Risk of Recurrent Arterial Ischemic Stroke in Childhood
A Prospective International Study

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Background and Purpose—Published cohorts of children with arterial ischemic stroke (AIS) in the 1990s to early 2000s reported 5-year cumulative recurrence rates approaching 20%. Since then, utilization of antithrombotic agents for secondary stroke prevention in children has increased. We sought to determine rates and predictors of recurrent stroke in the current era.

Methods—The Vascular Effects of Infection in Pediatric Stroke (VIPS) study enrolled 355 children with AIS at 37 international centers from 2009 to 2014 and followed them prospectively for recurrent stroke. Index and recurrent strokes underwent central review and confirmation, as well as central classification of causes of stroke, including arteriopathies. Other predictors were measured via parental interview or chart review.

Results—Of the 355 children, 354 survived their acute index stroke, and 308 (87%) were treated with an antithrombotic medication. During a median follow-up of 2.0 years (interquartile range, 1.0–3.0), 40 children had a recurrent AIS, and none had a hemorrhagic stroke. The cumulative stroke recurrence rate was 6.8% (95% confidence interval, 4.6%–10%) at 1 month and 12% (8.5%–15%) at 1 year. The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold when compared with an idiopathic AIS (hazard ratio, 5.0; 95% confidence interval, 1.8–14). The 1-year recurrence rate was 32% (95% confidence interval, 18%–51%) for moyamoya, 25% (12%–48%) for transient cerebral arteriopathy, and 19% (8.5%–40%) for arterial dissection.

Conclusions—Children with AIS, particularly those with arteriopathy, remain at high risk for recurrent AIS despite increased utilization of antithrombotic agents. Therapies directed at the arteriopathies themselves are needed.

Key Words: child ■ pediatrics ■ risk factor ■ stroke ■ vaccination

Childhood arterial ischemic stroke (AIS) causes lifelong disabilities in the majority of affected children.1,2 Prior studies suggest that the cumulative rate of recurrent AIS is high in these children, approaching 20% at 5 years after the index stroke, compounding disability.3,4 However, these studies evaluated earlier cohorts (study periods 1978–20004 and 1993–20043) and were geographically limited (set in England4 and Northern California3). Treatment with antithrombotic medication (antiplatelet or anticoagulation) for prevention of recurrent childhood stroke has, historically, varied dramatically by both epoch and country5; a third to half of the children in these 2 earlier cohorts received no antithrombotic medication.3,4 Since then, recurrence rates may have declined alongside improvements in pediatric stroke care and increased use of antithrombotic medications. Hence, the first goal of this study was to measure the rate of recurrent AIS in a contemporary and internationally representative cohort of children with AIS.

Understanding risk factors for recurrent AIS is critical for improving strategies for secondary stroke prevention. Prior recurrence studies focused on childhood arteriopathies as a major predictor of recurrence but were generally underpowered to perform more detailed analyses of risk factors. Recent studies of risk factors for first AIS in children provide evidence...
that minor infections act as a stroke trigger. In the case-control component of our multicenter, prospective Vascular Effects of Infection in Pediatric Stroke (VIPS) study, we confirmed this association, found that most infections preceding stroke are upper respiratory infections, and found that routine childhood vaccinations protect against childhood stroke. Hence, the second goal of this study was to determine whether the same measures of infection and vaccinations affect risk of recurrent AIS.

To measure rates and predictors of recurrent AIS in a contemporary cohort, we prospectively followed 355 children with centrally confirmed AIS enrolled in VIPS.

