Poststroke Outcomes Vary by Pathogenic Stroke Subtype in The Atherosclerosis Risk in Communities Study

Sara B. Jones, MPH; Souvik Sen, MD, MS, MPH; Kamakshi Lakshminarayan, MD, PhD; Wayne D. Rosamond, PhD, MS

Background and Purpose—Early risk of recurrence and mortality after stroke differs by subtype, but less is known about long-term recurrence and hospital readmissions. These differences have economic implications and will affect long-term disability and stroke survivor quality of life. We examined recurrent stroke, all-cause hospital readmission, and mortality by index pathogenic subtype.

Methods—We identified 987 Atherosclerosis Risk in Communities Study cohort participants with first-ever stroke and followed them for a median 5.3 years after first stroke. Outcomes were compared across index subtypes (infarction: thrombotic, cardioembolic, and lacunar; hemorrhagic: subarachnoid and intracerebral) using Kaplan–Meier analysis and Cox proportional hazards regression, adjusting for age, sex, and race.

Results—There were 183 recurrent strokes among 147 participants, 3234 hospitalizations among 746 participants, and 529 deaths; only 14% of participants were event-free over follow-up. The majority of recurrent events were of the same subtype, except for lacunar infarcts, which were followed ≈3 quarters of the time by nonlacunar events. Adjusted mortality was higher for intracerebral hemorrhage (hazard ratio, 2.3; 95% confidence interval, 1.7–3.0) compared with thrombotic stroke and lower for lacunar infarcts. Lacunar infarcts had somewhat higher recurrence compared with thrombotic infarcts (hazard ratio, 1.3; 95% confidence interval, 0.9–1.9), but lower all-cause readmission (hazard ratio, 0.8; 95% confidence interval, 0.7–1.0). Readmission was 40% higher for cardioembolic stroke relative to thrombotic stroke (hazard ratio, 1.4; 95% confidence interval, 1.1–1.7).

Conclusions—Although the highest mortality was observed for intracerebral hemorrhage, there was significant burden of recurrent stroke and hospital readmissions for lacunar and cardioembolic strokes, respectively. There may be opportunities to reduce the relatively high rate of poststroke readmissions.

Key Words: outcomes | readmission | stroke subtype

Stroke represents an important public health concern in the United States. It is the fourth leading cause of mortality, the leading cause of severe disability, and a top contributor to healthcare expenditures for the elderly. Recurrent events and hospital readmissions, which may be preventable, contribute to morbidity and costs. Although early risk of mortality and recurrence differ by index subtype, less is known about long-term recurrence and hospital readmission. These differences impact quality of life and may have economic implications. The study aim was to characterize mortality, recurrence, and hospital readmissions after stroke according to pathogenic subtype to better understand differential poststroke health outcomes in a population-based sample of US adults.

Methods

The study included all first-ever definite/probable strokes among Atherosclerosis Risk in Communities (ARIC) study cohort participants; methods of the ARIC study have been previously reported. Briefly, 15792 residents of 4 communities 45 to 64 years of age were recruited from 1987 to 1989. Information on clinical events and hospitalizations was collected at baseline, 3 subsequent clinic visits at 3-year intervals, during annual telephone calls, and on review of local hospital discharge lists. All stroke diagnoses (first-ever and recurrent) were based on computer-derived diagnosis and physician medical record review, with differences adjudicated by a second physician reviewer. Classification required evidence of sudden or rapid onset of neurological symptoms lasting >24 hours or leading to death, in the absence of evidence for a nonstroke cause.

Strokes were further classified according to pathogenic subtype as thrombotic brain infarction, lacunar infarction, cardioembolic stroke (CE), intracerebral hemorrhage (ICH), or subarachnoid hemorrhage according to criteria adopted from the National Survey of Stroke (Subtype Classification in the online-only Data Supplement). We identified 987 first-ever stroke events during a median 91 years of follow-up (Participant Flow Diagram in the online-only Data Supplement). These cases were followed up from the index event for recurrent stroke, all-cause hospital readmission, and mortality until the earliest of death, date of last contact if lost to follow-up, or end of follow-up on December 31, 2008. Outcomes were compared across subtypes using Kaplan–Meier analysis and Cox proportional hazards.
regression that estimated hazard ratios (HRs) and 95% confidence intervals (CIs) adjusting for age, sex, race, and in secondary analysis, Charlson comorbidity index. Recurrence after hemorrhagic subtypes is not reported because of small numbers of events.

Results
The distribution of index stroke subtypes was 48.7% thrombotic, 20.0% CE, 18.5% lacunar, 8.6% ICH, and 4.2% subarachnoid hemorrhage (Participant Characteristics in the online-only Data Supplement). Hemorrhagic stroke patients were slightly younger and more often women than individuals with ischemic strokes. During a median 5.3 years of follow-up after the index event, there were 183 recurrent strokes among 147 participants, 3234 hospital readmissions among 746 participants, and 529 deaths. Only 139 participants (14.1%) were event-free during follow-up.

