Timing of Incident Stroke Risk After Cervical Artery Dissection Presenting Without Ischemia

Nicholas A. Morris, MD; Alexander E. Merkler, MD; Gino Gialdini, MD; Hooman Kamel, MD

Background and Purpose—Cervical artery dissection is a common cause of stroke in young people. The temporal profile of stroke risk after cervical artery dissection presenting without ischemia remains uncertain.

Methods—We performed a crossover cohort study using administrative claims data on all emergency department visits and acute care hospitalizations from 2005 to 2011 in CA, 2006 to 2013 in NY, and 2005 to 2013 in FL. Using previously validated International Classification of Diseases, Ninth Revision, Clinical Modification codes, we identified patients with a cervical artery dissection and no previous or concurrent stroke or transient ischemic attack diagnosis. We compared the risk of stroke in successive 2-week periods during the 12 weeks after dissection versus the corresponding 2-week period 1 year later. Absolute risk increases were calculated using McNemar test for matched data. In a sensitivity analysis, we limited our population to patients presenting with typical symptoms of cervical artery dissection.

Results—We identified 2791 patients with dissection without ischemia. The absolute increase in stroke risk was 1.25% (95% confidence interval, 0.84–1.67%) in the first 2 weeks after dissection compared with the same time period 1 year later. The absolute risk increase was 0.18% (95% confidence interval, 0.02–0.34%) during weeks 3 to 4 and was no longer significant during the remainder of the 12-week postdissection period. Our findings were similar in a sensitivity analysis identifying patients who presented with typical symptoms of acute dissection.

Conclusions—The risk of stroke after cervical artery dissection unaccompanied by ischemia at time of diagnosis seems to be limited to the first 2 weeks. (Stroke. 2017;48:551-555. DOI: 10.1161/STROKEAHA.116.015185.)

Key Words: dissection ■ hospitalization ■ risk ■ stroke ■ vertebral artery dissection

Cervical artery dissection is a common cause of stroke in the young.1–3 Dissections can result from trauma or occur spontaneously; however, so-called spontaneous dissections may be because of unnoticed minor trauma with or without predisposing factors such as connective tissue disease, hypertension, or smoking.4–8 Population-based studies have documented an annual incidence of cervical artery dissection of 2.6 to 3.0 per 100,000 people, with over half presenting with stroke or transient ischemic attack.9,10 The true incidence may be much higher, since on top of the at least 6% to 10% that are diagnosed as asymptomatic cases there may be many times that number of asymptomatic traumatic dissections that never present.10,11 Short- and long-term outcomes of cervical artery dissection are uncertain, with data mostly derived from older, single-center, small retrospective studies with limited follow-up. More recent larger, multicenter, prospective studies demonstrate disparate results. The overall frequency of stroke and frequency of stroke as a first symptom vary widely among studies.12–16 There is a paucity of data on the time period during which patients with cervical artery dissection face a heightened stroke risk, though it is commonly thought to be up to weeks to months. Furthermore, nearly all of the literature on incidence and timing of stroke after cervical artery dissection focuses on recurrent ischemic events as opposed to incident stroke after a known dissection.16–21 In this study, we used administrative claims data from a large, heterogeneous population to evaluate the time period during which patients with cervical artery dissection who present without transient ischemic attack or stroke are at increased risk of incident stroke.

Methods

Study Design
We performed a crossover cohort study using data on all emergency department visits and inpatient discharges in CA, FL, and NY. These data were collected by the California Office of Statewide Health Planning and Development, the New York Statewide Planning and Research Cooperative System, and the Florida Agency for Health Care Administration. These 3 agencies provide these data to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization Project.22 Each patient is assigned a personal linkage number that allows them to be followed anonymously through all subsequent hospitalizations.23 Up to 25 discharge diagnoses are coded at each encounter using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system. This study was approved by the institutional review board at Weill Cornell Medicine.

