Dementia After Stroke
The Framingham Study

Cristina S. Ivan, MD; Sudha Seshadri, MD; Alexa Beiser, PhD; Rhoda Au, PhD; Carlos S. Kase, MD; Margaret Kelly-Hayes, RN, EdD; Philip A. Wolf, MD

Background and Purpose—Identification of risk factors for dementia after stroke is best performed in comparison with stroke-free controls, because older subjects at high risk for stroke also have a substantial risk of dementia in the absence of stroke. Previous case-control studies were hospital-based. We used a nested case-control design to prospectively evaluate these risk factors in the community-based Framingham Study cohort.

Methods—We compared 212 subjects who were free of dementia in January 1982 and sustained a first stroke after this date, with 1060 age- and sex-matched, stroke- and dementia-free controls. We calculated 10-year risks of dementia (by Diagnostic and Statistical Manual of Mental Disorders, Volume IV criteria) developing in cases and controls and also estimated the hazard ratios within subgroups defined by exposure to various demographic factors (age, gender, education), stroke-related features (right or left hemisphere, stroke type, second stroke), stroke risk factors (hypertension, diabetes, atrial fibrillation, smoking) and apolipoprotein E genotype.

Results—Dementia developed in 19.3% of cases and 11.0% of controls. Baseline stroke doubled the risk of dementia (hazard ratio [HR]: 2.0; 95% confidence interval [CI]: 1.5 to 3.1) and adjustment for age, sex, education, and exposure to individual stroke risk factors did not diminish the risk (HR: 2.4; 95% CI: 1.6 to 3.7). The HR was higher in younger subjects (age younger than 80 years [HR: 2.6; 95% CI: 1.5 to 4.5]), apolipoprotein E 3/3 homozygotes (HR: 3.4; 95% CI: 2.0 to 5.8), and high school graduates (HR: 2.4; 95% CI: 1.5 to 3.9).

Conclusion—Stroke increases a subject’s risk of dementia as compared with age- and sex-matched controls. Primary and secondary prevention of stroke should significantly decrease the risk of all dementia. (Stroke. 2004;35:1264-1269.)

Key Words: dementia ▪ vascular diseases ▪ stroke ▪ epidemiology ▪ risk factors

More than 700 000 strokes occur each year in the United States.1 Dementia is a frequent outcome after stroke2–10 and increases the probability of long-term disability and mortality.11–14 Older adults (age older than 65 years) who are at greatest risk for stroke also have a high risk for dementia in the absence of stroke.15 It is unclear if the same factors that contribute to dementia risk in people without a previous stroke also operate to elevate risk of cognitive impairment in people with a stroke.

The incidence and determinants of vascular dementia (VaD) have been studied in a population-based cohort.6,16 However, most previous studies that directly compared subjects with and without a stroke used hospital-based cohorts.4,5,8,10,17–19 Two significant drawbacks to these studies are the potential for referral bias and the inability to reliably exclude preexisting dementia. The population-based Framingham cohort has been undergoing ongoing surveillance for incident stroke since 1950 and for incident dementia since 1975. Almost all subjects with incident stroke have undergone early and periodic neurological and neuropsychological evaluation. Furthermore, cardiovascular risk factor data, collected biennially, are available for all subjects. Hence, the Framingham cohort is well suited to prospectively investigate the frequency, pattern, and determinants of dementia after stroke and to compare this with risk factors for dementia in the absence of stroke.

Subjects and Methods
We used a nested case-control study design to investigate systematically participants from the Framingham Study Original cohort who were documented to be stroke- and dementia-free in January 1982 for development of dementia after their first or subsequent strokes. We compared their risk of dementia with that of age-matched and sex-matched dementia-free and stroke-free subjects selected as controls. This study design enabled direct comparison of the risk factors for dementia between subjects who had sustained a previous stroke and those who had not.

