Urgency of Carotid Endarterectomy for Secondary Stroke Prevention

Results From the Registry of the Canadian Stroke Network

David J. Gladstone, MD, PhD, FRCP; Jiwon Oh, MD; Jiming Fang, PhD; Patty Lindsay, RN, PhD; Jack V. Tu, MD, PhD, FRCP; Frank L. Silver, MD, FRCP; Moira K. Kapral, MD, MSc, FRCP

Background and Purpose—The benefit of carotid endarterectomy for preventing recurrent stroke is maximal when surgery is performed within 2 weeks after ischemic stroke or transient ischemic attack; the benefit is reduced when surgery is delayed >2 weeks and essentially lost if delayed >3 months. Guidelines recommend endarterectomy within 2 weeks poststroke/transient ischemic attack for patients with symptomatic carotid stenosis. This study examined time to endarterectomy at designated stroke centers as a measure of evidence-based best practices for stroke prevention.

Methods—From the Registry of the Canadian Stroke Network, we identified all consecutive patients presenting with acute ischemic stroke or transient ischemic attack at 12 provincial stroke centers (Ontario, Canada, 2003 to 2006) and selected those with unilateral symptomatic carotid stenosis of moderate (50% to 69%) or severe (70% to 99%) degree. Using linkages to administrative databases, we identified patients who underwent carotid endarterectomy within 6 months after the symptomatic event and calculated the time intervals between the index event and surgery. We compared the timing of surgery according to age, sex, degree of stenosis, index event, geographic region, and year. Logistic regression assessed variables associated with early surgery.

Results—One hundred five patients underwent endarterectomy for unilateral symptomatic carotid stenosis (50% to 99%) within 6 months of the index event. The median time from index event to surgery was 30 days (interquartile range, 10 to 81). Only one third (38 of 105) received endarterectomy within the recommended 2-week target timeframe, and in one fourth (26 of 105), surgery was delayed >3 months. Surgery within 2 weeks was more likely if the index event was a transient ischemic attack rather than a stroke. Access to early endarterectomy varied markedly between hospitals across the province and improved over time from 2003 to 2006.

Conclusions—In this hospital-based cohort, the majority of patients undergoing carotid endarterectomy after a transient ischemic attack or stroke had surgery delayed well beyond the period of maximum effectiveness. To enhance secondary stroke prevention, greater efforts are needed to minimize delays to diagnosis and surgical treatment for patients with symptomatic carotid stenosis. (Stroke. 2009;40:00-00.)

Key Words: carotid endarterectomy ■ stroke prevention ■ symptomatic carotid stenosis ■ wait times

Symptomatic extracranial carotid artery stenosis (50% to 99%) poses a high immediate and short-term risk of stroke. Without surgery, the 90-day stroke risk may be as high as 20% to 30%. Carotid endarterectomy has proven highly effective for reducing this risk. However, only recently has it become appreciated that the benefit of endarterectomy is very dependent on the timing of surgery in relation to the presenting transient ischemic attack (TIA) or stroke event. A pooled analysis of the North American and European endarterectomy trials found that for patients with 50% to 99% carotid stenosis, surgery was most effective when performed within 2 weeks of the index ischemic event (with a number needed to treat of 5 to prevent one stroke over 5 years), and the benefit declined quickly over time (number needed to treat of 125 if surgery was delayed >3 months). This time-dependent benefit was especially pronounced for patients with moderate (50% to 69%) carotid stenosis, in which endarterectomy was beneficial within the first 2 weeks, but the benefit was lost (and there was net harm) when surgery was delayed >3 months (Table 1). Therefore, timely surgery is even more important for patients with moderate stenosis than for patients with severe stenosis. Additionally,
the benefit of carotid endarterectomy for women is largely realized within the first 2 weeks, with women deriving less benefit with later surgery compared with men, possibly due to sex differences in carotid plaque pathology.\textsuperscript{5,6} The safety of performing carotid endarterectomy early has been demonstrated in several recent studies with perioperative morbidity and mortality rates comparable to that for delayed surgery in otherwise stable patients.\textsuperscript{7–11}

These data have changed practice guidelines for carotid endarterectomy.\textsuperscript{12,13,13a} According to the American Academy of Neurology, “For patients with severe stenosis and a recent TIA or nondisabling stroke, [carotid endarterectomy] should be performed without delay, preferably within 2 weeks.”\textsuperscript{12} Similarly, the National Stroke Association recommends that “surgery should be performed as soon as the patient is fit for the procedure, preferably within 2 weeks of TIA (cerebral or retinal).”\textsuperscript{14} It is unclear whether these guidelines, published in 2005 and 2006, are being translated into clinical practice.