Methods

The study setting and methods for identifying, confirming, and characterizing cases of childhood AIS in VIPS have been previously published. VIPS centers are all academic institutions with local expertise in pediatric stroke and a history of participation in the International Pediatric Stroke Study, which was the enrollment network for VIPS. The 37 VIPS centers were located in 9 countries. After ethics approvals were obtained at each site, they prospectively enrolled 355 children (aged 29 days through 18 years at stroke ictus) between January 2010 and March 2014, with acute AIS in the preceding 3 weeks. Enrolling sites collected and submitted for central analysis (1) clinical data from chart review and parental interview, (2) mandatory brain and cerebrovascular imaging studies, and (3) biological samples. A central case classification team of 2 neuroradiologists and 1 neurologist reviewed the clinical presentation and brain imaging of every enrolled case to confirm the index AIS diagnosis, defined a priori as an acute infarct or embolic (spontaneous or iatrogenic, such as caused by a cardiac embolism) or hemorrhagic (primary or secondary, such as caused by sickle cell disease), arteriopathy, including those that could not be classified. Those with definite arteriopathy were then further classified as transient cerebral arteriopathy (TCA), arterial dissection, moyamoya (primary or secondary, such as caused by sickle cell disease), vasculitis (primary or secondary, such as caused by bacterial meningitis), or other arteriopathy, including those that could not be classified. Those with no arteriopathy were then further classified as idiopathic, cardioembolic (spontaneous or iatrogenic, such as caused by a cardiac procedure), or other identified causes.

Exposure to infection before the index stroke was measured through a structured parental interview, performed within 3 weeks of the stroke ictus, which included questions about clinical infections before the index stroke. Detailed information on routine childhood vaccinations was also collected; as a general marker of vaccination status, parents were asked whether their child had received all, most, some, few, or none of the routine vaccines expected for his/her age. Poorly vaccinated was defined as some/few/none of routine vaccines. Antithrombotic therapies used for secondary stroke prevention after the index AIS diagnosis were recorded and included any type of antiplatelet medication or anticoagulation.

Patients were followed up for a minimum of 12 months after their index stroke. Our a priori definition of recurrent AIS included 2 criteria: (1) imaging evidence of a new acute infarction in a territory of brain that was unaffected on the baseline parenchymal imaging and (2) new or worsening clinical signs and symptoms corresponding to the new area of infarction. Hemorrhagic stroke after the index AIS was also considered a form of recurrence and was defined as a symptomatic intracerebral or subarachnoid hemorrhage; hemorrhagic transformation of an infarction was not considered a recurrent stroke, even if symptomatic. Transient ischemic attacks were recorded but not included in our definition of recurrent stroke. Recurrent strokes were ascertained through a multi-tier process. First, because the VIPS site investigators were the pediatric stroke experts at their institutions, they were typically involved in the clinical care of children with recurrent AIS. Second, site investigators and study coordinators performed follow-up assessments at prespecified time points (4, 8, 12 months, and annually thereafter until March 2015). These assessments were performed in person if they coincided with a clinical visit, or else via telephone, and included the administration of the Pediatric Stroke Recovery and Recurrence Questionnaire, which includes questions about recurrent stroke. Finally, at the end of the study observation period, March 2015, sites attempted to contact the guardians of all enrolled patients to inquire about recurrent strokes. They also performed a final review of all available inpatient and outpatient medical records at their institution. Once a possible recurrent stroke was ascertained, the enrolling site obtained the relevant medical records and cerebrovascular imaging documenting the recurrence. After locally confirming that the event met criteria for a recurrent stroke, they completed and submitted a follow-up data collection form, including clinical presentation and therapies at the time of recurrence. The same central case confirmation team applied the same methodologies to confirm the recurrent stroke as used for the index stroke: 2 investigators independently reviewed the clinical data and all available imaging to confirm that both clinical and imaging criteria for recurrence were met, and a third adjudicated any disagreements. This team also classified the recurrent strokes as ischemic or hemorrhagic.

Data Analysis

We used survival analysis techniques to estimate rates of recurrent stroke; the primary outcome variable was the time from index stroke to recurrent stroke (the failure event). Cases were censored (ie, withdrawn from the time-to-event analysis) at either death or loss to follow-up using the date when they were last known to be stroke-free either by telephone interview with the guardians or by chart review, whichever came later. In our primary analysis, we included centrally confirmed recurrent strokes and a small number of recurrent strokes reported by the enrolling sites for which central review could not be performed (typically because confirmatory brain imaging was performed at an outside institution and DICOM files could not be obtained). We derived cumulative recurrence rates from hazard functions.

