 had AD at baseline. Compared to people with NCI, of whom 20–40% showed progression based on cognitive and functional measures, those with VCI were more likely to progress (50–65%), as were people with AD (50–80%) ($p<0.01$). More people with VCI showed progression of affective symptoms (30%) than those with NCI (12%) or AD (15% $p<0.01$). Progression of impaired judgment (rated clinically) in VCI (15%) was similar to AD (11%) but more common than in NCI (4%, $p<0.01$).

Conclusions: Most people with VCI show readily detectable progression by 30 months. Depressive symptoms were more common and more progressive in VCI than in Alzheimer's disease, whereas clinical evidence of progressive executive dysfunction was common in both AD and VCI.

Keywords: Vascular cognitive impairment; Disease progression; Executive dysfunction

1. Introduction

The concept of dementia in relation to cerebrovascular injury continues to be rethought, reflecting advances in the understanding of patterns and causes of cognitive impairment, and greater recognition of the importance of early detection [1–3]. The construct of vascular cognitive impairment (VCI)

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doi:10.1016/j.jns.2006.10.015

encompasses a continuum of cerebrovascular lesions and degrees of impairment.[4] VCI is defined as cognitive impairment that arises in association with cerebrovascular disease, and is judged to be related to cerebrovascular disease and its ischemic manifestations. Subtypes of VCI have been proposed to include vascular dementia (VaD), mixed vascular and neurodegenerative dementia (AD/VaD), and vascular cognitive impairment not meeting the full criteria for dementia (VCI-ND) [5].

The Consortium to Investigate Vascular Impairment of Cognition (CIVIC) study, a multi-center cohort study of patients with dementia,[6] aims to contribute data that can aid the evolution from consensus-based criteria for VaD to evidence-based criteria for VCI. For example, the CIVIC study has evaluated the predictive validity of clinical and radiographic characterization of VCI subtypes, and has highlighted the tenuous association between radiographic features and clinical profiles.[7] As new therapies become available, there is a particular need for appropriate data on disease outcomes.[8–14]] Empirical studies are also needed to better define phenotypes, a crucial challenge for genetic studies. [15] The importance of executive dysfunction in the clinical presentation of cerebrovascular disease is stimulating new lines of inquiry. [16,17]

Although there is more information on outcomes in VaD, few studies have been conducted on VCI outcomes. [18–21] Typically, studies that compare disease progression between VaD and other dementias subtypes have had short follow-up periods, few outcome measures, and do not reflect the new VCI construct.[22] Data on VCI-ND suggest that even mild disease is associated with adverse outcomes, perhaps as a consequence of early motor impairment, or early impacts on executive function [18]. CIVIC data show that death and institutionalization are increased in all VCI subtypes, compared to people with no cognitive impairment (NCI) [7]. Here, we evaluate other clinically important outcomes in relation to disease progression, including cognitive, behavioural, and functional changes. We report both mean levels of change by several standard instruments, and the proportion of people who show clinically detectable change.

2. Methods

2.1. Patients and measures

The CIVIC study enrolled 1347 patients from 9 Canadian memory clinics.[6,7] The study was based on usual care, and therefore dementia subtypes were diagnosed by clinicians using standard criteria described elsewhere.[23,24] To examine how expert clinicians actually diagnosed VCI in daily practice, a clinical report form incorporated all items from the Hachinski Ischemia Score,[25] and the criteria of the National Institute of Neurological Disorders and Stroke / Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),[26] the Alzheimer's Disease Treatment Centers of California,[27] and the International Classification of Disease, 10th edition [28].