Received August 22, 2016; final revision received November 23, 2016; accepted November 29, 2016.
From the Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute (N.A.M., A.E.M., G.G., H.K.) and Department of Neurology (A.E.M., H.K.), Weill Cornell Medicine, New York, NY; and Department of Neurology, Columbia University Medical Center, New York, NY (N.A.M.).
Presented in part at the International Stroke Conference of the American Heart Association, Houston, TX, February 22–24, 2017.
Correspondence to Alexander E. Merkler, MD, Weill Cornell Medicine, Department of Neurology, 525 E 68th St, F610, New York, NY 10065. E-mail alm9097@med.cornell.edu
© 2017 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.015185
Study Subjects
We defined cervical artery dissection as the presence of carotid artery or vertebral artery dissection using ICD-9-CM codes 443.21 and 443.29 in any emergency department or hospital discharge diagnosis position. These ICD-9-CM codes have previously been validated with a positive predictive value of 82.1% for dissection. We identified adults aged 18 years or older with a diagnosis of cervical artery dissection from 2005 to 2011 in CA, 2006 to 2013 in NY, and 2005 to 2013 in FL. These states were chosen because they encompass a demographically heterogeneous population that represents nearly 20% of the US population. The dates were chosen because they represent the most up-to-date data that include a linkage variable to allow longitudinal follow-up. To assess the time period during which patients with cervical artery dissection are at risk for an incident stroke, we excluded patients who had a stroke before or during the index encounter for cervical artery dissection. To ensure that we excluded any patient with a possible stroke before or at the same time as the dissection, we used an inclusive definition of cerebrovascular disease (ICD-9-CM codes 430–438). Finally, we excluded nonresidents of CA, NY, and FL to maximize the completeness of follow-up.

Measurements
All patients were followed for the primary outcome of ischemic stroke, defined as ICD-9-CM codes 433.x1, 434.x1, or 436 in any diagnosis code position in the absence of a primary discharge code for rehabilitation (V57) or any codes for subarachnoid hemorrhage (430), intracerebral hemorrhage (431), or brain trauma (800–804 and 850–854). This combination of diagnosis codes has been found to have a sensitivity of 86% and a specificity of 95% for ischemic stroke.

Statistical Analysis
Patients with multiple visits for cervical artery dissection were entered into the analysis at their index visit for dissection. The risk of ischemic stroke was assessed during successive 2-week periods from the time of the index visit for cervical artery dissection until 12 weeks after the visit. The risk in each of these 2-week periods was compared with the corresponding 2-week period 1 year later. This design allowed patients to serve as their own controls, thus mitigating the effects of unmeasured confounders. Absolute risk increases were calculated using McNemar test for matched data via Stata mcc command.

We performed 4 sensitivity analyses. In the first sensitivity analysis, to help ensure that we evaluated the risk of stroke after acute dissection, we limited our population to only patients who presented with neurological symptoms of cervical artery dissection such as headache, neck pain, cranial nerve palsies referable to the cavernous sinus or hypoglossal nerve, Horner syndrome, hoarseness, or symptoms referable to the posterior fossa, such as tinnitus or vertigo. In the second sensitivity analysis, we evaluated only those patients who underwent magnetic resonance imaging (MRI) at the initial encounter for dissection so as to ensure the exclusion of patients who already had infarction at the time of dissection. Of note, information on the use of MRI was only available for patients from NY. In the third sensitivity analysis, we assessed the risk of ischemic stroke after cervical artery dissection using a more inclusive definition of stroke (ICD-9-CM codes 430–438 in any diagnosis code position). In the final sensitivity analysis, to assess the impact of mortality or out-of-state migration, we limited our cohort to patients who had at least 1 emergency department visit or hospitalization after the crossover period 1 year after the index visit for dissection.

To assess whether or not traumatic dissections might have a different risk and timing of stroke, we performed a subgroup analysis evaluating patients with concomitant trauma of the head or neck (ICD-9-CM codes 800–806, 839.1, 839.2, 847.0, 850–854.1, 900.x, 920, 952.2, and 959.0). All statistical analyses were performed using Stata/MP (version 13; College Station, TX). The threshold of statistical significance was set at α=0.05.

Results
We identified 2791 patients with an index visit for cervical artery dissection without concomitant stroke or transient ischemic attack (Figure) in whom the mean age was 49.9 (±16.6) years, and 46.5% were women (Table 1). In the 12 weeks after cervical artery dissection, 47 patients (1.68%) developed a stroke, when compared with zero strokes in the corresponding 12-week period 1 year later.

There were significantly more strokes within the 0- to 2-week period after cervical artery dissection than during the same period 1 year later (47 versus 0 events), corresponding to an absolute risk difference of 1.25% (95% confidence Interval [CI], 0.84–1.67%). The absolute risk increase was 0.18% (95% CI, 0.02–0.34%) in the 3- to 4-week postdissection period. Starting at 5 weeks after dissection, the risk of stroke was no longer significantly elevated (Table 2).

In a sensitivity analysis that identified 541 patients with dissections associated with symptoms, 1.84% (95% CI, 0.53–3.17%) developed a stroke, all of which occurred within the first 4 weeks after dissection. This temporal profile of stroke risk after dissection was unchanged in a sensitivity analysis using more inclusive diagnosis codes for stroke. Similarly, there was no significant change in our results when we included only patients with MRI performed at the index visit for dissection. Data on the use of MRI was available for 461 patients, 277 of whom were confirmed to have undergone MRI. Five out of those 277 patients (1.08%; 95% CI, 0.2–2.25%) developed a stroke after dissection, and

Figure. Cohort ascertainment. Flow chart describing the ascertainment of patients with cervical artery dissection.
all occurred within the first 2-week period after diagnosis, when compared with no events in the same 2-week period 1 year later.

