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## Timing of Incident Stroke Risk Following Cervical Artery Dissection Presenting without Ischemia

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### Abstract

**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 2005–2011 in California, 2006–2013 in New York, and 2005–2013 in Florida. Using previously validated *ICD-9-CM* codes, we identified patients with a cervical artery dissection and no prior or concurrent stroke or TIA 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’s 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 2,791 patients with dissection without ischemia. The absolute increase in stroke risk was 1.25% (95% CI, 0.84–1.67%) in the first 2 weeks after dissection compared to the same time period 1 year later. The absolute risk increase was 0.18% (95% CI 0.02–0.34%) during weeks 3–4, and was no longer significant during the remainder of the 12 week post-dissection period. Our findings were similar in a sensitivity analysis identifying patients who presented with typical symptoms of acute dissection.

**Conclusions**—The risk of stroke following cervical artery dissection unaccompanied by ischemia at time of diagnosis appears to be limited to the first 2 weeks.

### Keywords

Stroke; Internal Carotid Artery Dissection; Vertebral Artery Dissection; Healthcare Administrative Claims

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## Subject Terms

Cerebrovascular Disease/Stroke; Ischemic Stroke; Risk Factors

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Cervical artery dissection is a common cause of stroke in the young.<sup>1–3</sup> Dissections can result from trauma or occur spontaneously; however, so-called spontaneous dissections may be due to unnoticed minor trauma with or without predisposing factors such as connective tissue disease, hypertension, or smoking.<sup>4–8</sup> Population-based studies have documented an annual incidence of cervical artery dissection of 2.6–3.0 per 100,000 persons, with over half presenting with stroke or transient ischemic attack (TIA).<sup>9,10</sup> The true incidence may be very much higher, since on top of the at least 6–10% that are diagnosed as asymptomatic cases there may be many times that number of asymptomatic traumatic dissections that never present.<sup>10,11</sup> 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.<sup>12–16</sup> There is a paucity of data regarding 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 regarding incidence and timing of stroke following cervical artery dissection focuses on recurrent ischemic events as opposed to incident stroke following a known dissection.<sup>16–21</sup> 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 TIA or stroke are at increased risk of incident stroke.

## Methods

### Study Design

We performed a crossover-cohort study using data on all emergency department (ED) visits and inpatient discharges in California, Florida, and New York. 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 three agencies provide these data to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization Project.<sup>22</sup> Each patient is assigned a personal linkage number that allows them to be followed anonymously through all subsequent hospitalizations.<sup>23</sup> 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.

### 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 ED or hospital discharge diagnosis position. These *ICD-9-CM* codes have previously been validated with a positive predictive value of 82.1% for dissection.<sup>24</sup> We identified adults aged 18 years or older with a

diagnosis of cervical artery dissection from 2005–2011 in California, 2006–2013 in New York, and 2005–2013 in Florida. These states were chosen as they encompass a demographically heterogeneous population that represents nearly 20% of the United States population. The dates were chosen because they represent the most up-to-date data that include a linkage variable to allow longitudinal follow-up. In order 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 prior to or during the index encounter for cervical artery dissection. To ensure that we excluded any patient with a possible stroke prior to or at the same time as the dissection, we used a very inclusive definition of cerebrovascular disease (*ICD-9-CM* codes 430–438). Finally, we excluded non-residents of California, New York, and Florida in order 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.<sup>25</sup>

### 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's test for matched data via Stata's *mcc* command.

We performed four 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 that presented with typical 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 exclusion of patients who already had infarction at the time of dissection. Of note, information regarding the use of MRI was only available for patients from New York. 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 one ED 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, 959.0).

All statistical analyses were performed using Stata/MP (version 13, College Station, TX). The threshold of statistical significance was set at  $\alpha = 0.05$ .

## Results

We identified 2,791 patients with an index visit for cervical artery dissection without concomitant stroke or TIA (Figure 1) in whom the mean age was 49.9 ( $\pm 16.6$ ) years and 46.5% were women (Table 1). In the 12 weeks after cervical artery dissection, 47 patients (1.68%) developed a stroke, as compared to zero strokes in the corresponding 12-week period 1 year later.

There were significantly more strokes within the 0–2 week period after cervical artery dissection than during the same period 1 year later (47 vs. 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 3–4 week post-dissection 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 four 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 regarding 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, 0–2.25%) developed a stroke after dissection, and all occurred within the first 2-week period after diagnosis, as compared to 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% vs. 1.79%; 95% CI, 1.15%–2.43%,  $p = .49$ ). The temporal profile of the stroke risk was similar between the groups.

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

## Discussion

In a large, heterogeneous patient population presenting with cervical artery dissection in the absence of TIA or stroke, we found that approximately 1.7% developed a stroke in the first 12 weeks following 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, 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.<sup>19</sup> Unlike our study, the majority of patients (195/225) in the CADISS trial presented with stroke. All strokes following randomization in the CADISS trial occurred in patients who initially presented with stroke. The CADISP Study, 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%).<sup>18</sup> 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 prior 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<sup>15–16,26</sup> while cerebral or retinal infarction is the inaugural event in only 11–33% of cases.<sup>10–11</sup> Our findings may aid in counseling patients regarding their risk of stroke.