The CIVIC study also included the Disability Assessment for Dementia (DAD), [29] which assesses function in several domains of personal and Instrumental Activities of Daily Living. Notably, the DAD distinguishes between effective performance, and performance that is compromised by impaired initiative. Cognition was summarized by the Mini-Mental State Examination (MMSE) [30] and staging by the Functional Assessment Staging Tool (FAST) [31] and the Global Deterioration Scale (GDS) [32]. The Functional Rating Scale (FRS) [33] extends the Clinical Dementia Rating [34] and includes additional behavioural observations. Behaviour was also assessed using the Geriatric Depression Scale [35] and co-morbidity using the Cumulative Illness Rating Scale (CIRS). [36] In all scores except the MMSE and DAD, a higher score means worse performance. The CIVIC protocol paralleled those of the Canadian Study of Health and Aging (CSHA) [37] and A Collaborative Cohort of Related Dementias (ACCORD) [38] to include clinical ratings of delusions and hallucinations. It also recorded impaired judgment, apathy, impairment in social functioning and loss of initiative with respect to function and hobbies, but otherwise had no routine tests of executive dysfunction. The checklist and initial clinical classification have proved to be reliable [39].

The CIVIC study was based on usual care; neuropsychological testing and neuroimaging were obtained at the discretion of the examining physician. The CIVIC protocol required annual follow-up over 30 months, either in clinic (where the original assessments were repeated) or by a telephone interview (which included the informant-based DAD, the FAST, and the Informant Questionnaire on Cognitive Decline in the Elderly [40]). The CSHA decedent interview [41] was administered to a caregiver by telephone to assess pre-morbid progression of cognitive and functional impairment in patients who had died. We excluded from analysis two heterogeneous groups — people with 'Cognitive Impairment, No Dementia'[42] other than VCI-ND, and those with other dementias. We thus compare patients across the VCI spectrum with the spectrum presented by NCI on the one hand, and AD on the other.

2.2. Analysis

Baseline demographics and assessment scores were compared between VCI, AD and NCI, and also within the VCI subtypes. For all analyses we used χ^2 for categorical data and ANOVA for continuous data. Baseline co-morbidity was measured using the CIRS. Change in function was operationalized as significant change on the DAD, or FRS-SB. Baseline cognitive stage was taken as the baseline GDS/FAST, and change in cognition was operationalized as significant a change in the GDS/FAST or MMSE. Change scores were calculated by subtracting follow-up scores from baseline values. Deterioration was indicated by a negative

change score for the DAD, and MMSE, or a positive change score for the FRS, GDS/FAST, and CIRS. Clinically significant progression was defined according to clinically detectable effect sizes (calculated as the change in the item divided by the pooled baseline standard deviation) of more than 0.20 or where possible published accepted standards. [43] Two-point changes on the FRS-SB or Geriatric Depression Scale, or a 5-point change on the DAD represent clinically detectable effect sizes (i.e. Cohen's $d>0.20$). [43] Individual items from the baseline and follow-up assessments that included information about the presence of violent behaviour, hallucinations, or delusions were also compared between the 3 groups (*i.e.*, NCI, VCI, and AD).

3. Results

3.1. Characteristics of the cohort

Exclusion of those with non-vascular CIND ($n=253$) and dementias other than AD or VaD ($n=156$) left 938 people eligible at baseline. Of these, 239 (24.5%) were lost to follow-up and 29 (3%) died. The remaining 697 underwent follow-up assessment by a physician or nurse (Fig. 1) of whom 229 had a baseline diagnosis of VCI, 343 had a baseline diagnosis of AD, and 125 had NCI, Demographically, people with VCI were more similar to patients with AD than to those with NCI. For example, people with VCI and those with AD each had a mean age of 75+/−(SD) 8, and 11+/−4 years of education, compared with a mean age of 63+/−12 and 12+/−3 respectively for people with NCI. Those with VCI were more often male (55%) compared to those with AD (35%) or NCI (40%). In general, people with VCI showed less cognitive impairment at baseline than people with AD (*e.g.* MMSE 23+/−6 *cf.* 20+/−6, respectively) likely reflecting the inclusion of VCI-ND within the VCI category. The level of functional impairment was similar (mean DAD 72+/−21 in VCI *vs.* 70+/−23 in AD and FRS-SB 20+/−7 in VCI vs. 22+/−6 in AD). People with VCI generally had higher levels of co-morbidity (CIRS 6.9+/−4.0) than did those with AD (4.3+/−3.1). In each of these cognitive and functional measures, people with NCI had scores in the normal range. The CIRS score amongst people with NCI was 3.8+/−9.2.

