Long-Term Cognitive Transitions, Rates of Cognitive Change, and Predictors of Incident Dementia in a Population-Based First-Ever Stroke Cohort

Velandai K. Srikanth, PhD; Stephen J. Quinn, PhD; Geoffrey A. Donnan, MD; Michael M. Saling, PhD; Amanda G. Thrift, PhD

Background and Purpose—There are few data on long-term cognitive outcomes after first-ever stroke. We aimed to study long-term cognitive transitions, rates of cognitive change, and factors associated with incident dementia and cognitive impairment—no dementia (CIND) 2 years after first-ever stroke.

Methods—A population-based cohort of incident first-ever stroke cases (n=99; mean age, 69.9 years) and an age- and sex-matched comparison group (nonstrokes, n=99) were followed up for 2 years by 3 serial examinations. Rates of cognitive change were compared by repeated-measures analyses. Factors associated with incident dementia and CIND at 2 years were determined by multinomial logistic regression.

Results—Significant stroke \times time interactions were present for all cognitive domains, with stroke cases showing a greater rate of decline compared with nonstrokes. Stroke recurrence during follow-up was responsible for significantly greater global decline. Strokes with recurrence (P=0.02), age (P=0.004), and baseline cognitive impairment (P<0.001) were independently associated with incident dementia at 2 years. Strokes without recurrence (P=0.008), age (P=0.001), and baseline cognitive impairment (P<0.001) were independently associated with CIND at 2 years.

Conclusions—Recurrent stroke contributes importantly to global cognitive decline after a first-ever stroke. Secondary stroke prevention will be important in ameliorating dementia related to stroke. Mechanisms underlying the progression of early cognitive impairment to dementia in stroke patients need further investigation. (Stroke. 2006;37:2479-2483.)

Key Words: aging • dementia • epidemiology • stroke • vascular cognitive impairment

Stroke and dementia are major public health problems affecting older people. There are few prospective data, and none from population-based studies, on long-term cognitive changes and predictors of incident dementia after a first stroke. It is also uncertain whether early poststroke cognitive status is associated with a high risk of future incident dementia. The study of these issues may help to understand mechanisms underlying stroke-related cognitive decline and assist in planning interventions to prevent dementia related to stroke.

On the basis of 3 points of assessment over 2 years, we aimed to investigate (1) transitions in cognitive state; (2) rates of cognitive decline; and (3) factors associated with long-term cognitive outcome, in a population-based, first-ever stroke cohort.

Methods

Sampling
Sampling methods have been described in detail previously. In brief, a cohort of consecutive first-ever incident stroke cases (n=99) was assembled between April 1, 1998, and April 30, 1999, within the population-based North East Melbourne Stroke Incidence Study (NEMESIS). The standard World Health Organization definition of stroke was used. First-ever strokes were defined as events occurring in patients with no history of prior stroke. Other eligibility criteria were (1) availability at 3 months after stroke; (2) good spoken English; (3) absence of persistent moderate to severe dysphasia (a score ≤4 on the language component of the National Institutes of Health Stroke Scale [NIHSS]); and (4) adequate vision and hearing. The comparison group (nonstrokes, n=99) was obtained by the neighborhood contact method matched individually to the index cases for age (±5 years) and sex.

Follow-Up and Assessments
Stroke cases were followed up and interviewed at 3 months (baseline), 12 months (first-year follow-up), and 24 months (second-year follow-up) after stroke. Nonstrokes were interviewed at enrollment and at intervals of 9 and 21 months after enrollment to be comparable with stroke cases. Deaths were recorded and confirmed by checking against the national death index. An interval (recurrent) stroke event was diagnosed on the basis of a standard questionnaire supported by information from medical records.
Other information collected at study onset included demographic details, vascular risk history, medication use, neurological impairment (NIHSS), physical function (Barthel Index),11 preexisting cognitive decline (Informant Questionnaire for Cognitive Decline in Elderly [IQCODE]),12 and mood (Irritability, Depression, and Anxiety scale [IDA]).13 Cognitive function was assessed at the 3 interview times with a comprehensive battery6 (supplemental Table I, available online at http://stroke.ahajournals.org).