In our analyses of predictors of recurrent stroke, we used the same definitions for all predictor variables as described in prior VIPS publications. The primary measure of infectious exposure was parental report of clinical infection in the week before index AIS, which was found to be a risk factor for childhood AIS in the VIPS case-control study. We also used previously established definitions for the other predictors of interest: age at the time of index AIS (categorical), lower- and middle-income country of enrollment (ie, Philippines, Serbia, and China), and markers of socioeconomic status (household income, urban/suburban/rural residence, and highest level of maternal education). To compare recurrence-free survival rates between subgroups, we first constructed stratified Kaplan–Meier survival curves and performed log-rank tests. We then used Cox proportional hazards regression techniques to model predictors of recurrent stroke. To construct our multivariable model, we used a univariate P value cutoff of <0.10 and included age and sex. All analyses were conducted using Stata v13 (StataCorp, College Station, TX) with ρ set at 0.05.

Results

Of 355 children with AIS, 1 died within the first week; the 354 survivors were followed up for a median of 2.0 (interquartile range, 1.0–3.0) years. A total of 278 had at least 12 months of follow-up; 14 died, and 63 were lost to follow-up during the first 12 months. Overall, 308 (87% of all cases) were treated with an antithrombotic agent after their index stroke diagnosis: 147 received an antiplatelet agent, 98 received anticoagulation (heparin or warfarin), and 63 received both.

Recurrent Stroke

The enrolling sites identified and confirmed recurrent strokes in 42 children; all were AIS (no hemorrhagic stroke). Of the 42
site-confirmed first recurrences, 37 underwent central review, and 35 (95%) of those were confirmed (Figure 1). The other 5 children with site-confirmed stroke did not have DICOM imaging available for central review; however, because the rate of central confirmation of a site-confirmed recurrence was high, we included these as recurrences. Hence, a total of 40 children had a recurrent stroke at a median of 23 (range, 2–372) days after the index stroke; and 6 children had >1 recurrence, with a median of 3 recurrences (range, 2–3). The cumulative rate of first recurrent stroke was 6.8% (95% confidence interval [CI], 4.6%–10%) at 1 month and 12% (95% CI, 8.5%–15%) at 1 year (Figure 2A). At the time of the first recurrent stroke, 26 of 40 (65%) were receiving an antithrombotic agent: 10 were receiving an antiplatelet agent, 13 anticoagulation (heparin or warfarin), and 3 both. Of the 16 children on anticoagulation, all but 2 were considered therapeutic at the time of the recurrence. Of the 13 children on antiplatelet therapy, all but 1 were on a standard daily dose of aspirin (81 mg in 9, 325 mg in 1, and ≈3.5 mg/kg in 2 smaller children), and 1 was also on clopidogrel (75 mg). Of the 14 children on no therapy at the time of recurrence, 12 had previously received an antithrombotic agent after their index stroke.

Other Outcomes
A total of 27 children had a transient ischemic attack after their index AIS, including 11 (28%) of the 40 children with recurrent stroke and 16 (5.1%) of the 315 without recurrent stroke. Hence, a total of 56 children (16% of the cohort of 355) experienced some recurrent ischemic event (stroke or transient ischemic attack) during the follow-up period. There were a total of 16 deaths: the aforementioned one in the first week after the index stroke, 5 between 1 week and 1 month, and 10 after the first month. Death occurred in 4 (10%) of the 40 children with recurrent stroke and 12 (3.8%) of the 315 without recurrent stroke.

