Preclinical Vascular Cognitive Impairment and Alzheimer Disease
Neuropsychological Test Performance 5 Years Before Diagnosis

Janet L. Ingles, PhD; Denise C. Boulton, MSc; John D. Fisk, PhD; Kenneth Rockwood, MD

Background and Purpose—Neuropsychological changes that precede a diagnosis of vascular cognitive impairment (VCI) and the differences between preclinical VCI and Alzheimer disease (AD) are not well understood. We compared the neuropsychological performances of people with incident VCI, incident AD, and no cognitive impairment (NCI) 5 years before their clinical diagnoses.

Methods—The Canadian Study of Health and Aging is a prospective, cohort study of 10,263 randomly selected persons age 65 years or older. We studied 332 individuals who had completed a battery of neuropsychological tests and were diagnosed with NCI at baseline. After 5 years, 41 were diagnosed with VCI, 25 with AD, and 266 with NCI.

Results—At baseline, the incident-VCI group performed worse on a wide range of neuropsychological tests compared with the NCI group. A test of abstract reasoning was selectively low in the incident-VCI group, relative to both the incident-AD and NCI groups. The incident-AD group performed worse at baseline on memory tests compared with incident-VCI and NCI groups.

Conclusions—This study suggests a preclinical phase may exist in VCI that differs from that in AD. Neuropsychological measures may aid the design of preventive strategies for VCI. (Stroke. 2007;38:1148-1153.)

Key Words: Alzheimer disease ■ cerebrovascular disorders ■ dementia ■ neuropsychology

Vascular dementia (VaD) and Alzheimer disease (AD) are the 2 most prevalent forms of dementia. Knowing prodromal features for each is important for the design of preventive strategies. Neuropsychological deficits, particularly memory problems, precede, often by many years, the diagnosis of AD. However, the cognitive changes that may precede VaD and the differences between preclinical VaD and AD have been less well studied.

Previously, we found that among elderly people who had vascular cognitive impairment (VCI) who did not meet dementia criteria (ie, vascular cognitive impairment, no dementia [VCI-ND]), low scores on tests of memory and semantic category fluency predicted incident cases of dementia 5 years later. Most of these incident cases had VaD. Other groups have also shown that reductions in memory, as part of a more global pattern of impairment, precede diagnoses of both VaD and AD by up to 4 years. Although few differences in the preclinical cognitive profiles of these 2 conditions have been observed, Jones et al found that semantic category fluency was more impaired in preclinical AD, whereas deficits in letter category fluency were present in both preclinical AD and VaD.

Still, findings of preclinical memory deficits common to both VaD and AD might simply reflect that dementia diagnoses traditionally require deficits in memory. People with preclinical cognitive impairment due to cerebrovascular disease that progresses, eg, in the domain of executive functioning, and that causes significant functional impairment even without the memory loss typical of AD have not been included in these investigations. The term VCI incorporates VaD and AD with a vascular component (referred to as mixed AD/VCI), as well as VCI-ND. The advantage of VCI as an outcome not restricted to the requirements of VaD is that it allows for inclusion of people who develop cognitive impairment that does not meet the criteria for dementia and who nevertheless have increased risks of institutionalization and death. In this secondary analysis of data from the Canadian Study of Health and Aging (CSHA), we compared the neuropsychological performances of people with incident VCI, incident AD, and no cognitive impairment (NCI) 5 years before their clinical diagnoses.

Subjects and Methods
The CSHA is a prospective, cohort study of 10,263 randomly selected, community-dwelling (n=9008) and institution-dwelling (n=1255) persons age 65 years and older. In 1991 to 1992 (CSHA-1), all institutionalized and community participants who scored <78 of 100 on the Modified Mini-Mental State Examination...
The neuropsychological test battery assessed constructs described in the DSM-III-R criteria for dementia, as detailed elsewhere. Short- and long-term memory was assessed with Buschke’s Cued Recall Test, the Rey Auditory Verbal Learning Test, the Benton Visual Retention Test, and the Information and Digit Span substests of the Wechsler Memory Scale. Abstract thinking was assessed with the Wechsler Adult Intelligence Scale, Revised (WAIS-R) Similarities subtest. Judgment was assessed with the WAIS-R Comprehension subtest. Other higher cortical functions were assessed with the Token Test, the Controlled Oral Word Association Test (ie, letter category fluency), Animal Naming (ie, semantic category fluency), visual identification of items, and subtest (ie, VaD, VCI-ND, and mixed AD/VCI). The construct was diagnosed by a staged process. In 1995 to 1996 (CSHA-2), follow-up data were collected and surviving participants were reassessed. The clinical assessment procedure was the same as in CSHA-1. All participants provided written, informed consent, and the protocol was approved at each participating institution. Separate approval for secondary analyses was also obtained from the research ethics committee of Capital Health, Halifax, Nova Scotia.