Subjects
The original cohort of the Framingham Study consisted of 5209 adults (2336 men) enrolled in 1948. Documentation of cognitive
status was initiated in 1975 (examination cycle 14) using a battery of neuropsychological tests and a dementia-free inception cohort was defined.23 A total of 3082 participants were alive on January 1, 1982 and of those, 2262 were enrolled in the dementia-free cohort and were also known to be stroke-free. Both cases and controls were drawn from this population.

Between January 1, 1982 and December 31, 2001 (a 20-year study period), 321 subjects had at least 1 stroke. We identified as “cases” 217 subjects who satisfied the following entry criteria: they sustained their first stroke before age 95 years, were dementia-free at the time, survived the stroke, and were available for evaluation 6 months after the index stroke. We excluded a total of 104 subjects: 9 had been diagnosed with dementia before their stroke, 61 died in the first month after the stroke, 28 did not have a follow-up cognitive examination at 6 months, and 6 were at least 95 years old at the time of their first stroke.

Each case was randomly assigned 5 age- and sex-matched controls who were required to be alive, stroke-free, and dementia-free, with at least 6 months of follow-up subsequent to the date of stroke in their assigned case. Age matching was performed to within 1 year. Five of the 217 cases could not be matched to the requisite 5 controls and were excluded. Thus our final study sample had 212 stroke cases (66% of the original 321) and 1060 controls. Study procedures were approved by the Institutional Review Board of Boston University and informed consent was obtained from all subjects.

Detection and Diagnosis of Dementia
Cases and controls were followed-up until dementia developed, until they died, or until their most recent evaluation within the study period (up to 10 years after the index stroke or December 2001, whichever came first). Since 1982, the Folstein Mini-Mental Status Examination (MMSE)20 has been administered at each biennial examination. Individuals who scored below an education-adjusted cutoff on the MMSE or had a decrease in MMSE score of ≥3 points were further evaluated by a neurologist and a neuropsychologist. The clinical diagnosis of dementia, type, and date of onset was then determined by a review panel. Framingham criteria for dementia conform to Diagnostic and Statistical Manual of Mental Disorders, Volume IV (DSM-IV) criteria, requiring impairment in memory and in at least 1 other area of cognitive function and documented functional disability.23 In addition, Framingham criteria require that dementia severity be ≥1 on the Clinical Dementia Rating Scale24 and that subjects have persistent cognitive impairment for a period of at least 6 months. Dementia type was categorized as probable vascular dementia (Alzheimer’s Disease Diagnostic and Treatment Centers criteria);23 probable Alzheimer dementia [AD] (National Institute of Neurological and Communicative Disorders [NINCDS] and Alzheimer’s Disease and Related Disorders Association [ADRDA] criteria);20 or as mixed dementia (combined VaD and AD). To diagnose dementia in testable aphasic patients, impairment in nonverbal memory was required.

Definition of Independent Variables
Age was dichotomized at younger than 80 years or 80 years and older and education status at the level of high school graduation. Stroke was defined as a focal neurological deficit of acute onset, persisting for >24 hours. Details of stroke surveillance and protocol for determining the final diagnosis, type, localization, and severity of stroke have been published elsewhere.26 An ischemic brain infarction was diagnosed if computed tomography or magnetic resonance imaging brain imaging showed no hemorrhage. It was classified as cardioembolic (CE) if a cardiac source of embolus was found. All other ischemic infarcts were classified as atherothrombotic brain infarcts (ABI). This category included large-artery infarcts, lacunar infarcts, and infarcts of unknown origin.

Data on cardiovascular risk factors have been collected prospectively at each biennial examination. We defined hypertension as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or being on antihypertensive medication. Diabetes mellitus was defined as recorded random blood glucose level ≥200 mg/dL (11.1 mmol/L), a previous diagnosis of diabetes mellitus, or the use of insulin or an oral hypoglycemic agent. Atrial fibrillation was diagnosed by a cardiologist who reviewed interim and examination electrocardiograms (EKG). Baseline cigarette smoking status was established by questions at each examination.