Approximately, 70% of recurrent strokes were of the same subtype; however, only 28% were the same when the index stroke was lacunar (Recurrent Stroke Distribution in the online-only Data Supplement). Poststroke survival was lowest for ICH (54.6% at 1 year) and highest for lacunar infarcts (90.4%; Figure 1.)

**Figure 1.** Kaplan–Meier analysis of mortality, recurrence, and readmission by pathogenic subtype. Survival curves are for all-cause mortality (A), first recurrent stroke event (B), and first hospital readmission for any cause (C) in the 10 years after index stroke event. Numbers of patients at risk at 2-year intervals are shown below the curves. Log-rank P values for differences in survival by stroke subtype were 0.05 for mortality, 0.05 for recurrent stroke, and <0.0001 for hospital readmission. Recurrent stroke outcomes are not shown for hemorrhagic stroke subtypes because of small numbers of events. CE indicates cardioembolic; ICH, intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.
Table. Incidence (95% Confidence Interval) of Mortality, Recurrence, and Hospital Readmission by Index Subtype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pathogenic Stroke Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombotic (n=481)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>7.5 (5.5–10.3)</td>
</tr>
<tr>
<td>1-year</td>
<td>19.6 (16.3–23.4)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>1.6 (0.7–3.2)</td>
</tr>
<tr>
<td>1-year</td>
<td>7.9 (5.7–11.0)</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td></td>
</tr>
<tr>
<td>All-cause readmission</td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>14.4 (11.5–18.0)</td>
</tr>
<tr>
<td>1-year</td>
<td>53.2 (48.6–57.9)</td>
</tr>
<tr>
<td>CVD-related readmission*</td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>1.8 (0.9–3.6)</td>
</tr>
<tr>
<td>1-year</td>
<td>13.3 (10.4–17.0)</td>
</tr>
</tbody>
</table>


Conclusions
Poststroke mortality was highest for ICH; however, there was significant morbidity for other stroke types, particularly all-cause hospital readmission after CE stroke. Although some studies have found no difference between hemorrhagic and ischemic strokes with regard to readmission,7 others reported higher 4-year readmission for ischemic stroke.8 One-year rehospitalization rates in a Canadian study were highest for ischemic strokes, (37.9%).9 We extend these results by examining readmission for ischemic subtypes, reporting higher readmission for CE and lower readmission for lacunar infarcts compared with thrombotic events. A hospital-based registry noted that infection was a common reason for rehospitalization, comprising 28% of all events in the year after stroke.7 This suggests there may be opportunities to reduce potentially preventable poststroke rehospitalizations, such as pneumonia and urinary tract infection.

Mortality in our study was lower than reported elsewhere, possibly reflecting differences in case mix and temporal changes in case fatality.9,10 As expected, hemorrhagic subtypes had the highest mortality. Consistent with our results, previous studies report that recurrence rates were highest for large-artery thrombosis and CE, while being no different or somewhat lower for lacunar infarcts.3–5,11–14

Figure 1: Table. cardioembolic (CE) strokes had the highest all-cause readmission, 65.5% at 1 year, whereas lacunar infarcts had the lowest at 41.2%. CVD-related readmissions showed the same patterns across ischemic subtypes (23.4% for CE and 5.9% for lacunar). After adjustment for age, sex, and race, mortality was higher for CE (HR, 1.3; 95% confidence interval (CI), 1.0–1.6) and ICH (HR, 2.3; 95% CI, 1.7–3.0) compared with thrombotic strokes and lower for lacunar (HR, 0.8; 95% CI, 0.6–1.0; Figure 2). All-cause readmission was 40% higher for CE compared with thrombotic strokes (HR, 1.4; 95% CI, 1.1–1.7). Additional adjustment for comorbidity did not appreciably change the results for recurrence or readmission. All-cause mortality estimates were attenuated for CE (HR, 1.14; 95% CI, 0.91–1.44) and increased for subarachnoid hemorrhage (HR, 1.22; 95% CI, 0.78–1.92).

Figure 2. Hazard ratios for mortality, recurrence, and readmission by subtype. Values above each bar indicate hazard ratios (95% confidence intervals [CIs]) for outcomes by pathogenic subtype with thrombotic stroke serving as the referent group for all comparisons. Recurrent stroke results are not shown for hemorrhagic subtypes because of small numbers of events. CE indicates cardioembolic; ICH, intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.
Strengths of our study were the population-based design, near-complete event ascertainment, validation of events, and long-term follow-up. The majority of studies examining readmissions by subtype used hospital-based cohorts or administrative databases, which often do not validate events and may not be representative of all strokes in a given region. Limitations include the small number of hemorrhagic events, which limited our ability to assess recurrence, and the inability to identify those readmissions that were potentially preventable.

