Urgent Carotid Surgery and Stenting May Be Safe After Systemic Thrombolysis for Stroke

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Background and Purpose—Early carotid surgery or stenting after thrombolytic treatment for stroke has become more common during recent years. It is unclear whether this carries an increased risk of postoperative complications and death. The aim of this nationwide population-based study was, therefore, to investigate the safety of urgently performed carotid procedures in patients treated with thrombolysis for stroke.

Methods—Using the national Vascular and Stroke registries, we identified 3998 patients who had undergone carotid endarterectomy or carotid artery stenting for symptomatic carotid stenosis between May 2008 and December 2012. Among these, 2% (79 of 3998) had undergone previous thrombolysis for stroke. We conducted a retrospective review of registry data and individual case records with regard to postoperative complications, including surgical-site bleeding, stroke, and death. The outcome was compared with the results for the remaining patient cohort (3919 of 3998) undergoing carotid surgery and stenting during the study period.

Results—The median time between thrombolysis and the carotid procedure was 10 days. Seventy-one patients underwent carotid endarterectomy, and 6 patients underwent carotid artery stenting. The 30-day death and stroke rate for the thrombolysis cohort was 2.5% (2 of 79), and for the whole cohort, it was 3.8% (139 of 3626; P=0.55). The postoperative bleeding rates requiring reoperation were not significantly different between the groups (3.8% [3 of 79] in the thrombolysis group versus 3.3% [119 of 3626] in the whole cohort; P=0.79). There was no correlation between time from lysis to surgery or stenting and complications at 30 days postoperatively.

Conclusions—Urgent carotid endarterectomy or carotid artery stenting after thrombolysis for stroke may be safe without increased risk of serious complications. (Stroke. 2014;45:776-780.)

Key Words: endarterectomy, carotid ■ stroke ■ thrombolytic therapy

In the past few years, there has been increasing evidence supporting the role of early carotid endarterectomy (CEA) for severe carotid stenosis in the emergent treatment of stroke.1 If undertaken beyond the first 2 weeks of the index insult, evidence suggests that the maximum benefit of surgery in reducing the risk of further cerebrovascular ischemic events is reduced.2

The use of thrombolysis in the hyperacute treatment of cerebrovascular ischemia has gradually increased since 1996, when recombinant tissue-type plasminogen activator (tPA) was approved for use in ischemic stroke.3,4 This, together with a move toward earlier surgery for patients with significant symptomatic carotid artery lesions, may suggest that the number of patients who have received thrombolytic treatment and are considered for surgical treatment will increase over time. However, little is known about the results and safety of early CEA or carotid artery stenting (CAS) after thrombolysis. The aim of this nationwide study was to report the outcomes of CEA/CAS after thrombolysis for stroke.

Methods

Study Data
We conducted a review of prospectively collected data in the Swedish National Registry for Vascular Surgery (Swedvasc) and the Swedish Stroke Registry (Riks-Stroke) from May 1, 2008, to December 11, 2012. Ethical approval was obtained from the local ethical review board.

The Swedvasc registry covers the 22 vascular centers in Sweden where either CEA or CEA/CAS are undertaken. Previous external validation for CEA has been 93.4% in the Swedvasc registry after comparing vascular registry data for CEA/CAS with the Swedish Hospital Discharge Register data and the National Population Registry (for mortality) by matching every individual patient using a unique 10-digit personal identity code.5,6 All citizens and permanent residents in Sweden have a 10-digit personal identity code used to identify the patient in the Swedvasc registry, the Stroke registry, and the Population registry. Mortality data in the Swedvasc register...
are fully accurate because the register is continuously cross-checked against the National Population Register.

The Swedish Stroke Register is the world’s longest-running national stroke quality-improvement register and includes all 76 hospitals in Sweden admitting patients with acute stroke.5,6 A detailed analysis of the stroke register data quality has shown that the concordance between hospital inpatient medical records versus data recorded in the stroke register is high (298%) for stroke subtype and clinical parameters. The vascular and stroke registries complement each other with regard to pre-, peri-, and postoperative data. Overlapping data between the registries concern comorbidities.

**Patient Data Collection**

Data about demographics (age, sex, presenting symptoms, comorbidities, date and type of procedure, and follow-up visits at 30 days) were collected from the vascular registry. These data were subsequently cross-matched with the stroke registry, which added data on diagnostics, neurological disability, and medications. All registry data were collected prospectively. In addition, individual patient records of those having undergone previous thrombolysis were accessed retrospectively (after patients had given their written consent) and scrutinized to ensure collection of complete data. It must be noted that not all patients (n=19) gave consent for examination of their medical records, resulting in some missing values about comorbidities, as can be seen in Table 1.