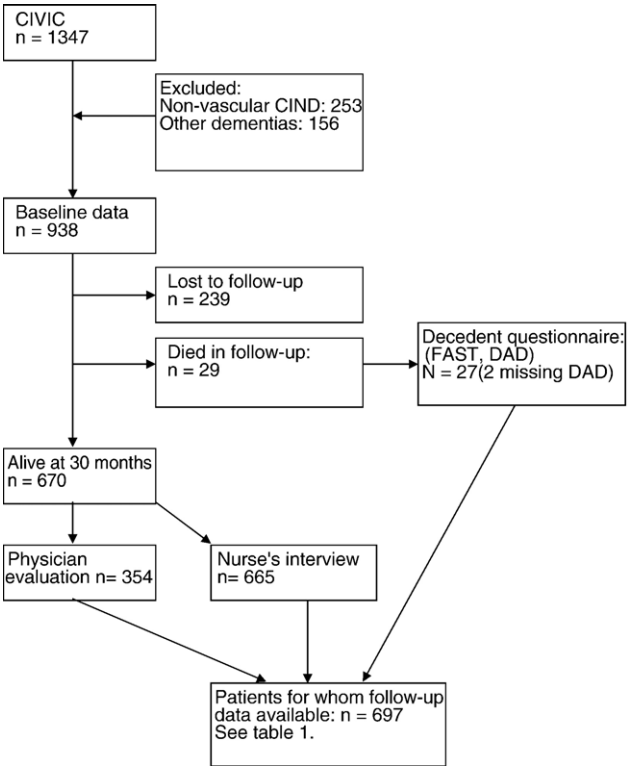

Fig. 1. Flowchart of sample selection.

Compared to people who were alive and contacted, those who were alive but lost to follow-up were about the same age (73+/−10 vs. 74+/−10 respectively) and showed similar degrees of cognitive impairment (MMSE 22+/−6 vs. 21+/−7) but greater functional disability (DAD 73+/−22 vs. 61+/−26). Similar differences were observed amongst those who had died with available post-baseline data. People who died with post-baseline data ($n=29$) were younger (mean age 77+/−8) than those who died with no post-baseline data other than vital status (82+/−7). People who died with post-baseline data were similarly cognitively impaired (MMSE 19+/−6 vs. 17+/−7) but had greater functional disability (DAD 63+/−26 vs. 45+/−24). Those who were lost to follow-up had similar baseline diagnoses compared with those who were followed-up, although slightly more people with VCI who were not contacted had died (54%) compared with those with VCI who were contacted, in whom the corresponding proportion was 45%.

Only 25 people were taking a cholinesterase inhibitor at any dose at baseline. In general, using unadjusted data, there were no significant difference in outcome measures between people taking and not taking these medications, and thus all results with respect to progression were combined across medication categories.

3.2. Mean degree of progression

People with VCI showed clinically detectable changes in most measures over the 30-month follow-up period (range 4–36 months) (Table 1). Most estimates of detectability were in the moderate range (Cohen's *d* from 0.42 to 0.49). Within the VCI subtypes, people with VCI-ND generally showed less deterioration than those with VaD or mixed dementia.

Across diagnoses, each of the MMSE, DAD, and FRS showed most progression in the very mild to moderate stages (Table 2). The least amount of change was captured in the most severe stage.

3.3. Proportion who progress

In addition to knowing mean change, it is important to estimate the proportion of people with a given baseline

Table 1
Mean change score according to Vascular Cognitive Impairment subtype

Measure *N*, mean+/− S.D., (range)	Vascular cognitive impairment, no dementia (VCI-ND)	Vascular dementia (VaD)	Mixed Alzheimer's disease/vascular dementia (AD/VaD)	ANOVA, *P* value
MMSE	45,−2.1+/−4.9 (−20−5)	39,−2.8+/−4.0 (−14−4)	56,−4.4+/−4.6 (−18−4)	0.034
DAD	63,−3.2+/−10.8 (−34−19)	59,−6.0+/−8.7 (−26−14)	72,−8.5+/−8.9 (−30−13)	0.005
FAST	71, 0.5+/−1.5 (−3−5)	63, 0.5+/−0.9 (−3−2)	64, 0.7+/−0.8 (−2−3)	0.660
FRS-SB	76, 2.9+/−6.6 (−16−22)	68, 3.0+/−5.2 (−10−20)	79, 4.4+/−5.0 (−10−20)	0.196

diagnosis who progress, versus those who improve or show little change. In comparison to people with NCI, people with all subtypes of VCI are significantly likely to worsen, as are people with AD (Fig. 2). For each measure, save the FAST, the proportion who progress is highest amongst those with VaD or mixed AD/VaD, and least for those with VCI-ND.