Predictors of Recurrent Stroke
In univariate analysis, the only significant predictor of recurrent stroke was definite arteriopathy, which increased the hazard of a recurrence 5-fold compared with idiopathic AIS (Table 1). The cumulative risk of recurrence at 1 year was 4.5% (95% CI, 1.7%–12%) for children with idiopathic stroke (n=90), 8.1% (3.4%–18%) for spontaneous cardioembolic stroke (n=65), 12% (4.8%–30%) for possible arteriopathy (n=34), and 21% (14%–29%) for definite arteriopathy (n=127; Figure 2B). Among those with definite arteriopathy, the 1-year recurrence rate was 32% (18%–51%) for moyamoya (n=34), 25% (12%–48%) for TCA (n=25), 19% (8.5%–40%) for arterial dissection (n=26), and 6.7% (1.0%–39%) for secondary vasculitis (ie, vasculitis in the setting of infectious meningitis; n=15). (There were no cases of primary vasculitis in VIPS.) Because not all children had follow-up vascular imaging, we could not assess arteriopathy progression as a predictor of recurrence. However, among the 26 children with definite arteriopathy and recurrent stroke, 19 had follow-up vascular imaging; the arteriopathy improved in 4, remained stable in 3, progressed in 6, and progressed and then later improved in 6.

Risk factors for childhood AIS identified in the VIPS case-control study—low socioeconomic status, recent infection, and undervaccination—did not predict risk of recurrent AIS (Table 1). In a multivariable model adjusting for age and sex, definite arteriopathy remained a strong predictor of recurrent stroke (Table 2).

Discussion
In this contemporary international cohort of children with AIS, we found high rates of recurrent stroke, particularly in children with arteriopathies. This occurred despite enrollment at academic centers with pediatric stroke expertise and increased utilization of antithrombotic medications for secondary stroke prevention compared with previously published cohorts. In a retrospective population-based cohort of 97 children with AIS in Northern California (1993–2004), 51% were treated with aspirin or anticoagulation, and the 1-year cumulative recurrence rate was 15% (95% CI, 12%–30%).3 In a single-center British cohort of 212 children with AIS (mixed retrospective and prospective; 1978–2000), 46% were treated with an antithrombotic, and the 5-year cumulative recurrence rate was 18% (95% CI, 11%–25%).4 In the VIPS cohort, 87% were treated with an antithrombotic after the baseline stroke, yet the overall 1-year cumulative recurrence rate was 12% (95% CI, 8.5%–15%). However, of the 40 children who had a recurrent stroke, only 65% were on an antithrombotic therapy at the time of recurrence. Because VIPS sites are tertiary care centers, the VIPS cohort may include higher risk patients than

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**Figure 1.** Flow diagram demonstrating how recurrent strokes were identified and confirmed in the Vascular Effects of Infection in Pediatric Stroke (VIPS) study cohort of 355 children with arterial ischemic stroke (AIS).
those included in the population-based Californian study. The British study was set at a more similar tertiary care center (Great Ormand Street Hospital) but did not report the 1-year stroke recurrence rate. These differences preclude direct comparisons between studies; however, there is no clear indication that rates of recurrent childhood AIS are declining.

The VIPS case-control study identified risk factors for childhood AIS, including recent infection, undervaccination, and low socioeconomic status; none of these factors independently affected risk of recurrent AIS. The only significant risk factor for recurrence was arteriopathy: 1 in 5 children with a definite arteriopathy had a recurrence by 1 year. (The risk for children with possible arteriopathy was intermediate between that of the definite and no arteriopathy groups, consistent with that representing a mixed group of children with and without arteriopathy.) Although prior studies of recurrent childhood AIS have varied considerably in their ability to detect and classify arteriopathy (eg, the Californian study reviewed reports of vascular imaging but not the vascular imaging itself), all have consistently suggested the importance of arteriopathies as the major factor defining recurrent stroke risk in children. One additionally found that progressive arteriopathies conferred a particularly high risk; although we could not assess this as a predictor in our statistical models, 12 of the 19 children with definite arteriopathy, follow-up vascular imaging, and recurrent stroke had a progressive arteriopathy. Another study demonstrated that severity of arterial stenosis predicts recurrence.