We identified 840 patients with traumatic cervical artery dissections, 12 of whom developed subsequent stroke. The stroke risk in patients with traumatic cervical artery dissections was not significantly different to those without evidence of a traumatic dissection (1.43%; 95% CI, 0.51–2.35% versus 1.79%; 95% CI, 1.15–2.43%; P=0.49). The temporal profile of the stroke risk was similar between the groups.

Last, our findings were unchanged in a sensitivity analysis limited to patients who had at least 1 visit after the crossover period, thereby assuring that they remained alive and resident in the same US state throughout follow-up.

Table 1. Characteristics of Patients With Dissection

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>No Stroke (N=2744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>49.9 (16.6)</td>
</tr>
<tr>
<td>Female</td>
<td>1297 (46.5)</td>
</tr>
<tr>
<td>Race†</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1923 (70.1)</td>
</tr>
<tr>
<td>Black</td>
<td>223 (8.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>327 (11.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>115 (4.2)</td>
</tr>
<tr>
<td>Other</td>
<td>157 (5.7)</td>
</tr>
<tr>
<td>Payment source</td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>479 (17.2)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>293 (10.5)</td>
</tr>
<tr>
<td>Private</td>
<td>1685 (60.4)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>137 (4.9)</td>
</tr>
<tr>
<td>Other</td>
<td>197 (7.1)</td>
</tr>
<tr>
<td>Income quartile</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>475 (17.3)</td>
</tr>
<tr>
<td>2</td>
<td>614 (22.4)</td>
</tr>
<tr>
<td>3</td>
<td>723 (26.4)</td>
</tr>
<tr>
<td>4</td>
<td>927 (33.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1139 (40.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>309 (11.1)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>92 (3.3)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>263 (9.4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>66 (2.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>107 (3.8)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>70 (2.5)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>147 (5.3)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>193 (6.9)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>444 (15.9)</td>
</tr>
</tbody>
</table>

*Data are presented as number (%) unless otherwise specified.
†Self-reported by patients or their surrogates. Numbers do not sum to group totals because of missing race/ethnicity data in 1.6% of patients.

Discussion

In a large, heterogeneous patient population presenting with cervical artery dissection in the absence of transient ischemic attack or stroke, we found that ≈1.7% developed a stroke in the first 12 weeks after the diagnosis of dissection, and that almost all of the strokes occurred in the first 2 weeks. Our findings were essentially unchanged in several sensitivity analyses.

Our results are in line with the CADISS trial (Cervical Artery Dissection in Stroke Study), a large, multicenter study that randomized patients presenting with cervical artery dissection to either anticoagulation or antiplatelet agents, and found an overall stroke recurrence rate of 2% at 3 months, with all recurrences occurring within the first 10 days.27–29 Unlike our study, the majority of patients (195/225) in the CADISS trial presented with stroke. All strokes after randomization in the CADISS trial occurred in patients who initially presented with stroke. The CADISP study (Cervical Artery Dissection and Ischemic Stroke Patients), a large observational study of consecutive admissions with cervical artery dissection in which most (64%) presented with stroke, found a similar rate of new stroke at 3 months (2.7%).18 Among the 198 patients in CADISP who did not initially present with stroke, 3 (1.5%) developed an incident event within 3 months. The number of events was too small to precisely establish the temporal profile of stroke risk. Our findings build on these previous studies by establishing that the risk of incident stroke after presentation with cervical artery dissection is essentially limited to the first 2 weeks after diagnosis. This is useful because headache and neck pain are the most frequent initial symptoms of cervical artery dissection cases,15,16,26 whereas cerebral or retinal infarction is the inaugural event in only 11% to 33% of cases.10,11 Our findings may aid in counseling patients on their risk of stroke.