Cognitive Diagnoses
Cognitive diagnoses were assigned at each follow-up period by an expert panel consisting of 2 neuropsychologists and a geriatrician. All diagnoses were made blinded to stroke/nonstroke status and prior cognitive status. Scores of >1 SD below the age- and education-derived normative means on at least 2 tests measuring a cognitive domain indicated impairment in that domain. After the baseline interview, participants were classified as cognitively impaired or not impaired. Dementia was diagnosed after the first- and second-year follow-ups according to the Diagnostic and Statistical Manual of Mental Disorders criteria, fourth edition,14 based on a progressive decline in memory and at least 1 other cognitive domain from baseline. Cognitive impairment–no dementia (CIND) was diagnosed in the absence of dementia when there was cognitive impairment without clinically evident progression from the previous assessment.

Statistical Analyses
\( \chi^2 \) and \( t \) tests were used to check for differences in proportions and means of characteristics between the first-ever stroke and nonstroke groups.

Cognitive tests were grouped according to the following domains on the basis of a generally accepted classification,15 namely, spatial ability, memory, attention/perceptual speed, executive ability, and orientation/general knowledge (supplemental Table I). With scores from all 3 time points, principal-components analysis with varimax rotation was performed on these domain-specific test groups to generate single components for each domain. Each component accounted for at least 70% of the variance in the test groups, representing a "pure" summary construct of the particular domain (supplemental Table I). Standardized regression factor scores were then generated from these components by Thomson’s method.16 Random-effects repeated-measures analysis was used to examine the stroke×time interaction on these factor scores. In a second model, wherein stroke status was defined as single stroke, stroke with recurrence, and nonstroke, the effect of stroke with recurrence on the rate of decline was examined by estimating the recurrence×time interaction. Covariates used in all analysis were baseline age, sex, years of education, and baseline Mini-Mental Status Examination.

The analyses were repeated with multiple imputation to account for loss to follow-up.

Unadjusted relative risks (RRs) were calculated for incident dementia at the second-year follow-up (among those free of dementia at the first-year follow-up) based on the occurrence of recurrent stroke (with reference to nonstrokes) and also whether or not they had baseline cognitive impairment. Univariable and multivariable multinomial logistic regression was used to study associations between baseline clinical and demographic factors and incident dementia or CIND at the second-year follow-up. The effect of stroke was examined by level of exposure, namely, stroke with and without recurrence.

To assess the potential impact of losses to follow-up to these results, we undertook the same analyses but with imputed values for missing cases. First, multivariable models that included potentially confounding variables among completers were developed separately for stroke cases and nonstrokes. This enabled us to predict the probability of developing dementia, CIND, or normal cognition in those lost to follow-up (noncompleters). From this information, the numbers of cases of dementia and CIND in each group were recalculated after assuming that all participants had completed follow-up. Unadjusted RRs were then recalculated for the outcomes of dementia and CIND from this complete data set.

Ethics committees at each participating institution approved the study, and informed consent was obtained from each participant.

Results
Of the original sample, 79 (80%) stroke cases (mean age, 69.9 years; SD, 12.6 years) and 78 (79%) nonstrokes (mean age, 69.9 years; SD, 12.2 years) completed all 3 assessments. Stroke cases were followed up for a mean of 2.14 years (SD, 0.1 year) after stroke onset. The mean duration between the first and last interview was 667.5 days (SD, 31.9 days) for strokes and 654.5 days (SD, 20.9 days) for nonstrokes. Eleven interval stroke events occurred in the stroke group (3 before and 8 after the first-year follow-up) and 2 in the nonstroke group. Further demographic information and reasons for attrition are presented in supplemental Table II, available online at http://stroke.ahajournals.org.