Clinical presentation was divided into major (stroke causing disabling symptoms) or minor stroke (regression of symptoms within 1 week or minimal remaining dysfunction). The modified Rankin score was used to assess neurological disability pre- and postoperatively, and the National Institutes of Health Stroke Scale score was used for assessment of neurological impairment before and 24 hours after thrombolysis.

All patients were assessed on arrival in hospital by a stroke physician and deemed suitable for thrombolysis. All underwent acute computed tomography of the brain, after which thrombolysis was commenced with systemic administration of recombinant tPA.

### Table 1. Demographics of the Study Cohort Undergoing Carotid Surgery and Stenting

<table>
<thead>
<tr>
<th></th>
<th>Thrombolysis Cohort n=79</th>
<th>Nonthrombolysis Cohort n=3919*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>71 (37–84)</td>
<td>73 (40–92)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>54/25</td>
<td>2631/1288</td>
<td>0.83</td>
</tr>
<tr>
<td>(68%/32%)</td>
<td>(67%/33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor stroke</td>
<td>46/79 (58%)</td>
<td>1344/3919 (34%)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Major stroke</td>
<td>33/79 (42%)</td>
<td>70/3919 (1.8%)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>15/54 (28%)</td>
<td>759/3077 (25%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Treated for hypertension</td>
<td>60/79 (76%)</td>
<td>2923/3650 (81%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21/79 (27%)</td>
<td>735/3650 (20%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Heart disease</td>
<td>19/67 (28%)</td>
<td>1117/3583 (31%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>24/79 (30%)</td>
<td>678/3698 (18%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Medication affecting coagulation before stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin only</td>
<td>36/78 (46%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel only</td>
<td>3/78 (4%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole only</td>
<td>3/78 (4%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>1/78 (1.3%)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* indicates female; M, male; NA, these data were not available for the nonthrombolysis cohort because they were not recorded in the Swedvasc register; and TIA, transient ischemic attack.

The denominator varies because of missing values in the registries; the number varies depending on the variable.

All patients underwent carotid imaging, with duplex ultrasound, computed tomography angiography, or magnetic resonance angiogram, depending on local protocol. Some patients underwent >1 of these examinations. The degree of stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.2 Patients underwent either open CEA by conventional endarterectomy or by the eversion method or CAS.

Recoded comorbidities included diabetes mellitus (ie, treated with oral antidiabetics or insulin), treatment for hypertension (ie, recorded in medical records as being prescribed antihypertensive medication), renal insufficiency (serum creatinine >150 mmol/L), heart disease (history of previous myocardial infarction, angina pectoris, heart failure, or previous coronary intervention), and previous stroke or transient ischemic attack. Major stroke was defined as a cerebrovascular lesion with residual symptoms not restituted within 1 week. Minor stroke was defined as a stroke with symptoms restituted within 1 week or with only minor residual dysfunction. Transient ischemic attack was defined as neurological symptoms restituted within 24 hours of first appearance of symptoms.

Postoperative follow-up took place 30 days after the procedure through outpatient assessment by a neurologist, stroke specialist, or vascular surgeon, depending on local practice at the participating centers.

A summary of recent (2009–2013) studies examining outcome of CEA after thrombolysis for stroke was conducted using a PubMed search and the following MeSH (medical subject headings) terms: thrombolytic therapy, CEA, stent, and stroke (please see Discussion).

### Statistics

All data were analyzed using IBM SPSS version 21 (IBM Corporation) except for the calculation of Fisher exact test, which was performed using the online interface at http://www.quantpsy.org/fisher/fisher.htm. Descriptive statistics, including median and range, were calculated as appropriate. P<0.05 was considered to be statistically significant.

### Results

#### Patient Characteristics

This study included the 3998 patients who underwent surgery or stenting of their carotid artery during the study period for symptomatic carotid artery stenosis. During the same period, another 864 patients underwent CEA/CAS for asymptomatic carotid artery stenosis. Among the symptomatic patients, 79 of 3998 (2%) patients had undergone systemic thrombolysis for stroke before CEA/CAS. The median age in this latter group was 71 years (range, 37–84), and 68% were men. Minor stroke (58%) was the dominating neurological presentation in the thrombolysis cohort (functional status determined after thrombolysis). The basic demographics of the patients who underwent systemic thrombolysis for stroke before CEA/CAS (n=79) and the corresponding variables for the remaining patients undergoing CEA/CAS (n=3919) during the study period are summarized in Table 1.