Participants in both CSHA-1 and CSHA-2 were diagnosed by the same criteria at a consensus conference of the examining physician, neuropsychologist, and nurse. From a Dementia diagnosis, etiologic diagnoses were based on NINCDS-ADRDA criteria for AD and ICD-10 criteria for VaD. A diagnosis of cognitive impairment but no dementia (CIND) was made if they had cognitive impairment that did not meet the DSM-III-R criteria for dementia (ie, they did not have both memory impairment and other cognitive impairment that caused functional deficits). Participants who did not meet the criteria for dementia or CIND were classified as having NCI. In CSHA-2, VCI was diagnosed by a staged process. A checklist that comprised every criterion from each set of VaD criteria then in use was completed. These criteria did not include the presence of vascular risk factors but required clinical signs of vascular involvement (eg, onset after stroke, stepwise progression, focal cognitive deficits, focal neurologic findings, or neuroimaging data when available). From this information, VCI was diagnosed and subtyped (ie, VaD, VCI-ND, and mixed AD/VCI). The construct and predictive validity of this subtype classification scheme was subsequently demonstrated in a clinic-based cohort study with the use of clinical features, neuropsychometric, and outcome data (ie, time to death and institutionalization).

Of the 1879 participants who completed the neuropsychological assessment at CSHA-1, 786 were classified as NCI. Four hundred fifty-five of these individuals were alive and participated in the CSHA-2 assessment process. Of these 455 individuals, 266 were diagnosed with NCI, 25 with probable AD, and 41 with VCI (13 with VaD, 18 with VCI-ND, and 10 with mixed AD/VCI). An additional 123 subjects had diagnoses that were not of interest in the current study. Thus, a total of 332 participants constituted our sample.

We examined differences in baseline neuropsychological test scores between the incident-VCI, incident-AD, and NCI groups by ANCOVAs with age, years of education, and 3MS test scores (as a baseline measure of severity of cognitive impairment) as covariates. To facilitate comparisons between the neuropsychological variables, raw scores were transformed into Z scores. Bonferroni post hoc tests adjusted for multiple between-group comparisons were used to compare the specific groups. We examined the ability of the neuropsychological variables to predict outcomes by conducting 3 sets of logistic-regression analyses (ie, incident VCI vs NCI; incident AD vs NCI; incident VCI vs incident AD), with age, sex, years of education, and baseline 3MS test scores as covariates.

### Results

The NCI group was younger than the incident-VCI (P<0.02) and incident-AD groups (P<0.001), although the latter 2 groups did not differ significantly in age (P>0.2, Table 1). The NCI group had more years of education than the incident-AD group (P<0.03) but did not differ from the incident-VCI group (P>0.1); the incident-VCI and AD groups did not differ in education (P>0.5). The NCI and incident-VCI groups had higher baseline 3MS scores than the incident-AD group (P<0.01 for both comparisons), although the scores of the NCI and incident-VCI groups did not differ significantly (P>0.08). There were no significant group differences in sex or residence distributions (P>0.1 for all comparisons).

At baseline, those with incident VCI performed worse than those with incident AD and NCI on the WAIS-R Similarities subtest (Table 2). The incident-VCI group also performed worse than the NCI group on the semantic category fluency test and the WAIS-R Digit Symbol and Block Design subtests. The incident-AD group performed worse than the incident-VCI group on the Cued Recall measure of Buschke’s Cued Recall Test (ie, total words recalled on cued recall trials/total number of cues provided) and worse than both the incident-VCI and NCI groups on the Wechsler Memory Scale Information subtest. Both the incident-AD and incident-VCI groups performed worse than the NCI group on the Free Recall measure of Buschke’s Cued Recall Test but did not differ significantly from each other. No significant baseline differences were found between the 3 groups on the remaining tests.