Trauma, as a distinct cause of cervical artery dissection that can cause ischemia, is worth considering separately. Previous studies found that ≤60% of patients who suffer blunt cerebrovascular injury and present without stroke will develop stroke if left untreated, although because none of these studies evaluated all trauma cases with angiography regardless of suspicion for vessel injury, the true rate could be significantly lower.27–29 Many of these patients have suffered significant neurological injury at the time of injury. In a single-center retrospective review, the stroke rate after blunt cerebrovascular injury was

<table>
<thead>
<tr>
<th>Time Interval After Dissection</th>
<th>Case Period (%)</th>
<th>Crossover Period (%)</th>
<th>Absolute Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0–2</td>
<td>1.25</td>
<td>0</td>
<td>1.25 (0.84 to 1.67)</td>
</tr>
<tr>
<td>Weeks 3–4</td>
<td>0.18</td>
<td>0</td>
<td>0.18 (0.02 to 0.34)</td>
</tr>
<tr>
<td>Weeks 5–6</td>
<td>0.11</td>
<td>0</td>
<td>0.11 (−0.01 to 0.23)</td>
</tr>
<tr>
<td>Weeks 7–8</td>
<td>0.04</td>
<td>0</td>
<td>0.04 (−0.03 to 0.11)</td>
</tr>
<tr>
<td>Weeks 9–10</td>
<td>0.04</td>
<td>0</td>
<td>0.04 (−0.03 to 0.11)</td>
</tr>
<tr>
<td>Weeks 11–12</td>
<td>0.07</td>
<td>0</td>
<td>0.07 (−0.03 to 0.17)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Data for the case period are for the indicated interval after cervical artery dissection.
†Data for the crossover period are for the indicated interval plus 1 y after cervical artery dissection.
reduced to 4% with early treatment.\textsuperscript{29} Little data exist to inform stroke risk after discharge after traumatic dissection without concomitant neurological injury. One series of 16 patients with traumatic dissection found that the mean time between trauma and stroke was 4.8 days with a range from 0 to 31 days.\textsuperscript{16} In our study of over 800 patients with traumatic cervical artery dissection presenting without stroke, the risk of stroke was 1.43%, not significantly different from that of nontraumatic dissections.

The results of our study must be considered in light of its limitations. First, we did not have access to information describing patients’ symptomatology, imaging characteristics, or treatment. As such, even with well-validated diagnostic codes, some patients may have escaped diagnosis and inclusion in our study because radiographic data could not be reviewed. Moreover, we cannot aid in settling the controversy on treatment with antiplatelet agents versus anticoagulation and can only assume that patients were treated with one or the other in line with current guidelines.\textsuperscript{39} Second, we likely missed cases of asymptomatic or minimally symptomatic cervical artery dissection that did not come to medical attention. However, this would be a conservative bias because these milder cases would be expected to face an even lower and briefer risk of stroke. Third, some patients may have presented in a delayed fashion after the onset of symptoms, obscuring the true timing of stroke risk after acute dissection. Our sensitivity analysis, including only patients presenting with acute symptoms of dissection, may mitigate this limitation because these patients are less likely to delay presentation. Fourth, our use of administrative claims may have led to misclassification of stroke events. However, the diagnosis code algorithms we used have good sensitivity and specificity. More importantly, misclassification would not be expected to vary over 2-week time blocks and thus should not have significantly affected our main finding on the temporal pattern of stroke risk. Fifth, some patients may have migrated out of state after the 3-month postdissection period. This would have lowered our risk estimates because, in these patients, strokes during the crossover period would not have been captured. However, our findings were unchanged in a sensitivity analysis limited to patients who had at least 1 visit in the same state after the crossover period, thus ensuring that they were subject to full follow-up throughout the study period. Sixth, although it may be informative to evaluate the more chronic risk of incident stroke after dissection, the crossover design of the study does not lend itself to such an analysis. Future studies will need to evaluate long-term risk. Finally, stroke risk immediately after dissection was compared with the risk 1 year later, and it could be argued that this comparison period is an artificially high-risk period because patients may have continued to be at a higher risk of stroke given a persistent dissection. However, this is not the case in our data because we found no stroke diagnoses during the 1-year control period after dissection.

**Conclusions**

Among patients presenting with acute cervical artery dissection and no evidence of stroke, we found that the risk of incident stroke was clustered mainly within the first 2 weeks. Further research is necessary to delineate the optimal type and duration of antithrombotic therapy for stroke prevention in these patients.

**Acknowledgments**

We are grateful to Monica Chen for copyediting and clerical assistance.

**Sources of Funding**

This study was supported by grant K23NS082367 (Dr Kamel) from the National Institute of Neurological Disorders and Stroke, a grant from the Michael Goldberg Stroke Research Fund (Dr Kamel), and funding from the Feil Family Foundation (Dr Gialdini).

**Disclosures**

None.

**References**


Timing of Incident Stroke Risk After Cervical Artery Dissection Presenting Without Ischemia

Nicholas A. Morris, Alexander E. Merkler, Gino Gialdini and Hooman Kamel

Stroke. 2017;48:551-555; originally published online February 23, 2017;
doi: 10.1161/STROKEAHA.116.015185

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/48/3/551

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/