TABLE 1. Baseline Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Stroke Risk Factors</th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>82/212</td>
<td>39%</td>
<td>410/1060 39%</td>
</tr>
<tr>
<td>Age at entry (mean + SD)</td>
<td>79.2±6.6</td>
<td>78.5±6.7</td>
<td>Matched</td>
</tr>
<tr>
<td>High school graduate</td>
<td>131/203</td>
<td>65%</td>
<td>677/1036 65%</td>
</tr>
<tr>
<td>ApoE ε4 genotype</td>
<td>22/127</td>
<td>22%</td>
<td>153/694 17%</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>145/179</td>
<td>81%</td>
<td>671/925 73%</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>42/166</td>
<td>25%</td>
<td>109/840 13%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8/204 4%</td>
<td>28/1008 3%</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker</td>
<td>76/178</td>
<td>43%</td>
<td>397/910 44%</td>
</tr>
</tbody>
</table>

*Hypertension was defined as either SBP ≥140 mm Hg or DBP ≥90 mm Hg, or using antihypertensive medicines.
†Diabetes mellitus as a recorded random blood glucose level ≥200 mg/dL (11.1 mmol/L), a previous diagnosis of diabetes mellitus, or the use of insulin or a hypoglycemic agent.

Statistical Analyses
All statistical analyses were performed using SAS software (SAS Institute). We compared 10-year risks of dementia developing in cases and controls using Cox proportional hazards regression models, unadjusted, and after adjustment for various demographic factors (age, sex, education), stroke-related features (right and left hemisphere, stroke type, second stroke), stroke risk factors (hypertension, diabetes, atrial fibrillation, smoking) and apoE genotype. We also calculated HRs within subgroups defined by exposure to each of these risk factors.

Results
During the study period (1982 to 2001), stroke occurred in 321 subjects; 212 (61% women) met entry criteria. The mean age of subjects at initial stroke was 79.2 (SD 6.6) years; mean age for matched controls was 78.6 (SD 6.6) years. Among the 212 cases, 46 had a second stroke during the follow-up period (9 of the 46 had a third stroke, and 4 had a fourth stroke). Table 1 summarizes the baseline characteristics of cases and controls. As expected, cases were more likely to have hypertension and diabetes than control subjects.

During the 10-year follow-up period, dementia developed in 19.3% of the stroke cases (41/212) compared with 11.0% of matched controls (117/1060). Overall, the presence of baseline stroke doubled the risk of dementia (HR: 2.0; 95% CI: 1.4 to 2.9) after adjustment for age, sex, and educational status. Additional adjustment for apoE ε4 genotype status, stroke location, stroke type, presence of a second stroke, as well as individual stroke risk factors, did not appreciably alter the risk (Table 2). Subjects who had dementia after stroke were, as expected, most likely to have VaD, which was diagnosed in 51% (21 of 41 subjects), or a mixed VaD and AD, seen in 37% (15 of 41 subjects). Five subjects had other types of dementia. This was in contrast to controls, 79% of whom (92 of 117 subjects) had AD develop. Only 4% of controls (5 of 117 subjects) had VaD or mixed dementia diagnosed, and the remaining 17% (20 of 117) had other types of dementia. The clinical
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dementia was increased 4-fold in cases. However, in subjects who had 2 apoE alleles, the risk of dementia was similar in stroke cases and controls. This result was independent of age, sex, education, hemispheric location, and type of stroke. This doubling of the risk occurred uniformly over the entire 10-year study period (Figure). Our results are similar to those reported by Kokmen et al, who also observed a doubling of the overall risk. However, we did not observe the 9-fold increase in relative risk, which they reported in the first year after a stroke. One reason for our lower relative risk in the first year may be our rigorous exclusion of subjects with preexisting dementia (before stroke) based on an ongoing dementia screening process, rather than a medical records linkage system. Another reason may be our definition of dementia that required survival and ascertainment of cognitive status at 6 months after the index stroke, thus excluding subjects who died early or improved cognitively within this 6-month period.