In both groups, completers and noncompleters were similar with regard to age, sex, years of education, ever-smoker status, hypercholesterolemia, heart disease, diabetes mellitus, and baseline mood scores (supplemental Table II). Among stroke cases, completers were more likely to have a history of hypertension (\( P=0.04 \)) and less likely to be neurologically impaired (NIHSS, \( P=0.06 \)) or disabled (Barthel Index, \( P=0.04 \)) at study onset. Among nonstrokes, completers were less likely to have preexisting cognitive decline (IQCODE, \( P=0.04 \)) or neurological impairment (NIHSS, \( P=0.09 \)).

Transitions in Cognitive State
During the entire study period, dementia was diagnosed in 24 stroke cases and 22 nonstrokes (Table I). Of these, 13 stroke cases and 8 nonstrokes had developed a new (incident) dementia between the first-year and second-year follow-up interviews. CIND was diagnosed in 43 stroke cases and 26
nonstrokes during the entire study period. A new (incident) CIND was diagnosed in equal numbers of stroke cases and nonstrokes (n=10) between the first-year and second-year follow-up interviews. The majority of stroke cases (33/43, 77%) and nonstrokes (14/26, 54%) with CIND began with cognitive impairment at baseline. Among stroke cases and nonstrokes who were cognitively intact at baseline, similar proportions developed incident dementia (10.6% [5/47] and 4.7% [3/64], respectively, \(P=0.23\)) or CIND (17% [8/47] and 15.6% [10/64], respectively, \(P=0.84\)) between the first- and second-year follow-up. Among those who were cognitively impaired at baseline, similar proportions in the 2 groups developed incident dementia (15.4% [8/52] and 14.2% [5/35], respectively, \(P=0.88\)) between the first- and second-year follow-up. Fewer stroke cases than nonstrokes improved from being cognitively impaired at baseline to being unimpaired at 2 years (5.8% [3/52] and 17% [6/35], respectively, \(P=0.08\)).

Rates of Cognitive Change Over Time
In repeated-measures analysis, significant stroke×time interactions were present for all cognitive domains after adjusting for covariates (Table 2). Overall, stroke cases declined most in spatial ability (mean change in regression factor score, \(-0.36\) between baseline and second-year follow-up) and to a lesser extent in other domains (Table 2). Nonstrokes, in contrast, showed improved or stable performance in all domains. First-ever stroke patients without recurrence differed from nonstrokes mainly in the rate of change in spatial ability (decline) and attention/speed (lack of improvement) but showed similarly stable behavior in other domains (the Figure). Compared with nonstrokes and single strokes, those with stroke recurrence showed significantly greater rates of decline in memory (\(P=0.06\)), attention/speed (\(P<0.001\)), executive ability (\(P=0.03\)), orientation/general knowledge (\(P=0.009\)), and to a lesser extent in spatial ability (\(P=0.09\)) (the Figure). This was most evident between the first- and second-follow-ups (Table 2, the Figure). The results of these analyses were unchanged when repeated with multiple imputation to account for loss to follow-up (data not shown).

Risk and Predictors of Dementia and CIND at 2 Years After Stroke
Stroke cases who experienced a recurrent event during follow-up were at a high risk of developing incident dementia at the second-year follow-up (RR, 4.5; 95% CI, 1.9 to 10.6; \(P=0.003\)). No significant increase in risk was seen among stroke cases without recurrent stroke (RR, 1.7; 95% CI, 0.7 to 4.1; \(P=0.20\)). These results remained similar when all cases of dementia diagnosed during the study period were considered. Among those with baseline cognitive impairment, the risk of incident dementia at the second-year follow-up was significantly elevated for both stroke cases (RR, 10.4; 95% CI, 3.3 to 32.9; \(P<0.001\)) and nonstrokes (RR, 6.5; 95% CI, 1.8 to 23.1; \(P=0.002\)). However, the risk of incident dementia was not significantly elevated for stroke cases without baseline cognitive impairment (RR, 2.4; 95% CI, 0.6 to 9.2; \(P=0.20\)). All observed associations remained largely unchanged if one assumes complete follow-up and the use of predicted probabilities from multivariable regression (data not shown).