3.4. Incident problems in executive function, behavioural symptoms and progression of mood symptoms

Incident behavioural symptoms were common. For example, in those with a baseline diagnosis of NCI, behavioural problems were identified in one third. The proportion was much larger in people with VCI (55%) and with AD (55%) ($\chi^2=25.0$, $p<0.001$). For each diagnostic group, the most common findings were disturbances in judgment (31% of those with VCI and 22% of those with AD) and other aspects of executive function (39% of those with VCI and 39% of those with AD). Incident hallucinations and delusions were reported in only one person with NCI at baseline, versus 10% in those with VCI and 7% in those with AD. Between the various VCI subgroups, fewer people with VCI-ND (43%) reported new onset behavioural symptoms than did people with VCI who met dementia criteria (64%; $\chi^2=13.0$, $p<.01$). Progression of impaired judgment was more common in people with VCI (15%) than in those without cognitive impairment (3.6%) but similar to those with Alzheimer's disease (11%).

Table 2
Outcomes in people with NCI (stages 1,2, $N=125$) or VCI (stages 3–7, $n=229$) by Functional Assessment Staging Tool stage at baseline

FAST stage *n* (mean±S.D.)		ΔMMSE	ΔDAD	ΔFRS
1	Normal adult	−0.6+/−1.4	−1.0+/−4.9	0.7+/−2.1
2	Normal adult, subjective complaints	−0.2+/−2.2	−1.7+/−5.3	1.2+/−3.9
3	Possibly incipient dementia	−2.8+/−4.8	−6.1+/−10.1	4.8+/−6.4
4	Mild dementia	−3.3+/−4.6	−7.4+/−8.6	4.2+/−5.3
5	Moderate dementia	−4.2+/−5.0	−9.3+/−7.7	3.3+/−4.1
6/7	Moderately severe/ terminal dementia	−1.9+/−3.8	−5.9+/−7.7	1.0+/−3.5