Our results, based on a community-based cohort, were similar to the frequency of dementia after stroke reported in several small hospital-based cohorts with follow-up periods as short as 3 months. Desmond et al reported a slightly higher frequency of dementia after stroke (26.3% at 3 months after index stroke; HR: 3.8 compared with controls) in their hospital-based series. They did not exclude patients with previous dementia or previous stroke. In addition, they used the more sensitive but less specific DSM-III rather than DSM-IV criteria and assessed cognitive status at 3 months when some patients might have still been recovering cognitively. Finally, stroke patients who are admitted to a hospital are likely to have sustained a more severe stroke than those from a community-based cohort.

The majority of stroke subjects developed either VaD or mixed dementia (AD with VaD). The large proportion of subjects with mixed dementia after stroke (37%) suggests that a combination of vascular and degenerative pathologies may underlie the development of dementia after stroke. The distribution of vascular, mixed, and AD dementia subtypes in our cohort was similar to that reported by Desmond et al in their hospital-based series. Overall, the occurrence of a stroke had a substantial deleterious impact on cognition in groups of individuals thought to be at a lower baseline risk for dementia in the general population, namely males, older

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**Subgroup Analysis**

Demographic factors indicated that 18.3% of men with stroke developed dementia as compared with 7.8% of their matched controls (HR: 2.7; 95% CI: 1.4 to 5.2). In women, the effect of stroke was similar (HR: 1.7; 95% CI: 1.1 to 2.7). In subgroup analysis by age, baseline stroke increased the risk in subjects aged younger than 80 years (HR: 2.6; 95% CI: 1.5 to 4.5); the impact was lower in subjects aged 80 years or older (HR: 1.6; 95% CI: 1.0 to 2.7). Similarly, the impact of stroke was greater in subjects who had completed high school (HR: 2.9; 95% CI: 0.9 to 2.9) (Table 3).

Brain imaging was available in >90% of all subjects with stroke; 40% of strokes affected the left hemisphere, 48% the right hemisphere, and in 12% the strokes were bilateral or in the posterior fossa. The relative risk for dementia was comparable in subjects with a right hemisphere stroke (HR: 2.2; 95% CI: 1.3 to 3.5) and those with a left hemispheric stroke (HR: 2.0; 95% CI: 1.0 to 3.8). Most initial strokes were ABI (67%), whereas 24% had a CE event. The remaining 8% had a vasculitic, hemorrhagic, or unknown cause for their stroke. ABI doubled the risk of dementia (HR: 2.0; 95% CI: 1.3 to 3.1); CE did not significantly increase the risk (HR: 1.2; 95% CI: 0.4 to 3.6). Among subjects with recurrent strokes, 9 out of 46 cases (19.6%) developed dementia (HR: 1.8; 95% CI: 0.8 to 4.1).

The apoE genotype data were available in 821 subjects. The ε4 allele was present in 17.3% of the cases (22/127) and in 22.0% of the controls (153/694); in these subjects, the risk for dementia was similar in stroke cases and controls. However, in subjects who had 2 apoE ε4 alleles, the risk of dementia increased 4-fold in cases.

**Discussion**

In our carefully chosen study sample, free of baseline dementia, stroke cases had a 2-fold increased risk for dementia compared with controls. This result was independent of age, sex, education, hemispheric location, and type of stroke. This doubling of the risk occurred uniformly over the entire 10-year study period (Figure). Our results are similar to those reported by Kokmen et al, who also observed a doubling of the overall risk. However, we did not observe the 9-fold increase in relative risk, which they reported in the first year after a stroke. One reason for our lower relative risk in the first year may be our rigorous exclusion of subjects with preexisting dementia (before stroke) based on an ongoing dementia screening process, rather than a medical records linkage system. Another reason may be our definition of dementia that required survival and ascertainment of cognitive status at 6 months after the index stroke, thus excluding subjects who died early or improved cognitively within this 6-month period.