The objectives of this study were: (1) to evaluate how quickly carotid endarterectomy is being performed at designated stroke centers in Ontario; (2) to explore what factors influence timely access to carotid endarterectomy; and (3) to compare the timing of endarterectomy before and after the publication of updated clinical practice guidelines.

\section*{Methods}

\section*{Description of the Registry}

This study used data from the Registry of the Canadian Stroke Network (Phase 3), an ongoing prospective database of all consecutive acute cerebrovascular events at designated stroke centers.\textsuperscript{15} Participating institutions are large-volume tertiary care centers with specialized stroke care resources and expertise. Eligible patients are identified by trained research coordinators at each site who review daily emergency department records and hospital admission logs. Standardized data collection forms with clearly defined fields are used to record patient demographics, most responsible diagnosis, presenting signs and symptoms, side of symptoms, stroke severity, Oxfordshire Community Stroke Project classification of stroke types,\textsuperscript{16} stroke severity as measured by the Canadian Neurological Scale,\textsuperscript{17} medical history and risk factors, medications, diagnostic tests, treatments, and discharge disposition. Specialized software is used for data entry; this software checks the ranges and internal consistency of data to increase data quality. The database captures all brain imaging and vascular imaging performed in the emergency department or in the hospital for admitted patients (including carotid Doppler ultrasound, CT angiography, MR angiography, or digital subtraction angiography). The degree of carotid stenosis is recorded for the right and left side and classified as: trace (<30%), mild (30% to 49%), moderate (50% to 69%), severe (70% to 99%), or occluded (100%).

\section*{Description of the Cohort}

For this study, we retrospectively assembled a cohort of patients from the registry who had unilateral symptomatic carotid stenosis (50% to 99%) and underwent carotid endarterectomy within 6 months of their presenting symptomatic event. We first identified all patients presenting to the emergency department with an acute ischemic stroke or TIA between July 2003 and September 2006 at 12 designated stroke centers in Ontario, Canada’s largest province. These sites include all 9 of the Ontario regional (primary) stroke centers plus 3 district stroke centers; these hospitals represent different geographic regions of the province and have been designated by the provincial government as part of the Ontario Stroke System of regionalized stroke care. We excluded patients presenting with transient monocular blindness, posterior circulation events, intracerebral hemorrhage, or an in-hospital stroke/TIA event. We only included patients who had carotid imaging performed as part of the index hospital presentation and documenting moderate (50% to 69%) or severe (70% to 99%) stenosis of the symptomatic carotid artery. We excluded patients who did not receive carotid imaging before discharge and patients with mild stenosis (<50%) or complete occlusion of the symptomatic carotid artery. To ensure that we included only patients with symptomatic (and not asymptomatic) carotid stenosis, we restricted the cohort to only those patients whose symptomatic stenosis was either contralateral to the presenting neurologic symptoms or ipsilateral to an area of acute cerebral ischemia detected on neuroimaging. Furthermore, we excluded patients with moderate or severe stenosis of the contralateral (asymptomatic) carotid artery to avoid inadvertently capturing any patients who may have been operated on for asymptomatic stenosis. Using linkages to the Canadian Institute for Health Information administrative database of all procedures performed at all acute care Ontario hospitals, we selected all patients who underwent carotid endarterectomy within 6 months after the index event onset date (Itemen-
Results

Of 10,213 ischemic stroke and TIA events in our registry meeting our inclusion criteria, 6,270 (61.4%) received carotid imaging in hospital, and of those, 1,011 (16.1%) were found to have a presumed symptomatic carotid stenosis of 50% to 99%. Among those patients, 177 (17.5%) underwent endarterectomy within 6 months of the index event. After excluding patients with bilateral carotid stenosis, there were 105 patients with unilateral stenosis who underwent endarterectomy (80% with severe stenosis, 20% with moderate stenosis), and this group represents the final cohort for all subsequent analyses. Patient characteristics are shown in Table 2. The mean age was 70.1 ± 0.9 years and three fourths were men. The median time from symptom onset to emergency department presentation was 6.7 hours (interquartile range, 1.2 to 31.7) with 71% of patients arriving to the hospital within 24 hours of onset.

Of the cohort that underwent carotid endarterectomy within 6 months, the median time from index event to surgery was 30 days (interquartile range, 10 to 81). Overall, approximately one third (38 of 105) underwent surgery within 2 weeks, half (53 of 105) received surgery within 1 month, and one fourth (26 of 105) had surgery >3 months after the presenting event.

Time to endarterectomy in relation to subgroups is shown in Table 3. In the multivariable analysis, early surgery (within 2 weeks) was significantly more likely to occur if the index event was a TIA rather than a completed stroke (OR, 2.6; 95% CI, 1.1 to 6.1); age, sex, and degree of stenosis were not significant predictors of early surgery.