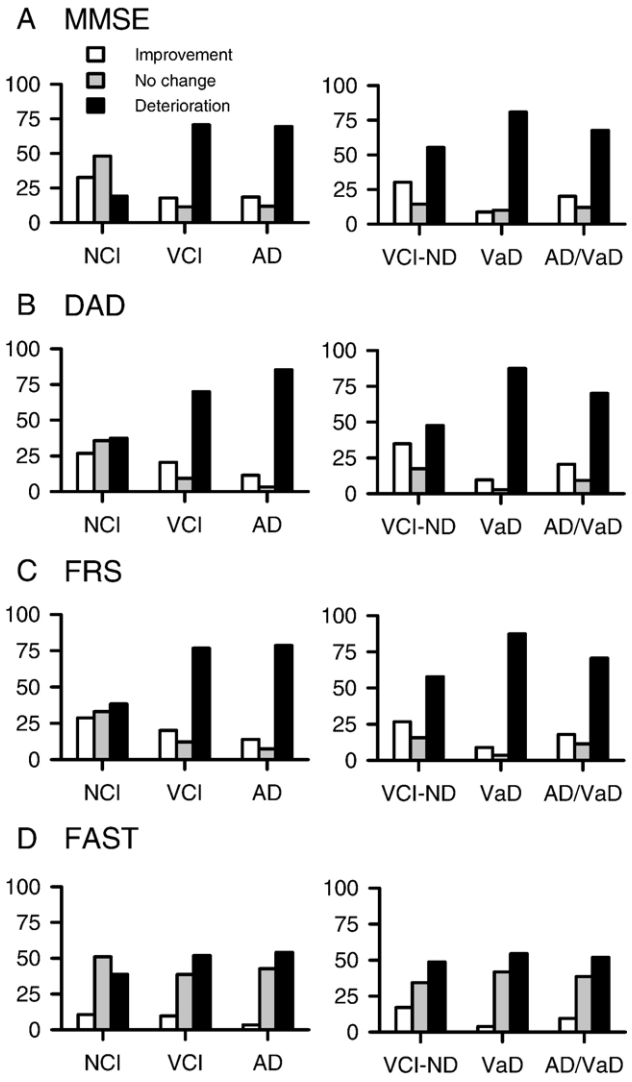

Fig. 2. Follow-up scores on measures of cognition (Mini-Mental State Examination — MMSE), and function (Disability Assessment for Dementia — DAD), Functional Rating Scale (FRS) and Functional Assessment Staging Tool (FAST), by baseline diagnoses: NCI (No Cognitive Impairment), VCI (Vascular Cognitive Impairment) AD (Alzheimer's disease), VCI-ND (Vascular Cognitive Impairment-No Dementia), VaD (Vascular Dementia, and mixed AD/VaD.

Progression of depressive symptoms was more likely in people with VCI (30%) than in those with either NCI (12%) or AD (15%; $\chi^2=10.3$, $p<0.01$). There were no significant differences in progression of depressive symptoms between VCI subtypes.

4. Discussion

This report from the clinic-based, multi-centre CIVIC cohort study offers three contributions to the empirical understanding of VCI. VCI, and each of its subtypes, including VaD, showed readily detectable clinical evidence of disease

progression. Progression was least in people with VCI-ND and greatest in those with VaD; people with mixed VaD/AD tended to have outcomes similar to those with AD. Depressive symptoms were both more common in VCI, and more likely to progress, than in NCI or AD, without significant differences in VCI subtype. Clinical evidence of executive dysfunction, while common in VCI, was just as prevalent in AD.

Our data must be interpreted with caution. The CIVIC study is based in tertiary care memory clinics, not in stroke clinics, so its generalizability to that setting is not clear. Neither is it population based. The study built on usual care, and relied chiefly on computerized tomography, so we cannot make neuroimaging correlations with the same precision afforded by MRI, and thus have restricted ourselves to what is readily, clinically identifiable in a group of people in whom the contribution of neuroimaging is restricted to diagnosis [7]. Similarly, we do not have routine neuropsychological testing. The usual care design was critical to having us understand how VCI is diagnosed in daily practice. Although one quarter of our patients were lost to follow-up, most of those came from a single centre, and we have been careful to characterize and compare those for whom we do and do not have follow-up data. The minor differences between those studied and those lost to follow-up appear to reflect a centre effect, rather than a systematic bias in our estimates.

Our sample size of 229 people with VCI with complete data is too small to detect subtle differences, but does have adequate power for effect sizes in larger than 0.35, which would be readily detectable by experienced clinicians.[43] In consequence, effects demonstrated here are large enough to reflect clinically meaningful differences between VCI, NCI and AD, as well as within VCI subgroups.

That progression was noted in all VCI subgroups, including VaD, is of interest. It contrasts with the common experience of stabilization over a six month period in the placebo arm of VaD clinical trials. [44,45] Stabilization in those trials, compared with clear progression here, might reflect that the usual six months' clinical trial duration is too short an interval and/or that the careful monitoring of vascular risk factors mandated in clinical trials is more stabilizing than routine care. Alternatively, the progression may indicate that strict application of the NINDS-AIREN criteria, [26] which have dominated the clinical trials, and which in the CIVIC study had a sensitivity of only 10%, [6] select a group less inclined to progress. The CIVIC experience with progression is more in accordance with what has been described in population studies [18] in which VCI is clearly not benign. The data on progression by stage also offer the pragmatic insight that many measures which are useful in very mild to moderate VCI have floor effects as the condition produces severe cognitive and functional impairment.