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**TABLE 2. Relative Risk of Dementia in Subjects With Stroke as Compared to Controls: Crude Risks and Risks After Adjustment for Age, Sex, Education, ApoE Genotype, Stroke Recurrence, and Stroke Risk Factors**

<table>
<thead>
<tr>
<th>Variable Adjusted for:</th>
<th>Dementia/N*</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None: crude risk</td>
<td>158/1272</td>
<td>2.2</td>
<td>1.5–3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, sex, and education</td>
<td>153/1239</td>
<td>2.0</td>
<td>1.4–2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoE ε4 genotype†</td>
<td>92/801</td>
<td>2.8</td>
<td>1.7–4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke type† (hemisphere, ABI/CE)</td>
<td>153/1239</td>
<td>2.0</td>
<td>1.4–2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second stroke†</td>
<td>153/1239</td>
<td>2.0</td>
<td>1.4–2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second stroke and stroke risk factors† (hypertension, diabetes, atrial fibrillation, current smoking)</td>
<td>114/844</td>
<td>2.4</td>
<td>1.6–3.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval; apoE, apolipoprotein E; ABI, atherothrombotic brain infarcts; CE, cardioembolic.

*N represents total number of cases plus controls with information available regarding status of each vascular risk factor within 3 years of entry (stroke for cases and match year for controls).

†Adjusted for age, sex, and education in addition to listed variable.
individuals (younger than 80 years), those who had completed a high school education, and those without an ApoE ε4 gene. Thus, having a stroke appears to nullify the lower prestroke risk of dementia these groups enjoyed. Similar to our own observations, Kokmen et al also found that although the incidence of dementia after the first ischemic stroke increased strikingly with age, the standardized morbidity ratio (an estimate of excess risk in the cohort compared with the risk in the population with the same age and sex distribution as in cohort) was highest in the younger age groups and decreased with increasing age.6

Previous studies3,17 comparing subjects who did and did not develop dementia after a stroke found diabetes mellitus to be an independent predictor for the development of poststroke dementia. In our analysis, none of the individual stroke risk factors that we studied (diabetes mellitus, atrial fibrillation, hypertension, smoking) significantly altered the impact of stroke on the risk of dementia. Thus, these stroke risk factors may increase the risk of dementia primarily by increasing the risk of clinical stroke. Another possible explanation is that we missed a true effect because of relatively small subject numbers within each subgroup analyzed. This may also explain why we found similar relative risks of dementia in subjects who had sustained a single stroke and in those who had sustained >1 stroke, when each group was matched to their respective controls.

We did not address the entire spectrum of vascular cognitive impairment but restricted this analysis to clinical dementia after clinical stroke. Further, we have not analyzed certain brain imaging variables such as white matter hyperintensity and silent cerebral infarcts because these were not available at comparable time points in all controls. Our study population was overwhelmingly white. The validity of these results in other racial groups can only be demonstrated by similar analyses using other cohorts. We used a stringent definition of dementia and may have underestimated the overall inci-