Childhood arteriopathies are heterogeneous, ranging from genetic disorders, like many of the primary and secondary forms of moyamoya, to acquired arteriopathies, like arterial dissection and vasculitis secondary to meningitis. TCA is a monophasic childhood arteriopathy that unilaterally affects the intracranial internal carotid artery, its proximal branches, or both. It is one of the most common arteriopathies in a previously healthy child with AIS and conferred a high risk of recurrence in the VIPS cohort, yet its mechanism remains elusive. Reduction in stroke recurrence rates in children depends on a better understanding of all childhood arteriopathies so that secondary stroke prevention strategies can move beyond antithrombotic agents toward therapies directed at the arterial pathology itself. For example, studies using advanced
### Table 1. Characteristics of 355 Children With Arterial Ischemic Stroke, With vs Without Recurrent Stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrent Stroke (n=40, n (%))</th>
<th>No Recurrent Stroke (n=315, n (%))</th>
<th>HR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age group, y</td>
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<tr>
<td>0–3</td>
<td>10 (25.0)</td>
<td>106 (33.7)</td>
<td>Ref (…)</td>
<td>…</td>
</tr>
<tr>
<td>4–7</td>
<td>12 (30.0)</td>
<td>57 (18.1)</td>
<td>2.1 (0.9–4.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>8–11</td>
<td>6 (15.0)</td>
<td>40 (12.7)</td>
<td>1.6 (0.6–4.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>12–15</td>
<td>6 (15.0)</td>
<td>67 (21.3)</td>
<td>1.0 (0.4–2.7)</td>
<td>0.97</td>
</tr>
<tr>
<td>16+</td>
<td>6 (15.0)</td>
<td>45 (14.3)</td>
<td>1.5 (0.6–4.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Male sex</td>
<td>25 (62.5)</td>
<td>174 (55.2)</td>
<td>1.3 (0.7–2.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>LAMI country</td>
<td>1 (2.5)</td>
<td>24 (7.6)</td>
<td>0.3 (0.1–2.5)</td>
<td>0.30</td>
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<td><strong>Socioeconomic status</strong></td>
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<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Urban</td>
<td>12 (30.0)</td>
<td>106 (33.7)</td>
<td>Ref (…)</td>
<td>…</td>
</tr>
<tr>
<td>Suburban</td>
<td>13 (32.5)</td>
<td>140 (44.4)</td>
<td>0.8 (0.4–1.8)</td>
<td>0.64</td>
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<tr>
<td>Rural</td>
<td>15 (37.5)</td>
<td>67 (21.3)</td>
<td>1.8 (0.8–3.9)</td>
<td>0.13</td>
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<tr>
<td>Household income (US $)</td>
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<tr>
<td>&lt;$10,000</td>
<td>1 (2.5)</td>
<td>54 (17.1)</td>
<td>Ref (…)</td>
<td>…</td>
</tr>
<tr>
<td>$10,000–30,000</td>
<td>6 (15.0)</td>
<td>62 (19.7)</td>
<td>4.9 (0.6–40.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>$31,000–50,000</td>
<td>6 (15.0)</td>
<td>41 (13.0)</td>
<td>7.1 (0.8–58.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>$50,000–100,000</td>
<td>14 (35.0)</td>
<td>76 (24.1)</td>
<td>8.5 (1.1–65.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>5 (12.5)</td>
<td>59 (18.7)</td>
<td>4.2 (0.5–35.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>Missing</td>
<td>8 (20.0)</td>
<td>23 (7.3)</td>
<td></td>
<td></td>
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<tr>
<td>Maternal education, highest level</td>
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<td></td>
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<tr>
<td>Less than high school</td>
<td>6 (15.0)</td>