The disease burden experienced by stroke survivors is of increasing concern given the aging of the population, improvements in case fatality, and growing healthcare costs. The high rate of hospital readmissions highlights the need for prevention not only of recurrent events but also of all-cause readmissions. Readmissions may result from gaps in secondary prevention and medical care and, therefore, might be prevented with improved coordination of care and discharge planning. Prevention and management strategies targeted according to stroke subtypes may be warranted.

Acknowledgments
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Disclosures
None.

References
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Supplemental Methods

S1: Classification of stroke etiologic subtype in the Atherosclerosis Risk in Communities Study

Minimum criterion for stroke diagnosis was evidence of sudden or rapid onset of neurological symptoms lasting >24 hours or leading to death, in the absence of evidence for a nonstroke cause. Exclusionary conditions included major brain trauma, neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, vasculitis involving the brain, peripheral neuropathy, hematologic abnormalities, or central nervous system infection. Etiologic classifications were defined as follows:

(A) Thrombotic brain infarction: Definite thrombotic stroke required either (1) autopsy evidence of a nonhemorrhagic infarct of the brain or (2) evidence from the hospital record of 1 major or 2 minor neurological signs or symptoms lasting at least 24 hours or until the patient died, and CT or MRI findings showing an infarct or area of decreased density (excluding evidence of hemorrhage). A case was considered a probable TBI if 1 major or 2 minor symptoms had sudden onset lasting >24 hours; and CT or MRI findings within the first 48 hours were negative or nonspecific, with no sign of hemorrhage; and a spinal tap was not done, was traumatic, or yielded clear, colorless spinal fluid.

(B) Cardioembolic stroke: Definite CE required either (1) autopsy evidence of an infarcted area in the brain and a source of emboli in a vessel of any organ or presence of an embolus in the brain, or (2) 1 major or 2 minor symptoms showed rapid onset lasting >24 hours and the medical records revealed evidence of valvular heart disease, atrial fibrillation, or flutter, acute or recent (within 4 weeks) myocardial infarction, cardiac or arterial procedure intracardiac thrombus, or bacterial endocarditis. In this latter case, CT or MRI findings must have shown an area of decreased density indicative of edema or ischemia, with no evidence of hemorrhage. A diagnosis of probable CE was made if there was evidence of 1 major or 2 minor symptoms and medical record review identified a source of cerebral embolus; and if a CT or MRI within the first 48 hours was either negative or nonspecific, with no
evidence of hemorrhage; and a spinal tap was either not done, was traumatic, or yielded clear, colorless spinal fluid.

(C) Lacunar infarcts: All definite thrombotic brain infarctions were further classified as either lacunar or nonlacunar. Lesion size and neuroimaging reports were evaluated, and a final diagnosis of lacunar infarction was made on the basis of physician review. A definite lacunar infarction was assigned if 2 criteria were met: (1) anatomic findings typical of lacunar infarctions (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) estimated infarct size of ≤2 cm or an infarct of unstated size. In the rare event that these criteria were met but the neuroimaging report explicitly stated that the infarct was not lacunar, the latter prevailed.

(D) Subarachnoid hemorrhage: Definite SAH required either (1) angiographic identification of a saccular aneurysm as a source of bleeding and bloody or xanthochromic spinal fluid; or (2) CT or MRI findings indicating a blood clot in the fissure of Sylvius, between the frontal lobes, in the basal cisterns, or within a ventricle, with no associated intraparenchymal hematoma; or (3) autopsy or surgical procedures that uncovered a bleeding saccular aneurysm. A diagnosis of probable SAH was made if (1) angiographic evidence of a saccular aneurysm was identified as the source of bleeding and the spinal tap was not done, was traumatic, or was missing; or (2) within a few minutes or hours of symptom onset there was evidence of a severe headache, depressed state of consciousness, meningeal irritation, or retinal hemorrhages, and spinal fluid was bloody or xanthochromic.