### TABLE 3. Relative Risk of Dementia in Stroke Cases Compared to Controls Within Subgroups Defined by Various Demographic, Stroke-Related, and Genetic Risk Factors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Controls Dementia/N</th>
<th>Cases Dementia/N</th>
<th>Adjusted* RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All groups</td>
<td>117/1060 11.0</td>
<td>41/212 19.3</td>
<td>2.0</td>
<td>1.4–2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>32/410 7.8</td>
<td>15/82 18.3</td>
<td>2.7</td>
<td>1.4–5.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Women</td>
<td>85/650 13.1</td>
<td>26/130 20.0</td>
<td>1.7</td>
<td>1.1–2.7</td>
<td>0.018</td>
</tr>
<tr>
<td>Entry age younger than 80 y</td>
<td>44/562 7.5</td>
<td>20/109 18.4</td>
<td>2.6</td>
<td>1.5–4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Entry age 80 y or older</td>
<td>82/498 16.5</td>
<td>21/103 20.4</td>
<td>1.6</td>
<td>1.0–2.6</td>
<td>0.075</td>
</tr>
<tr>
<td>No HS degree</td>
<td>52/359 14.5</td>
<td>16/72 22.2</td>
<td>1.7</td>
<td>0.9–2.9</td>
<td>0.079</td>
</tr>
<tr>
<td>HS degree</td>
<td>62/677 9.2</td>
<td>23/131 17.6</td>
<td>2.4</td>
<td>1.5–3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoE 22/23/33</td>
<td>37/541 6.8</td>
<td>24/105 22.9</td>
<td>3.4</td>
<td>2.0–5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoE 24/34/44</td>
<td>32/153 20.9</td>
<td>3/22 13.6</td>
<td>1.2</td>
<td>0.4–4.1</td>
<td>NS</td>
</tr>
<tr>
<td>R hemisphere</td>
<td>65/505 12.9</td>
<td>23/101 22.8</td>
<td>2.1</td>
<td>1.3–3.4</td>
<td>0.004</td>
</tr>
<tr>
<td>L hemisphere</td>
<td>38/420 9.1</td>
<td>14/84 16.7</td>
<td>1.8</td>
<td>0.9–3.4</td>
<td>0.078</td>
</tr>
<tr>
<td>ABI</td>
<td>82/715 11.5</td>
<td>31/143 21.7</td>
<td>2.0</td>
<td>1.3–3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>CE</td>
<td>23/255 9.0</td>
<td>4/51 7.8</td>
<td>1.3</td>
<td>0.5–3.9</td>
<td>NS</td>
</tr>
<tr>
<td>No second stroke</td>
<td>92/830 11.1</td>
<td>32/166 19.3</td>
<td>2.1</td>
<td>1.4–3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second stroke</td>
<td>25/230 10.9</td>
<td>9/46 19.6</td>
<td>1.8</td>
<td>0.8–4.1</td>
<td>NS</td>
</tr>
<tr>
<td>No hypertension</td>
<td>34/254 13.4</td>
<td>10/34 29.4</td>
<td>2.5</td>
<td>1.2–5.3</td>
<td>0.016</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63/671 9.4</td>
<td>26/145 17.9</td>
<td>2.3</td>
<td>1.4–3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td>94/731 12.9</td>
<td>30/124 24.2</td>
<td>2.2</td>
<td>1.4–3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8/109 7.3</td>
<td>6/42 14.3</td>
<td>2.2</td>
<td>0.8–6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Current nonsmoker</td>
<td>60/513 11.7</td>
<td>21/102 20.6</td>
<td>2.1</td>
<td>1.3–3.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Current smoker</td>
<td>36/397 9.1</td>
<td>15/76 19.7</td>
<td>2.3</td>
<td>1.2–4.3</td>
<td>0.009</td>
</tr>
</tbody>
</table>

NS = P > 0.05.

HS indicates high school; R, right; L, left; ABI, atherothrombotic brain infarcts; CE, cardioembolic.

*Adjustment was made for age (younger than 80 y vs 80 y or older), sex, HS degree, right/left hemisphere, ABI, and second stroke.
dence of dementia after stroke, but clearly a stroke at least doubles the risk of dementia.

Our data, assessing the long-term impact of a stroke over a decade of follow-up of a community-based cohort, reiterate the importance of stroke prevention measures, not only to reduce mortality, morbidity, and disability directly attributable to the stroke but also to decrease the risk and population burden of dementia.