The baseline analyses were repeated after excluding those with a diagnosis of mixed AD/VCI (n=10) from the incident-VCI group. The pattern of results was the same, with the exception that the NCI versus VCI comparison was statistically significant for letter category fluency (P=0.05) but did not reach significance for the WAIS-R Block Design subtest (P=0.08).

Table 3 presents the neuropsychological tests that contributed independently to the logistic-regression analyses. For incident VCI versus NCI, low baseline scores on the Free Recall measure of Buschke’s Cued Recall Test; the WAIS-R Similarities, Comprehension, Digit Symbol, and Block Design subtests; and the letter and semantic fluency tests were associated with incident VCI. For incident AD versus NCI, low baseline scores on the Free and Cued Recall measures of dementia.

### Table 1. Demographic Characteristics of the 3 Groups at CSHA-1

<table>
<thead>
<tr>
<th></th>
<th>Incident VCI (n=41)</th>
<th>Incident AD (n=25)</th>
<th>NCI (n=266)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>79.2 (6.4)</td>
<td>81.8 (5.0)</td>
<td>76.3 (6.1)</td>
</tr>
<tr>
<td>% Female</td>
<td>56.0</td>
<td>76.0</td>
<td>61.3</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>9.2 (3.7)</td>
<td>8.2 (3.1)</td>
<td>10.4 (4.1)</td>
</tr>
<tr>
<td>% Institutionalized</td>
<td>17.1</td>
<td>16.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Mean 3MS Score (SD)</td>
<td>86.4 (7.3)</td>
<td>80.3 (10.6)</td>
<td>89.2 (7.9)</td>
</tr>
</tbody>
</table>

AD = AD; VCI = VCI; AD/VCI = mixed AD/VCI; NCI = NCI; 3MS = 3-Minute Summary Test; WAIS-R = Wechsler Adult Intelligence Scale, Revised; CSHA = Canadian Study of Health and Aging.
Buschke’s Cued Recall Test, the Rey Auditory Verbal Learning Test, the Wechsler Memory Scale Information subtest, letter category fluency, and the WAIS-R Digit Symbol subtest were associated with incident AD. For incident VCI versus incident AD, there was a trend toward an association between low baseline scores on the WAIS-R Similarities subtest and incident VCI, although this did not reach statistical significance ($P < 0.058$).

**Discussion**

In this population-based study, individuals with NCI who progressed to VCI after 5 years performed worse at baseline on a number of neuropsychological tests (ie, Free Recall measure of Buschke’s Cued Recall Test; WAIS-R Similarities, Block Design, and Digit Symbol subtests; and semantic category fluency) relative to those who remained cognitively unimpaired. Each of these neuropsychological variables, as well as the WAIS-R Comprehension subtest and letter category fluency, also contributed to a predictive model for VCI. Those who progressed to AD performed worse at baseline on tests of memory (ie, Free Recall measure of Buschke’s Cued Recall Test and Wechsler Memory Scale Information subtest) relative to those who remained cognitively unimpaired. Additional memory tests (ie, Cued Recall measure of Buschke’s Cued Recall Test and Rey Auditory Verbal Learning Test) and tests of executive abilities (ie, letter category fluency and WAIS-R Digit Symbol subtest) contributed to the predictive model for AD. At baseline, tests of memory (ie, Cued Recall measure of Buschke’s Cued Recall Test and Wechsler Memory Scale Information subtest) were selectively low in the incident-AD group relative to the incident-VCI group. Only a test of abstract reasoning, the WAIS-R Similarities subtest, was selectively low at baseline in the incident-VCI group relative to the incident-AD group. This test was also the only 1 included in a predictive model distinguishing incident-VCI and incident-AD groups.