(E) Intracerebral hemorrhage: Definite ICH required (1) an area of increased density indicative of ICH identified by CT or MRI; or (2) the demonstration of an ICH at autopsy or during surgery; or (3) in the absence of a technically adequate CT or MRI, there was 1 major or 2 minor symptoms of sudden onset lasting >24 hours, bloody (nontraumatic) or xanthochromic spinal fluid, and evidence from cerebral angiography of a vascular mass without evidence of aneurysm or arteriovenous malformation. A diagnosis of probable ICH was made if (1) a decreased level of consciousness or coma lasted at least 24 hours and (2) a nontraumatic spinal tap was spinal fluid was bloody or xanthochromic and (3) CT or MRI imaging was not performed or was inadequate.
S2: Flow of participants through the study

ARIC baseline cohort
N=15,792

Excluded (N=308)
- History of stroke at baseline (N=284)
- Missing information on stroke history (N=45)

Lost to follow-up prior to December 31, 2008 (N=488)

Incident Stroke Cases
N=987

Lost to follow-up prior to December 31, 2008 (N=24)

Thrombotic infarct
N=481

Cardioembolic infarct
N=197

Lacunar infarct
N=183

Intracerebral hemorrhage
N=85

Subarachnoid hemorrhage
N=41

Outcomes
- Death (N=258)
- Recurrence (N=80)
- Readmission (N=386)
- None (N=63)

Outcomes
- Death (N=108)
- Recurrence (N=17)
- Readmission (N=146)
- None (N=24)

Outcomes
- Death (N=79)
- Recurrence (N=39)
- Readmission (N=142)
- None (N=38)

Outcomes
- Death (N=63)
- Recurrence (N=9)
- Readmission (N=45)
- None (N=9)

Outcomes
- Death (N=21)
- Recurrence (N=2)
- Readmission (N=27)
- None (N=5)
### Supplemental Tables

#### S3. Characteristics (%) of stroke events by index subtype in the Atherosclerosis Risk in Communities Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thrombotic</th>
<th>Cardioembolic</th>
<th>Lacunar</th>
<th>Intracerebral hemorrhage</th>
<th>Subarachnoid hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>481</td>
<td>197</td>
<td>183</td>
<td>85</td>
<td>41</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>2,867.2</td>
<td>714.6</td>
<td>1,069.9</td>
<td>283.0</td>
<td>288.9</td>
</tr>
<tr>
<td>Age, median(IQR)</td>
<td>67(62-72)</td>
<td>70(64-75)</td>
<td>67(62-71)</td>
<td>66(60-74.5)</td>
<td>64(57-71)</td>
</tr>
<tr>
<td>Sex-race group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White men</td>
<td>35.8</td>
<td>35.0</td>
<td>26.8</td>
<td>20.0</td>
<td>24.4</td>
</tr>
<tr>
<td>Black men</td>
<td>17.7</td>
<td>13.2</td>
<td>21.9</td>
<td>17.7</td>
<td>7.3</td>
</tr>
<tr>
<td>White women</td>
<td>25.4</td>
<td>30.0</td>
<td>18.0</td>
<td>30.6</td>
<td>36.6</td>
</tr>
<tr>
<td>Black women</td>
<td>21.0</td>
<td>21.8</td>
<td>33.3</td>
<td>30.6</td>
<td>31.7</td>
</tr>
<tr>
<td>Medical history at baseline</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hypertension</td>
<td>56.6</td>
<td>53.8</td>
<td>60.4</td>
<td>64.7</td>
<td>46.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24.4</td>
<td>28.2</td>
<td>37.6</td>
<td>16.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>9.0</td>
<td>9.0</td>
<td>7.3</td>
<td>3.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean (SD)</td>
<td>2.2 (1.2)</td>
<td>2.7 (1.3)</td>
<td>2.0 (1.1)</td>
<td>1.9 (1.1)</td>
<td>1.7 (1.1)</td>
</tr>
</tbody>
</table>
### Distribution of recurrent stroke subtypes according to index stroke subtype

<table>
<thead>
<tr>
<th>Initial Stroke Subtype</th>
<th>Recurrent Stroke Etiologic Subtype</th>
<th>Thrombotic</th>
<th>Cardioembolic</th>
<th>Lacunar</th>
<th>Intracerebral Hemorrhage</th>
<th>Subarachnoid Hemorrhage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic</td>
<td></td>
<td>57 (71.3%)</td>
<td>11 (13.8%)</td>
<td>9 (11.3%)</td>
<td>3 (3.8%)</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td></td>
<td>2 (11.8%)</td>
<td>13 (76.5%)</td>
<td>2 (11.8%)</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Lacunar</td>
<td></td>
<td>20 (51.3%)</td>
<td>7 (18.0%)</td>
<td>11 (28.2%)</td>
<td>1 (2.6%)</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Intracerebral Hemorrhage</td>
<td></td>
<td>3 (33.3%)</td>
<td>1 (11.1%)</td>
<td>2 (22.2%)</td>
<td>3 (33.3%)</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Subarachnoid Hemorrhage</td>
<td></td>
<td>2 (100%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

* Number (%) of initial strokes with no recurrent stroke are as follows: thrombotic, 401 (83.4); CE, 180 (91.4); lacunar, 144 (78.7); IPH, 76 (89.4); SAH, 39 (95.1).