Acknowledgments

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References


Editorial Comment

Dementia After Stroke

Stroke and dementia were implicitly associated by the advent of the concept of multi-infarct dementia, but it was Tatemichi et al who put this in temporal context and brought it to popular attention by observing a 26.3% dementia incidence 3 months after hospitalization for stroke. Several subsequent studies largely confirmed Tatemichi’s work but gave incidence estimates for poststroke dementia from 6% to 32%2,3 with most studies producing estimates toward the upper end of this range. As Ivan et al4 point out, these works are potentially inaccurate for several reasons, including cross-sectional study design, the use of hospital-based cohorts with the risk of selection bias, lack of controls, and no (or imperfect) exclusion of previous dementia...
Dementia, to which should be added the effect of the diagnostic criteria used.

What is remarkable about the data from Ivan et al is that it took ≈10 years for 19.3% of the cases of dementia to develop, a level that in most other studies would have been achieved within 3 months. Approximately 40% of apparently incident cases in most studies are caused by preexisting dementia, most of which is Alzheimer disease (AD).5–7 Nine such cases were excluded for that reason here and, if these are added to the numerator and denominator, would amount to 18% of cases, largely explaining the difference. The remainder may be accounted for other reasons among the 28 cases that were not followed-up with cognitive examination at 6 months.

Thus, Ivan et al have produced a much lower estimate for the incidence of poststroke dementia than previous studies. However, the single most common manifestation of vascular dementia (VaD) is now known to be a subcortical dementia based on small-vessel disease rather than the older concept of multiple larger cortical infarcts. The mini-mental state examination (MMSE) is useful as a screening tool for AD but is insensitive to subcortical dementia;8 in addition, the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) definition of dementia is based on AD. Both of these factors will result in an underestimate of the incidence of VaD, a feature common to all poststroke dementia studies to date.

The incident cases have been classified into VaD, AD, and mixed dementia using the Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC)9 criteria to identify VaD. None of the criteria for VaD are validated and they produce wildly varying results, even when applied to the same population.10,11 The ADDTC, used here, is one of the more sensitive but might still underestimate cases by ≈15%. There are no criteria at all for mixed dementia and the authors have not stated how this diagnosis was made. Thus the dementia etiologies reported by Ivan et al must be regarded as approximate. Because screening for dementia (the MMSE) and its confirmation (DSM IV) were both based on AD and the tool for identification of VaD identified vascular events, this methodology is likely to classify mixed dementia as VaD.12 This is also probably for statistical reasons, because the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS) study13 showed that 78% of the elderly have cerebrovascular disease at autopsy. The absolute figure further supports this notion because 7% of the stroke cases demented with an AD component as compared with 8.7% of the controls. Coexistent stroke does not protect against AD, rather, quite the converse; it profoundly accelerates its progression and advances its presentation.14 There should, therefore (and paradoxically), have been more mixed and AD cases recognized as an absolute proportion of the whole stroke group.

The MRC-CFAS study13 also raised doubts about the validity of the criteria for the histological diagnosis of AD. Furthermore, there are no histopathological criteria at all for diagnosing VaD; pathologists often make very subjective decisions.15 That the diagnoses of 16 cases were confirmed at autopsy is therefore not as strong a statement as it initially appears.

This work has the great strength of detailed premorbid knowledge of the study population and the consequent ability to exclude preexisting dementia and the presence of a stroke-free control group, so that the true effects of stroke can be more clearly assessed. It does not fully resolve the question of the magnitude of the incidence of poststroke dementia because the definitions used here will underestimate the incidence of VaD and mixed dementia. Nonetheless, the error will be an underestimate, and the study shows that dementia occurs after stroke in 19.3% of stroke cases as compared with 11% in a stroke-free matched group. This amounts to a minimum of 58,000 additional cases of dementia in the United States each year. Unlike AD, these are preventable by the modification of stroke risk factors. The numbers involved also indicate the importance of assessing cognition as part of the evaluation of stroke outcome, especially in research and also in routine clinical practice.

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