Timing of endarterectomy varied widely among institutions across the province with median times to surgery for each hospital ranging from 2 days to 129 days (Figure 1). Over the study timeframe, there was an improvement in the median time to endarterectomy, decreasing from 74 days in 2003 to 21 days in 2006 (P = 0.022 for median regression analysis; Figure 2). The proportion of patients undergoing early carotid endarterectomy (within 2 weeks) improved significantly over time: 18.2% in 2003, 23.0% in 2004, 45.5% in 2005, and 44.8% in 2006 (P = 0.036; Cochran-Armitage trend test).

Compared with our cohort of patients who underwent carotid endarterectomy within 6 months, the 834 (82.5%) who did not undergo surgery within 6 months were significantly older, had more severe strokes and more medical comorbidity (previous stroke, angina, atrial fibrillation, pulmonary edema, dementia), fewer were functionally independent before admission, and more were declared “palliative” in the hospital (P < 0.004 for each variable); the carotid stenosis was severe in one third and moderate in two thirds. The 6-month mortality rate was 3.4% among the endarterectomy cohort compared with 12.9% for the nonsurgical group (P = 0.0003).

Discussion

This study reveals that for most patients in need of carotid endarterectomy, surgery is not being performed as urgently as current guidelines recommend. Only a minority of patients who underwent endarterectomy in this hospital-based Ontario cohort did so within the recommended 2-week target time frame after a cerebral ischemic event, and half had surgery...
delayed >1 month. One in 4 patients underwent endarterectomy >3 months poststroke/TIA, at which time the major benefit of endarterectomy has already been lost.

Patients with TIA (who are arguably the best candidates for early stroke prevention surgery) were significantly more likely than patients with a completed stroke to undergo endarterectomy within 2 weeks, yet half of them still had their surgery delayed >2 weeks. We observed an encouraging trend toward more timely access to carotid endarterectomy over time between 2003 and 2006. This improvement may reflect a true practice change after the important publication by Rothwell and colleagues of the carotid endarterectomy pooled analysis in 2004 followed by new carotid endarterectomy guidelines in 2005 and 2006. The improvement may also reflect recent efforts of the Ontario Stroke System, a major provincial investment in organized stroke care over the past few years that has already proven beneficial in other areas of the stroke care continuum. In other countries, published carotid endarterectomy wait times have been considerably longer than those observed in

Table 3. Timing of Carotid Endarterectomy After Stroke/TIA for Patients With Symptomatic Carotid Stenosis in the Registry of the Canadian Stroke Network, Ontario Sites, 2003 to 2006

<table>
<thead>
<tr>
<th></th>
<th>Median Time to Surgery (interquartile range), Days</th>
<th>Percentage of Patients Undergoing Endarterectomy Within Specified Time Periods After the Index Stroke or TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Within 2 Weeks</td>
</tr>
<tr>
<td>Overall cohort</td>
<td>30 (10–81)</td>
<td>38/105 (36.2%)</td>
</tr>
<tr>
<td>Women (n=27)</td>
<td>48 (12–123)</td>
<td>10/27 (37%)</td>
</tr>
<tr>
<td>Men (n=78)</td>
<td>24 (9–76)</td>
<td>28/78 (35.9%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>1.1 (0.4–2.6)</td>
</tr>
<tr>
<td>P value</td>
<td>0.138</td>
<td>0.915</td>
</tr>
<tr>
<td>Age &gt;75 years (n=33)</td>
<td>21 (9–42)</td>
<td>13/33 (39.4%)</td>
</tr>
<tr>
<td>Age ≤75 years (n=72)</td>
<td>46 (10.5–97)</td>
<td>25/72 (34.7%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>1.2 (0.5–2.9)</td>
</tr>
<tr>
<td>P value</td>
<td>0.122</td>
<td>0.644</td>
</tr>
<tr>
<td>TIA (n=33)</td>
<td>14 (5–43)</td>
<td>17/33 (51.5%)</td>
</tr>
<tr>
<td>Ischemic stroke (n=72)</td>
<td>46 (12–101)</td>
<td>21/72 (29.2%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>2.6 (1.1–6.0)</td>
</tr>
<tr>
<td>P value</td>
<td>0.003</td>
<td>0.029</td>
</tr>
<tr>
<td>Moderate carotid stenosis (n=21)</td>
<td>42 (10–94)</td>
<td>9/21 (42.9%)</td>
</tr>
<tr>
<td>Severe carotid stenosis (n=84)</td>
<td>27.5 (10–77.5)</td>
<td>29/84 (34.5%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td>1.4 (0.5–3.8)</td>
</tr>
<tr>
<td>P value</td>
<td>0.920</td>
<td>0.478</td>
</tr>
</tbody>
</table>