<td>37 (11.7)</td>
<td>Ref (…)</td>
<td>…</td>
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<tr>
<td>High school graduate</td>
<td>9 (22.5)</td>
<td>74 (23.5)</td>
<td>0.7 (0.3–2.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>Some college education</td>
<td>13 (32.5)</td>
<td>96 (30.5)</td>
<td>0.8 (0.3–2.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>6 (15.0)</td>
<td>62 (19.7)</td>
<td>0.6 (0.2–1.9)</td>
<td>0.4</td>
</tr>
<tr>
<td>Graduate education</td>
<td>4 (10.0)</td>
<td>34 (10.8)</td>
<td>0.8 (0.2–2.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (5.0)</td>
<td>12 (3.8)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Stroke classification</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No arteriopathy</td>
<td>10 (25.0)</td>
<td>184 (58.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4 (10.0)</td>
<td>86 (27.3)</td>
<td>Ref (…)</td>
<td>…</td>
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<tr>
<td>Cardioembolic†</td>
<td>5 (12.5)</td>
<td>60 (19.0)</td>
<td>1.8 (0.5–6.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.5)</td>
<td>38 (12.1)</td>
<td>0.6 (0.1–5.1)</td>
<td>0.61</td>
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<td>Possible arteriopathy</td>
<td>4 (10.0)</td>
<td>30 (9.5)</td>
<td>2.9 (0.7–11.6)</td>
<td>0.13</td>
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<tr>
<td>Definite arteriopathy</td>
<td>26 (65.0)</td>
<td>101 (32.1)</td>
<td>5.0 (1.8–14.4)</td>
<td>0.003</td>
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<td>Transient cerebral arteriopathy</td>
<td>6 (15.0)</td>
<td>19 (6.0)</td>
<td>6.3 (1.8–22.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>5 (12.5)</td>
<td>21 (6.7)</td>
<td>5.0 (1.3–18.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>10 (25.0)</td>
<td>24 (7.6)</td>
<td>7.4 (2.3–23.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary vasculitis</td>
<td>1 (2.5)</td>
<td>14 (4.4)</td>
<td>1.5 (0.2–13.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Other</td>
<td>4 (10.0)</td>
<td>23 (7.3)</td>
<td>3.3 (0.8–13.2)</td>
<td>0.09</td>
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<tr>
<td><strong>Markers of infection</strong></td>
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<td>Infection in the week prior to index stroke</td>
<td>6 (15.0)</td>
<td>58 (18.4)</td>
<td>0.8 (0.3–1.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Poorly vaccinated (some/few-none routine vaccines)‡</td>
<td>2 (5.1)</td>
<td>25 (8.3)</td>
<td>0.6 (0.2–2.6)</td>
<td>0.54</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
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<tr>
<td>Antithrombotic treatment after index stroke</td>
<td></td>
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<tr>
<td>Antiplatelets</td>
<td>15 (37.5)</td>
<td>132 (41.9)</td>
<td>0.98 (0.4–2.7)</td>
<td>0.98</td>
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<td>Anticoagulation</td>
<td>13 (32.5)</td>
<td>85 (27.0)</td>
<td>1.3 (0.5–3.7)</td>
<td>0.58</td>
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<tr>
<td>Both</td>
<td>7 (17.5)</td>
<td>56 (17.8)</td>
<td>1.1 (0.3–3.4)</td>
<td>0.91</td>
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<tr>
<td>Neither</td>
<td>5 (12.5)</td>
<td>42 (13.3)</td>
<td>Ref (…)</td>
<td>…</td>
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(Continued)
techniques for imaging vessel walls suggest that TCA may be an inflammatory arteriopathy,17 and hence immunosuppres-
sant medications may prove effective at reducing recurrent
stroke risk in children with that disease.