Depressive symptoms were more common in VCI, and more likely to progress, than in people with NCI or with AD, reaffirming the importance of the frontal/subcortical ischemia described in VCI, especially in relation to depressive symptoms. [46] It also suggests the need for careful study of depressive symptoms as part of VCI, rather than excluding such patients from drug studies. Notably too, progression of affective symptoms in VCI appears to support the notion of "vascular depression"[55] presenting clinically as a "depression–executive dysfunction syndrome of late life"[56] That disturbances in judgment and other aspects of executive function were seen in all VCI subtypes confirms other work [47–52]. We suggest that executive dysfunction might be no more common in VCI than in AD. In consequence, we must be cautious against making the executive dysfunction claim in VCI as exclusive to VCI. Although without standardized tests of executive function this suggestion is preliminary, it supports other observations that executive dysfunction is what makes any cognitive disorder disabling. [53,54]

Coupled with other CIVIC reports, [6,7,57,58] a picture of how VCI is diagnosed emerges. In general, the CIVIC physicians considered cognitive, functional and behavioural disorders to diagnose cognitive impairment syndromes. To assign a cause of the specific syndrome they considered vascular risk factors, (e.g. hypertension, dyslipidemia) clinical features that favour a vascular etiology (e.g. sudden onset, lateralized signs) and neuroimaging (chiefly CT) features. The presence of many vascular risk factors favours a VCI diagnosis, but recognizing that vascular risk factors are also risks for AD, vascular risk factors alone are not sufficient. Operationally, it appears therefore that vascular risk factors were mostly considered negatively — *i.e.* without vascular risk factors, a VCI diagnosis is less likely, unless the clinical and neuroimaging features are suggestive; for example, if only the latter, a 'mixed' dementia diagnosis is most likely. Similarly, in the absence of neuroimaging features, a VCI diagnosis is unlikely, unless the clinical features strongly suggest it. (Note that this proposal to allow a diagnosis of mixed dementia by either clinical or neuroimaging features is in keeping with other recommendations [59,60]). By contrast, clinical evidence of executive dysfunction seems to be a feature of dementia in general, and not specifically of VCI. The CIVIC data therefore suggest both that clinicians combine a probabilistic reckoning of risk factor, clinical, and imaging features to make a VCI diagnosis, and that such an approach identifies patients with recognizable characteristics and with distinct outcomes. The CIVIC data are therefore poised to contribute to the review of VaD criteria now under way in many quarters.

Acknowledgements

The CIVIC study was funded by grants from the Medical Research Council of Canada through the PMAC/MRC program, with support from Hoechst Marion Roussel Canada, and by the Alzheimer Society of Canada. Additional funding for these analyses came from the Canadian Institutes of Health Research (CIHR) grant number MOP 62823 and from the Alzheimer Society of Canada 09-00.

Kenneth Rockwood and Chris MacKnight receive support from the CIHR through Investigator and New Investigator awards, respectively. Kenneth Rockwood is also supported by

the Dalhousie Medical Research Foundation as Kathryn Allen Weldon Professor of Alzheimer Research. David Hogan receives career support as the Brenda Strafford Foundation Chair in Geriatric Medicine at the University of Calgary.

Author contributions: Kenneth Rockwood designed the study, and co-supervised national data collection with Howard Feldman. Kenneth Rockwood and Paige King wrote the original draft. Xiaowei Song carried out the analyses. Each of the other authors contributed patients, supervised all aspects of local data collection and read and approved the final draft.