Recombinant tPA was commenced within 360 minutes from the onset of symptoms (median, 150 minutes; range, 40–360 minutes). The median National Institutes of Health Stroke Scale score (available for 66 of 79 patients) on arrival was 8 (range, 2–25), and the median score after lysis was 3 (range, 0–18). The median preoperative modified Rankin score was 2.0 (range, 0–5).

#### Carotid Surgery and Stenting After Thrombolysis

Carotid surgery and stenting were undertaken at a median of 10 days (range, 0–108 days; interquartile range, 6, 10,
Complications and Follow-Up

The 30-day death and stroke (minor and major) rate for the nonthrombolysis cohort was 3.8% (139 of 3626) compared with the thrombolysis cohort of 2.5% (2 of 79), with no significant difference between the groups \( (P=0.55) \). In the thrombolysis cohort at 30-day follow-up, 2 patients (2.5%) experienced a postoperative stroke: 1 minor hemispheric stroke and 1 retinal artery infarction (both had undergone CEA). The median postoperative modified Rankin score was 0.5 (range, 0–4).

There were no cerebral hemorrhages, cranial nerve injuries, or cardiac events reported. None of the 79 patients died within 2 years of surgery.

Three patients in the thrombolysis cohort (3.8%) required reoperation secondary to surgical-site bleeding. The postoperative bleeding rates requiring reoperation were not significantly different between the groups (3.8% in the thrombolysis group versus 3.3% in the control group; \( P=0.79 \)).

Please see Tables 2 and 3 for a summary of the complications observed in the study cohorts and further characteristics of the patients who experienced any complications within 30 days, respectively. There was no correlation between time from lysis to CEA/CAS and the presence of any complication at 30 days postoperatively (Pearson \( r=0.164; P=0.189 \)). Furthermore, there was no increased likelihood of complication if surgery was undertaken within 2 weeks of thrombolysis compared with procedures undertaken outside this time frame \( (P=0.15; \text{Fisher exact test}) \). Thrombolysis did not influence the overall 30-day postoperative complication rate (Pearson \( \chi^2=3.24; P=0.072 \)).

Discussion

In this population-based study, there were low complication rates for patients undergoing CEA/CAS for carotid artery stenosis after systemic thrombolysis for stroke. This is, to our knowledge, the largest reported cohort of such patients, demonstrating that the national registries for vascular surgery and stroke provide a unique opportunity to analyze a rather small but increasing stroke cohort. In the cohort receiving thrombolysis, there was a 2.5%, 30-day stroke rate and no deaths, and the most common complication was reoperation for surgical-site bleeding (3.8%).

We found no correlation between postoperative complications and time from lysis to intervention or if the intervention was performed within 2 weeks. The median time between thrombolysis and the carotid procedure in this study was 10 days. As can be seen in Table 3, all complications in this cohort were observed in those undergoing surgery within 1 week after thrombolysis. However, the number of patients is small and is not sufficient for any firm conclusions to be made.

Table 2. Major Complications After Carotid Surgery and Stenting in Patients With and Without Preceding Thrombolysis

<table>
<thead>
<tr>
<th>Complications</th>
<th>Thrombolysis Cohort (n=79)</th>
<th>Nonthrombolysis Cohort (n=3919*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of complications†</td>
<td>5/79 (6.3%)</td>
<td>551/3626 (15%)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>2/79 (2.5%)</td>
<td>62/3626 (1.7%)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>0</td>
<td>46/3626 (1.3%)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0</td>
<td>42/3626</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>0</td>
<td>27/3626</td>
</tr>
<tr>
<td>Cranial nerve injury</td>
<td>0</td>
<td>175/3626</td>
</tr>
<tr>
<td>Reoperation for surgical-site bleeding</td>
<td>3/79 (3.8%)</td>
<td>119/3626 (3.3%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>54/3626 (1.5%)</td>
</tr>
<tr>
<td>Death within 30 d‡</td>
<td>0</td>
<td>31/3626 (0.9%)</td>
</tr>
</tbody>
</table>