Trauma, as a distinct cause of cervical artery dissection that can cause ischemia, is worth considering separately. Prior studies found that up to 60% of patients who suffer blunt cerebrovascular injury and present without stroke will develop stroke if left untreated, although since none of these studies evaluated all trauma cases with angiography regardless of suspicion for vessel injury, the true rate could be significantly lower.<sup>27–29</sup> 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 reduced to 4% with early treatment.<sup>29</sup> Little data exist to inform stroke risk after discharge following 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.<sup>16</sup> 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 non-traumatic 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 as radiographic data could not be reviewed. Moreover, we cannot aid in settling the controversy regarding treatment with antiplatelet agents versus anticoagulation, and can only assume that patients were treated with one or the other in line with current guidelines.<sup>30</sup> 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 since 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 following the onset of symptoms, obscuring the true timing of stroke risk following acute dissection. Our sensitivity analysis including only patients presenting with acute symptoms of dissection may mitigate this limitation as 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 regarding the temporal pattern of stroke risk. Fifth, some patients may have migrated out of state after the 3-month post-dissection period. This would have lowered our risk estimates since, 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 one visit in the same state after the crossover period, thus ensuring that they were subject to full follow-up throughout the study period. Sixth, while 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 since 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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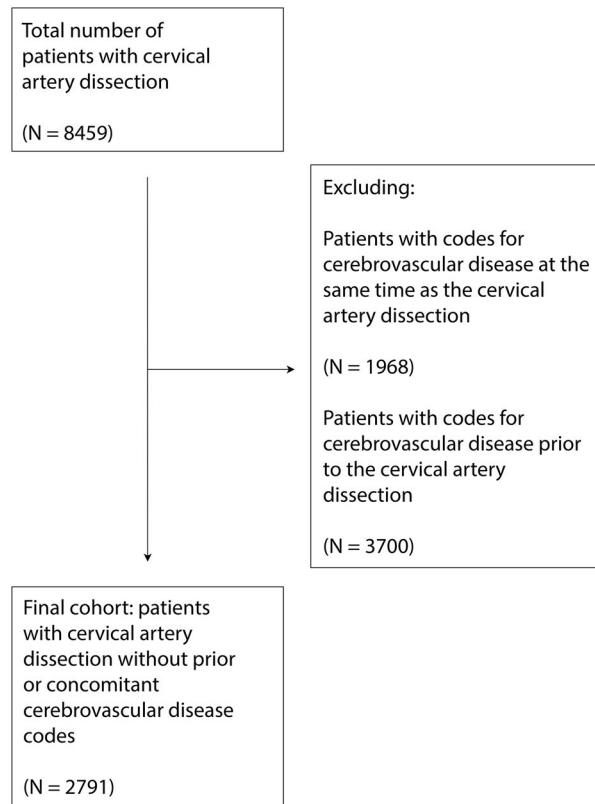
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**Figure 1.**

**Cohort Ascertainment**

*Legend:* Flow-chart describing the ascertainment of patients with cervical artery dissection.

**Table 1**

## Characteristics of Patients with Dissection

Characteristic <sup>a</sup>	No Stroke (N = 2744)
Age, mean (SD), y	49.9 (16.6)
Female	1,297 (46.5)
Race <sup>b</sup>	
White	1,923 (70.1)
Black	223 (8.1)
Hispanic	327 (11.9)
Asian	115 (4.2)
Other	157 (5.7)
Payment source	
Medicare	479 (17.2)
Medicaid	293 (10.5)
Private	1,685 (60.4)
Self-pay	137 (4.9)
Other	197 (7.1)
Income quartile	
1	475 (17.3)
2	614 (22.4)
3	723 (26.4)
4	927 (33.8)
Hypertension	1,139 (40.8)
Diabetes	309 (11.1)
Congestive heart failure	92 (3.3)
Coronary heart disease	263 (9.4)
Peripheral vascular disease	66 (2.4)
Chronic obstructive pulmonary disease	107 (3.8)
Chronic kidney disease	70 (2.5)
Atrial fibrillation	147 (5.3)
Tobacco use	193 (6.9)
Alcohol use	444 (15.9)

Abbreviations: IQR, interquartile range; SD, standard deviation

<sup>a</sup>Data are presented as number (%) unless otherwise specified.

<sup>b</sup>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.

**Table 2**Risk of Stroke during Sequential 2-Week Intervals after Cervical Artery Dissection<sup>a,b</sup>

Time Interval after Dissection	Case Period (%)	Crossover Period (%)	Absolute Risk Difference (95% CI)
Weeks 0–2	1.25	0	1.25 (0.84–1.67)
Weeks 3–4	0.18	0	0.18 (0.02–0.34)
Weeks 5–6	0.11	0	0.11 (–0.01–0.23)
Weeks 7–8	0.04	0	0.04 (–0.03–0.11)
Weeks 9–10	0.04	0	0.04 (–0.03–0.11)
Weeks 11–12	0.07	0	0.07 (–0.03–0.17)

Abbreviations: CI, confidence interval

<sup>a</sup>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 year after cervical artery dissection.

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