References

[1] Gorelick PB, William M. Feinberg lecture: cognitive vitality and the role of stroke and cardiovascular disease risk factors. Stroke 2005;36:875–9.
[2] Bowler JV. Vascular cognitive impairment. J Neurol Neurosurg Psychiatry 2005;76(Suppl 5):v35–44.
[3] Pantoni L, Sarti C, Alafuzoff I, Jellinger K, Munoz DG, Ogata J, et al. Postmortem examination of vascular lesions in cognitive impairment: a survey among neuropathological services. Stroke 2006;37:1005–9.
[4] Hachinski V. Vascular dementia: a radical redefinition. Dementia 1994;5:130–2.
[5] Rockwood K, Bowler J, Erkinjuntti T, Hachinski V, Wallin A. Subtypes of vascular dementia. Alzheimer Dis Assoc Disord 1999;13(Suppl 3): S59–65.
[6] Rockwood K, Davis H, MacKnight C, Vandorpe R, Gauthier S, Guzman A, et al. The Consortium to Investigate Vascular Impairment of Cognition: methods and first findings. Can J Neurol Sci 2003;30:237–43.
[7] Rockwood K, Black SE, Song X, Hogan DB, Gauthier S, MacKnight C, et al. Clinical and radiographic subtypes of vascular cognitive impairment in a clinic- based cohort study. J Neurol Sci 2006;240(1–2):7–14.
[8] Erkinjuntti T, Roman G, Gauthier S, Feldman H, Rockwood K. Emerging therapies for vascular dementia and vascular cognitive impairment. Stroke 2004;35(4):1010–7.
[9] Desmond DW. The neuropsychology of vascular cognitive impairment: is there a specific cognitive deficit? J Neurol Sci 2004;226:3–7.
[10] Craig D, Birks J. Galantamine for vascular cognitive impairment. Cochrane Database Syst Rev 2006;1: (CD004746).
[11] Craig D, Birks J. Rivastigmine for vascular cognitive impairment. Cochrane 2005;2: (CD004744).
[12] Malouf R, Birks J. Donepezil for vascular cognitive impairment. Cochrane Database Syst Rev 2004;1: (CD004395).
[13] Schmidtke K, Hull M. Cerebral small vessel disease: how does it progress? J Neurol Sci 2005;229–230:13–20.
[14] McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev 2006;2: (CD003154).
[15] Leblanc GG, Meschia JF, Stuss DT, Hachinski V. Genetics of vascular cognitive impairment: the opportunity and the challenges. Stroke 2006;37(1):248–55.
[16] O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. Lancet Neurol 2003;2(2):89–98.
[17] Roman GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, Lopez-Pousa S, et al. Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. J Neurol Sci 2004;226(1–2):81–7.
[18] Ingles JL, Wentzel C, Fisk JD, Rockwood K. Neuropsychological predictors of incident dementia in patients with vascular cognitive impairment, without dementia. Stroke 2002;33(8):1999–2002.
[19] Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular cognitive impairment investigators of the Canadian study on health and aging. Neurology 2000;54:447–51.
[20] Galluzzi S, Sheu CF, Zanetti O, Frisoni GB. Distinctive clinical features of mild cognitive impairment with subcortical cerebrovascular disease. Dement Geriatr 2005;19(4):196–203.
[21] Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, Berman K, et al. Clinical determinants of dementia and mild cognitive impairment following ischaemic stroke: the Sydney stroke study. Dement Geriatr Cogn Disord 2006;21(5–6):275–83.
[22] Ballard C, O'Brien J, Morris CM, Barber R, Swann A, Neill D, et al. The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2001;16:499–503.
[23] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.
[24] American Psychiatric Association. Diagnostic and Statistical manual. 3rd ed., revised. Washington, D.C.: APA; 1987.
[25] Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, et al. Cerebral blood flow in dementia. Arch Neurol 1975;32:632–7.
[26] Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. Neurology 1993;43:650–60.
[27] Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the state of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42:473–80.
[28] World Health Organization International Classification of Diseases. The ICD-10 Classification of Mental and Behavioural Disorders: clinical descriptors and diagnostic guidelines. 10th ed. Geneva: WHO; 1992.
[29] Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. Am J Occup Ther 1999;53:471–81.
[30] Folstein MF, Folstein SE, McHugh PR. The Folstein Mini-Mental State Examination: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[31] Reisberg B. Functional Assessment Staging (FAST). Psychopharmacol Bull 1988;24:653–9.
[32] Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139(9):1136–9.
[33] Feldman H, Schulzer M, Wang S, Tuokko H, Beattie BL. The Functional Rating Scale in Alzheimer's disease assessment: a longitudinal study. In: Iqbal K, Mortimer JA, Winblad B, Wisniewski HM, editors. Research Advances in Alzheimer's Disease and Related Disorders Chichester. UK: Wiley; 1995. p. 235–41.
[34] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology Nov 1993;43(11):2412–4.
[35] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey MB, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiat Res 1983;17:37–49.
[36] Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. J Am Geriatr Soc 1993;41:38–41.
[37] Rockwood K, McDowell I, Wolfson C, editors. Canadian Study of Health and Aging. Technical papers. Int Psychogeriatr, vol. 13; 2001. p. 1–237. Suppl1.
[38] Feldman H, Levy AR, Hsiung GY, Peters KR, Donald A, Black SE, et al. A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. Neuroepidemiology 2003;22:265–74.
[39] Wentzel C, Darvesh S, MacKnight C, Shea C, Rockwood K. Inter-rater reliability of the diagnosis of vascular cognitive impairment at a memory clinic. Neuroepidemiology 2000;19:186–93.