By univariable multinomial logistic regression, factors associated with incident dementia at second-year follow-up were stroke (\(P=0.04\)), age (\(P=0.001\)), years of education (\(P=0.02\)), baseline cognitive impairment (\(P<0.001\)), baseline NIHSS (\(P=0.004\)), and IDA scores (\(P=0.005\)). Stroke was significantly associated with dementia in the presence (\(P=0.01\)) but not in the absence (\(P=0.21\)) of recurrent stroke. Factors associated with CIND at second-year follow-up were stroke (\(P=0.004\)), age (\(P=0.001\)), baseline cognitive impair-
ment ($P<0.001$), baseline NIHSS ($P=0.006$), and IDA scores ($P=0.04$).

In multivariable analysis, stroke with recurrence ($P=0.02$), age ($P=0.004$), and baseline cognitive impairment ($P<0.001$) were independently associated with incident dementia at second-year follow-up (Table 3). When the presence/absence of CIND at first-year follow-up was added as a term in the model, the effect of baseline cognitive impairment on incident dementia was no longer statistically significant ($\beta=1.09$, $P=0.30$) with CIND at first-year follow-up, largely explaining its effect ($\beta=1.92$, $P=0.07$). Strokes without recurrence ($\beta=0.008$), age ($P=0.001$), and baseline cognitive impairment ($P<0.001$) were independently associated with CIND at second-year follow-up, with CIND at first-year follow-up completely explaining the effect of baseline cognitive impairment ($\beta=1.99$, $P=0.02$). No significant interactions were observed.

### Discussion

We found that stroke recurrence was associated with an increased rate of long-term global cognitive decline after a first-ever stroke. Stroke recurrence, early poststroke cognitive impairment, and increasing age were independently associated with diagnosis of new clinical dementia 2 years after a first-ever stroke. These are the first prospective data on long-term cognitive transitions in a population-based first-ever stroke cohort.

Although a single stroke was associated with reduced spatial ability, attention, and mental speed, stroke recurrence had a more global effect, suggesting a dose-response effect of stroke on cognitive decline. Similarly, in a previous study, recurrent stroke was found to be associated with a greater decline in the Mini-Mental Status Examination score between 2 time points.2 Our study had a longer follow-up period and 3 points of measurement, enabling us to show that the steeper rate of decline occurred between the first- and second-year follow-ups (Table 2 and the Figure), when the majority of recurrent strokes occurred. Our results, like those from previous hospital-based5 and pathological17,18 studies, emphasize the importance of multiple strokes in the pathogenesis of dementia. Similarly, results from the PROGRESS study19 showed that antihypertensive therapy was associated with a reduced incidence of dementia, mainly in those experiencing another stroke during follow-up. Furthermore, we found that the association of recurrent stroke with incident dementia was independent of baseline cognitive impairment. This leads one to speculate on possible mechanisms underlying this association. First, multiple strategic infarctions may be mimicking a dementia syndrome. Alternatively, the increased volume of brain injury may reduce the threshold for expression of subclinical neurodegenerative disease, this being more consistent with previous data.17,18 Aggressive stroke prevention may therefore play an important role in delaying clinical dementia and thus reducing the future burden of dementia related to stroke.