The results suggest the existence of a preclinical phase of VCI during which widespread but subtle reductions in cognitive ability may be detected some years before a clinical diagnosis can be rendered. Our findings extend those of
previous studies that have shown a relatively global pattern of cognitive decline in preclinical VaD by demonstrating similarly widespread lowering of cognitive test performance in preclinical VCI, a diagnosis that does not require clinical evidence of memory deficits. Using this broader diagnosis may have facilitated our identification of different patterns of neuropsychological performance in preclinical VCI and AD. In those studies that have found preclinical cognitive performance to be similar in VaD and AD, it must be acknowledged that the diagnostic outcomes are also similar (ie, both VaD and AD require memory deficits). Although we did not replicate the findings of Jones et al of poorer semantic category fluency in preclinical AD relative to preclinical VaD, we note that VCI is a heterogeneous condition and that different forms may well present with different prodromal cognitive profiles. For example, people with VaD who have significant subcortical pathology may be more impaired on tests of executive functioning and visual construction, whereas those with little subcortical pathology may be more impaired on tests of language and memory. Our findings are also consistent with the frequently reported executive dysfunction (including reduced abstract reasoning) of VaD compared with the memory impairment that characterizes AD. We show that this differential pattern of cognitive performance may be evident in a population-based sample even 5 years before a clinical diagnosis is evident. Therefore, measuring such neuropsychological variables might aid the design of preventive strategies for both VCI and AD through appropriate selection of people at risk in the population.

Neuropsychological test performance in relation to VCI has been investigated in the CSHA before. The importance of memory and semantic fluency test performance for predicting risk of progression to dementia (VaD and AD combined) in patients with VCI-ND has been demonstrated. Similarly, Klages et al evaluated apolipoprotein E genotype, memory test performance, and other clinical variables in a subsample of the 332 studied here. They found that apolipoprotein E status was no longer predictive of VCI or AD once memory test performance was taken into account and that free recall was an important predictor of both VCI and AD, as in the current results. Owing to their more limited sample size, however, they did not attempt to examine potential differences in neuropsychological risk factors for VCI and AD.

All of our participants were classified by clinical consensus at baseline as having NCI. Although people who later progressed to VCI and AD performed worse on a number of neuropsychological tests relative to those who maintained their NCI diagnosis, these reductions were subtle and fell <1SD below the performance of the NCI group. We have therefore referred to our participants who later progressed to VCI and AD as being in “preclinical” phases at baseline. It could be argued, however, that our terminology is inconsistent with a prime tenet of the VCI concept: ie, that VCI includes people with wide-ranging levels of cognitive ability, from the “brain-at-risk” stage in which patients have “no frank cognitive deficit,” to severe VaD. Thus, the relatively lower levels of neuropsychological test performance in our incident-VCI group may indicate that these participants in fact had VCI at baseline, albeit at an early stage. Establishing when the “preclinical” phase of a disorder ends and the actual disorder begins is a difficult task. This is particularly true for

### TABLE 3. Results of Logistic-Regression Analyses Predicting Diagnostic Category at CSHA-2

<table>
<thead>
<tr>
<th>Incident VCI vs NCI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buschke’s Cued Recall Test: Free Recall Total</td>
<td>3.11</td>
<td>1.99-4.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WAIS-R Similarities</td>
<td>2.04</td>
<td>1.32-3.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WAIS-R Comprehension</td>
<td>1.55</td>
<td>1.01-2.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Letter Category Fluency</td>
<td>1.84</td>
<td>1.11-3.05</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Semantic Category Fluency</td>
<td>2.14</td>
<td>1.34-3.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WAIS-R Digit Symbol</td>
<td>2.54</td>
<td>1.41-4.59</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>WAIS-R Block Design</td>
<td>1.92</td>
<td>1.26-2.94</td>
<td>&lt;0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident AD vs NCI</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buschke’s Cued Recall Test: Cued Recall Measure</td>
<td>3.24</td>
<td>1.81-5.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Buschke’s Cued Recall Test: Total Trials 1–5</td>
<td>3.02</td>
<td>1.41-6.50</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test: Information Subtest</td>
<td>1.67</td>
<td>1.10-2.53</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Letter Category Fluency</td>
<td>2.20</td>
<td>1.03-4.70</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>WAIS-R Digit Symbol</td>
<td>2.85</td>
<td>1.21-6.71</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Incident VCI vs Incident AD</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>WAIS-R Similarities</td>
<td>2.41</td>
<td>0.97-5.98</td>
<td>&lt;0.06</td>
</tr>
</tbody>
</table>

All analyses were adjusted for baseline age, sex, years of education, and 3MS scores.