[40] Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychol Med 1994;24:145–53.
[41] Stewart M, McDowell I, Hill G, Aylesworth R. Estimating antemortem cognitive status of deceased subjects in a longitudinal study of dementia. Int Psychogeriatr 2001;13(Supp1):99–106.
[42] Ebly EM, Hogan DB, Parhad IM. Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. Arch Neurol 1995;52:612–9.
[43] Cohen J. Statistical power analysis of the behavioural sciences. 2nd Ed. New York; 1988.
[44] Roman GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. Dement Geriatr Cogn Disord 2005;20:338–44.
[45] Pantoni L. Treatment of vascular dementia: evidence from trials with non-cholinergic drugs. J Neurol Sci 2004;226(1–2):67–70.
[46] Lind K, Edman A, Karlsson I, Sjogren M, Wallin A. Relationship between depressive symptomatology and the subcortical brain syndrome in dementia. Int J Geriatr Psychiatry 2002;17:774–8.
[47] Frisoni GB, Galluzzi S, Bresciani L, Zanetti O, Geroldi C. Mild cognitive impairment with subcortical vascular features: clinical characteristics and outcome. J Neurol 2002;249(10):1423–32.
[48] Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz L, Looi JC, Wen W, et al. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. Neurology 2004;62(6):912–9.
[49] Garrett KD, Browndyke JN, Whelihan W, Paul RH, DiCarlo M, Moser DJ, et al. The neuropsychological profile of vascular cognitive impairment-no dementia: comparisons to patients at risk for cerebrovascular disease and vascular dementia. Arch Clin Neuropsychol 2004;19:745–57.
[50] Nyenhuis DL, Gorelick PB, Geenen EJ, Smith CA, Gencheva E, Freels S, et al. The pattern of neuropsychological deficits in Vascular Cognitive Impairment-No Dementia (Vascular CIND). Clin Neuropsychol 2004;18:41–9.
[51] Nordahl CW, Ranganath C, Yonelinas AP, DeCarli C, Reed BR, Jagust WJ. Different mechanisms of episodic memory failure in mild cognitive impairment. Neuropsychologia 2005;43:1688–97.
[52] Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. J Neurol Neurosurg Psychiatry 2004;75:61–71.
[53] Royall DR, Palmer R, Chiodo LK, Polk MJ. Executive control mediates memory's association with change in instrumental activities of daily living: the Freedom House Study. J Am Geriatr Soc 2005;53:11–7.
[54] Voss SE, Bullock RA. Executive function: the core feature of dementia? Dement Geriatr Cogn Disord 2004;18:207–16.
[55] Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915–22.
[56] Alexopoulos GS. "The depression-executive dysfunction syndrome of late life": a specific target for D3 agonists? Am J Geriatr Psychiatry 2001;9:22–9.
[57] Song X, Mitnitski A, Rockwood K. Index variables for studying outcomes in vascular cognitive impairment. Neuroepidemiology 2005;25:196–204.
[58] King P, Song X, Rockwood K. Cognitive impairment of acute onset in the consortium to investigate vascular impairment of cognition (CIVIC) study: Occurrence, correlates and outcomes. Am J Geriatr Psychiatry 2006;14:893–6.
[59] Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA 2004;292:2901–8.
[60] O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry 2006;14:724–33.