Although parental report of clinical infection before the
index AIS did not affect risk of recurrent stroke in our study,
infection may play a role in the pathogenesis of childhood
arteriopathies that do themselves confer a high risk of recur-
rence. Varicella zoster virus is a well-established cause of
TCA,18 and recent evidence suggests that it may play a role
in other arteriopathies, such as giant cell arteritis.19 TCA
continues to occur in children vaccinated for varicella zos-
ter virus,7 suggesting other pathogens may contribute to this
disease; a better understanding of this relationship is needed
before immunosuppression is used for secondary stroke
prevention.

Our study also provides important data on the timing of
recurrent stroke in children: 75% occurred within the first 12
weeks after the index stroke, and only 1 occurred beyond a
year (at 372 days after the index stroke). Prior studies of recur-
rent childhood AIS have demonstrated similar find-
ing.2,3,11 This implies that a secondary stroke prevention trial in chil-
dren would require a relatively short duration of follow-up.

Limitations of this study include loss to follow-up, lack
of repeat vascular imaging in all cases, lack of long-term fol-
low-up, and the lack of continuous assessment or validation
of the use of antithrombotic medications. Another limitation
is the study setting, with children enrolled solely at tertiary
care centers; hence, the results may not be generalizable to
children who receive stroke care in a community setting.

Because of unavailability of DICOM images, when some
children received care for their recurrent AIS at an outside
hospital, we were unable to centrally review and confirm all
recurrent strokes; however, the central confirmation rate was
high for the site-confirmed recurrences. Predictors related
to history of clinical infection and vaccinations were mea-
sured through parental report; however, because they were
measured at the time of the index stroke, there should not
have been recall bias related to the recurrent stroke outcome.

Strengths of VIPS are that it is international and prospective,
and that the causes of stroke, particularly arteriopathy, were
carefully classified through central review of clinical and
imaging data. It is also the largest study of recurrent stroke
in childhood.

Conclusions
Despite increased treatment with antithrombotic agents com-
pared with cohorts from the 1970s to early 2000s, rates of recur-
rent stroke in children with AIS remain high, with >1 in
10 children suffering a recurrence within 1 year. Arteriopathy
is both the common and the strongest risk factor for recur-
rence, indicating a clear direction for future research aimed
at improving secondary stroke prevention in this age group.

Appendix
Patricia A. Plumb (University of Texas Southwestern Medical
Center, Dallas), Susan L. Benedict (Primary Children’s Medical
Center, Salt Lake City), Timothy J. Bernard (Denver Children’s
Hospital), Christine K. Fox (UCSF), Gabrielle A. DeVeber (The
Hospital for Sick Children, Toronto, Canada), Neil R. Friedman
(Cleveland Clinic Children’s Hospital), Warren D. Lo (The Ohio
State University and Nationwide Children’s Hospital, Columbus
OH), Rebecca N. Ichord (Children’s Hospital of Philadelphia),
Marilyn A. Tan (University of the Philippines-Philippine General
Hospital, Manila), Mark T. Mackay (Royal Children’s Hospital
Melbourne), Adam Kirton (Alberta Children’s Hospital), Marta

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrent Stroke (n=40), n (%)</th>
<th>No Recurrent Stroke (n=315), n (%)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic treatment at the time of recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>15 (37.5)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>14 (35.0)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Both</td>
<td>5 (12.5)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Neither</td>
<td>6 (15.0)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; Ref, reference.

*Reference group is idiopathic stroke for all HRs shown.
†Spontaneous (as opposed to iatrogenic, procedure related) cardioemolic strokes.
‡Excludes any who answered unknown; n=39 for recurrent stroke; n=303 for no recurrent stroke.
I. Hernandez-Chavez (Pontificia Universidad Catolica de Chile), Peter Humphreys (Children’s Hospital of Eastern Ontario), Lori C. Jordan (Vanderbilt University Medical Center, Nashville), Sally Sultan (Columbia University Medical Center, New York), Michael J. Rivkin (Boston Children’s Hospital), Mubeen F. Rafay (Children’s Hospital, Winnipeg, University of Manitoba), Luigi Titomanlio (L’Hôpital Robert Debré-Paris), Gordana S. Kovacevic (Mother and Child Healthcare Institute, Serbia), Jerome Y. Yager (Stollery Children’s Hospital), Catherine Amlie-Lefond (Seattle Children’s Hospital), Nomazulu Dlamini (Evelina London Children’s Hospital), John Condie (Phoenix Children’s Hospital), Ann Yeh (Women and Children’s Hospital of Buffalo), Rachel Kneen (Alder Hey Children’s Hospital), Mingming J. Lim (Evelina London Children’s Hospital), Jessica L. Carpenter (Children’s National Medical Center, Washington, D.C.), Steven Lim (Evelina London Children’s Hospital), Robert Forsyth (Institute of Neuroscience, Newcastle University, United Kingdom).

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References
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