*The denominator varies because of missing values in the registries; the number varies depending on the variable.
†\( P=0.03 \); thrombolysis cohort vs nonthrombolysis cohort.
‡Death not included in the total complication rate.
about the optimal time frame during which to offer CEA/CAS after thrombolysis. As has already been shown, a move toward earlier operative procedures may increase procedural risk, in particular if undertaken within 48 hours after a qualifying neurological event (mortality and stroke rate, 11.5%). This risk seems to decrease markedly, although already after 3 days from the index symptoms.1

Of the 28,462 patients 18 to 80 years of age with ischemic stroke recorded in the Swedish national stroke registry from 2007 to 2010, 1908 patients (6.7%) received thrombolytic therapy, with a trend toward increasing frequencies over time.4 However, the numbers undergoing CEA/CAS after thrombolysis remain small and were in this large national cohort only 2%, which is a smaller proportion than previously reported.10,11

The recent studies examining outcome of CEA after thrombolysis for stroke are summarized in Table 4. There are no previous reports on CAS. Briefly, Crozier et al10 reported 10 patients who had undergone CEA after receiving thrombolytic therapy for stroke, for whom there were no deaths or postoperative cerebrovascular hemorrhage. Consistent with this, another report by Rathenborg et al11 also found that thrombolysis did not seem to increase the risk of serious complications in patients undergoing subsequent CEA, although a slightly higher bleeding complication rate (9%) was reported. Bartoli et al12 also reported favorable outcomes of CEA undertaken on a median time of 8 days after thrombolysis; however, unlike the above authors, this group did report 1 hemorrhagic stroke that resulted in death. Finally, in a small series published recently consisting of 7 patients undergoing CEA after successful thrombolysis,13 there was 1 postoperative intracranial hemorrhage but no other complications at 30 days. As has been previously described,14 the half-life of recombinant tPA in the systemic circulation is short, and unless CEA/CAS is undertaken immediately after cessation of thrombolysis, this is unlikely to contribute significantly to any increased risk of bleeding in this patient category.

The selection of patients for CEA/CAS after thrombolytic therapy is of importance. In our study, the patients in the thrombolysis cohort were slightly younger, more often had a history of previous neurological events compared with the entire cohort, and presented with minor stroke in the majority of cases. Thrombolysis in patients with minor stroke has previously been associated with younger age, less blood pressure medication, and more specialized hospital type.9 All postoperative complications were seen in the group undergoing CEA, and there were no complications after CAS. However, considering the small number of patients having undergone CAS, it is not possible to draw any conclusions about the preferred operative technique.

This study has several limitations: numbers are still small, carrying a risk of type II statistical error, its retrospective design, and, moreover, it is based on registry data collection with its attendant limitations. Nonetheless, previous validation of the Swedvasc registry has shown excellent external and internal validity,3 and data quality has been improved by merging the databases, which all use the same personal identity code to identify patients, as well as by reviewing individual case records. As has been commented on previously, not all patients gave their consent for retrospective review of medical records. However, this did not result in loss of outcome data because these were obtained from the registries, and we do not think that this has influenced the results of the study.

Conclusions

In this nationwide population-based study, urgent procedures for significant carotid artery stenosis do not seem to carry an increased overall risk of complications after thrombolysis for stroke. However, it may be possible that earlier surgery could carry an increased risk of complications, a risk that must be balanced against that of further cerebral ischemic events.

It is, therefore, of utmost importance that centers continue to prospectively record their outcomes after these procedures.
procedures to investigate further the safety of undertaking carotid procedures after systemic thrombolysis for stroke. The efficacy of such procedures in the prevention of further ischemic insults must also be evaluated, and we urge others to prospectively record death and stroke rates for patients with a significant (50%–99%) ipsilateral carotid stenosis undergoing thrombolysis but who do not, for whatever reasons, proceed to surgery or stenting and are managed with medical therapy alone.

Future studies should focus on patient selection, timing, and type of carotid procedure after thrombolysis, and the role of perioperative medical therapy in reducing risk of peri- and postprocedural stroke associated with CEA/CAS.

Appendix

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Disclosures

None.

References

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The version of the article, “Urgent Carotid Surgery and Stenting May Be Safe After Systemic Thrombolysis for Stroke” by Koraen-Smith et al (Stroke. 2014;45:776–780) that published online ahead-of-print on February 13, 2014, a correction was needed.

The published article was a prior version.

This has been corrected in the online and print version of the article.