*Low test scores were associated with incident VCI.
†Low test scores were associated with incident AD.
‡Low test scores were associated with incident VCI.
neuropsychological tests in which a wide range of scores can be generated by individuals who are, and will remain, cognitively healthy. Identification of cognitive measures that are specific and sensitive to the progression of deficits in VCI will be a challenge for future research.

Our results must be interpreted with caution, given the relatively small number of cases in the incident-VCI and -AD groups. Because of sample size limitations, neuropsychological predictors of the different VCI subgroups (ie, VaD, VCI-ND, and mixed AD/VCI) could not be evaluated. Additional differences between the predictors of VCI and AD might also have been detected with a larger sample. Limited sample size also prevented us from using the CSHA-2 neuropsychological data as a baseline in an attempt to replicate our findings by using the third phase of the CSHA (conducted in 2001 to 2002) to identify incident cases (14 subjects with incident AD, 18 with incident VCI, and 29 with NCI). Similarly, we were unable to examine neuropsychological predictors 10 years before diagnosis by using CSHA-1 as the baseline and CSHA-3 as the follow-up (6 subjects with incident AD, 8 with incident VCI, and 11 with NCI).

The lack of neuroimaging data is an additional weakness of our study and prevented further subtyping of the VCI cases. Different subtypes of VCI may well present with different clinical courses. For example, subcortical small-vessel dementia appears to have an insidious onset and an extended prodromal period, in contrast to the abrupt onset of the multi-infarct, strategic infarct, and intracranial hemorrhage subtypes of VCI. The clinical course of mixed AD/VCI may be more similar to that of AD and may be characterized by progressive memory impairment in addition to executive dysfunction. Although the pattern of baseline neuropsychological results changed little when the mixed AD/VCI cases were excluded from our incident-VCI group, as noted earlier, sample size limitations meant that we were unable to examine VCI subgroups in detail. Mixed AD/VCI cases in which the vascular component was present only on neuroimaging would also have been missed in our study. However, the effect of this is conservative: ie, it would have made our AD cases look more like VCI cases, a factor that might account for some of the negative findings. On the other hand, this should also make the finding of poor abstract reasoning in preclinical VCI robust.

We note, too, that although the CSHA battery included tests of abstract thinking, judgment, verbal fluency, and psychomotor speed, other classic measures of executive functions (eg, Trail Making, Card Sorting), were not included. Given the predominance of executive dysfunction in VCI, additional differences between the neuropsychological profiles of preclinical VCI and AD may have been detected with better measurement of this domain. In addition, the 3MS screening tool is a relatively weak measure of executive function, and some incident VCI cases may have been excluded from the baseline neuropsychological assessment by virtue of having been screened negative. Comprehensive assessment of executive function in preclinical VCI and AD will be particularly important in future population-based and clinic-based studies because of the strong association between executive dysfunction and functional outcomes in dementia. Replication of our findings, especially in studies with routine baseline and follow-up that combines neuropsychological and neuroimaging studies, could help identify groups of individuals to whom preventive maneuvers might be targeted.

Acknowledgments
The data reported in this article were collected as part of the Canadian Study of Health and Aging. The study was coordinated through the University of Ottawa and the federal government’s Laboratory Centre for Disease Control. K.R. and J.F. were funded by an operating grant from the Canadian Institutes of Health Research.

Source of Funding
This was funded by the Seniors’ Independence Research Program, administered by the National Health Research and Development Program of Health and Welfare Canada (project No. 6606-3954-MC [S]).

Disclosures
None.

References
Preclinical Vascular Cognitive Impairment and Alzheimer Disease: Neuropsychological Test Performance 5 Years Before Diagnosis
Janet L. Ingles, Denise C. Boulton, John D. Fisk and Kenneth Rockwood

*Stroke*. 2007;38:1148-1153; originally published online February 22, 2007;
doi: 10.1161/01.STR.0000259716.04739.60
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/4/1148

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/