### Table 3. Predictors of Cognitive Outcome at the Second-Year Follow-Up: Multivariable Multinomial Logistic Regression (139 Stroke Cases and Nonstrokes)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dementia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke without recurrence</td>
<td>0.66</td>
<td>0.64</td>
<td>−0.58, 1.92</td>
<td>0.30</td>
</tr>
<tr>
<td>Stroke with recurrence</td>
<td>2.59</td>
<td>1.06</td>
<td>0.50, 4.68</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline cognition†</td>
<td>2.52</td>
<td>0.65</td>
<td>1.24, 3.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at stroke onset</td>
<td>0.09</td>
<td>0.03</td>
<td>0.03, 0.17</td>
<td>0.004</td>
</tr>
<tr>
<td>Constant</td>
<td>−9.68</td>
<td>2.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CIND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke without recurrence</td>
<td>1.26</td>
<td>0.47</td>
<td>0.32, 2.19</td>
<td>0.008</td>
</tr>
<tr>
<td>Stroke with recurrence</td>
<td>0.49</td>
<td>1.29</td>
<td>−2.05, 3.02</td>
<td>0.71</td>
</tr>
<tr>
<td>Baseline cognition†</td>
<td>1.83</td>
<td>0.51</td>
<td>0.83, 2.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at stroke onset</td>
<td>0.08</td>
<td>0.02</td>
<td>0.03, 0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>−7.07</td>
<td>1.76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Incident cases among those dementia-free at the first-year follow-up.
†Presence/absence of cognitive impairment at baseline (3 months after stroke and at enrollment for nonstrokes).
We found an increased risk of incident dementia at 2 years in stroke cases who were cognitively impaired at baseline but not in those who were cognitively normal. This suggests that the impact of a single stroke on dementia is unlikely to be a delayed phenomenon. It is possible that a single stroke, by virtue of its early cognitive effects, may lower the threshold for future clinical expression of preexisting neurodegenerative disease. Furthermore, in multivariable regression, the presence of CIND at 1 year largely explained the association between baseline cognitive impairment and dementia. Together with our previous finding that a single stroke was strongly associated with CIND at first follow-up, this provides evidence that the majority of those who were cognitively impaired at baseline progressed through the state of CIND to dementia. We speculate that CIND in stroke patients is likely to represent a mixture of the effects of cerebrovascular disease and neurodegenerative disease, but this requires further investigation.

Actual transitions in diagnostic state have been reported only in 2 hospital-based studies. In a Singapore sample, of patients with CIND at 6 months were cognitively intact at 1 year. High rates of improvement from CIND (44%) and dementia (19%) were also found at 2 years after stroke in a Spanish study. In contrast, cognitive improvement was not frequently observed in our stroke sample. Definitional differences may partly explain the varying results between these studies and ours. Our dementia criteria most likely identified people with an Alzheimer-type dementia, given the primacy of memory impairment and the requirement for progression. This therefore constrains the possibility of “recovery” from dementia. In addition, as acknowledged by the Spanish investigators, aphasic individuals may have been misclassified as cases of dementia, so improvements in language may have led to a perception of “recovery from dementia.” In contrast, we excluded people with significant aphasia, thus eliminating the possibility of misdiagnosis.

The strengths of our study include its prospective design, the population-based nature of the sample, an appropriately selected comparison group, the length of follow-up, and high follow-up rates. Importantly, the blinded procedures and nondependence on physical function for dementia diagnoses eliminated diagnostic bias as well as problems of circularity commonly associated with dementia criteria. Potential limitations include the possibility of bias because of the sampling of less severe stroke cases and loss to follow-up. Given the milder nature of the initial stroke sample, our results may also underestimate the overall risk of progression to dementia. However, it appears that even such less severe strokes contribute to progression to dementia and thus are not inconsequential.

Acknowledgments
The authors would like to thank the efforts of the research nurses and neuropsychologists toward data collection and Dr Leigh Blizzard and Prof David Hosmer for expert statistical advice. The authors would also like to acknowledge the Australian Institute of Health and Welfare for matching participants with the National Death Index.

Sources of Funding
Dr V. Srikanth was supported by a National Health and Medical Research Council postgraduate medical scholarship. The project was also supported by grants from the National Health and Medical Research Council, Austin Hospital Medical Research Foundation, Victorian Health Promotion Foundation, Foundation for High Blood Pressure Research, National Stroke Foundation, Parke-Davis Pfizer (Cardiovascular and Lipids research grant), and the Perpetual Trustees Ltd. The funding sources had no involvement in study design or the collection, analysis, and interpretation of the data.

Disclosures
None.

References
Long-Term Cognitive Transitions, Rates of Cognitive Change, and Predictors of Incident Dementia in a Population-Based First-Ever Stroke Cohort
Velandai K. Srikanth, Stephen J. Quinn, Geoffrey A. Donnan, Michael M. Saling and Amanda G. Thrift

Stroke. 2006;37:2479-2483; originally published online August 31, 2006; doi: 10.1161/01.STR.0000239666.46828.d7
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 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/37/10/2479

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/