Figure 1. Regional variations in stroke onset-to-endarterectomy times across 12 stroke centers in Ontario, 2003 to 2006. Error bars represent 95% CIs.
our cohort.2,10 It is notable that our study focused only on patients attending designated stroke centers where rapid access to stroke care is expected to be greater than that available at community hospitals. Our results may, therefore, underestimate the problem of timely access to carotid endarterectomy for patients who initially present to smaller hospitals. However, even among the designated stroke centers included in this study, there were striking variations between hospitals in access to timely endarterectomy, suggesting the need for provincial standardization and monitoring of this process of care issue. The hospitals in our study that performed the most endarterectomies tended to have shorter wait times compared with hospitals with low endarterectomy volumes.

The timing of carotid endarterectomy for symptomatic carotid disease is a key benchmark for secondary stroke prevention because delays to endarterectomy are associated with an increased risk of recurrent stroke. For example, in an Oxfordshire population-based study in which the median endarterectomy wait time was 100 days (interquartile range, 59 to 137) and only 6% of patients underwent surgery within 2 weeks (43% underwent surgery within 3 months), one in 3 patients had a recurrent stroke while awaiting surgery.2 Similarly, in an Austrian retrospective study in which only 28% of patients underwent carotid endarterectomy within 4 weeks, the risk of recurrent stroke in those awaiting surgery was 12% at 4 weeks.10 A prospective study of patients with severe symptomatic carotid stenosis reported a 10% early risk of recurrent events while awaiting endarterectomy.19 Although our study was not designed to assess stroke risk in those awaiting carotid endarterectomy, we can only infer from this literature that some patients in our registry who were potential endarterectomy candidates may have had a recurrent stroke while awaiting surgery.

Potential reasons for delays to carotid endarterectomy include patient factors (delayed symptom recognition and presentation to medical attention), physician factors (delayed diagnosis and referrals), resource availability (rapid access to vascular imaging), and institutional/system-level factors relating to operating room availability and staffing. In our study, patient factors were not likely to have been responsible for any significant delays, because most patients in our cohort presented to hospital within 24 hours of their clinical event. The Registry of the Canadian Stroke Network database did not record the time from clinical presentation to carotid imaging so we could not calculate the average delays to imaging in this study. However, because all patients in this study had vascular imaging as part of their initial hospital presentation, delays in the identification of carotid stenosis probably did not play a major role in prolonging the time to surgery in this study. Our database did not record the time of surgical referral or consultation, so we could not calculate the actual surgical wait times, and we did not have data on surgeon volumes at each hospital. We do acknowledge that in some cases, there may have been legitimate reasons for delaying surgery, ie, for patients who were medically or neurologically unstable. Other potential reasons for delays to endarterectomy include a shortage of surgeons who perform this procedure in Ontario and a lack of awareness about the timing of endarterectomy among family physicians and internists (who care for the majority of patients with stroke in Ontario). The overall rate of carotid endarterectomy within 6 months among all patients presenting with a presumed acute symptomatic carotid stenosis (18%) was much lower than expected; we can only speculate that there may have been a bias against operating on patients who were older and had more medical comorbidity, more severe strokes, and moderate rather than severe carotid stenosis.

Several limitations of this study must be noted. The sample size is small, although it is comparable to other recent studies examining this issue. Ontario is Canada’s largest province and is highly representative of healthcare delivery in Canada. The results of this study should be relevant to all hospitals that perform carotid endarterectomy for secondary stroke prevention. We intentionally restricted our cohort to patients with unilateral carotid disease to be sure that we only selected patients operated on for the symptomatic side and to avoid inadvertently including patients who underwent surgery for asymptomatic contralateral stenosis. We therefore cannot comment on the results for patients with bilateral carotid stenosis. Additionally, because of the retrospective nature of the analysis, we can only comment on the timing of endarterectomy for patients who underwent surgery; we were unable to determine how many patients were identified as surgical candidates and referred for endarterectomy but never received surgery due to recurrent stroke or death while awaiting the procedure. The small sample size limited our ability to evaluate predictors of early versus late surgery. For example, the cohort was not large enough to compare times to endarterectomy as function of socioeconomic status, although previous reports have suggested a relationship.20

Another important limitation of the study is that we only included patients with stroke/TIA who presented to hospital (and underwent carotid imaging in hospital), so we cannot comment on access to endarterectomy for the many patients with symptomatic carotid disease who are managed entirely on an outpatient basis before surgery. We excluded patients who were discharged from the hospital without carotid imaging, because our registry did not contain outcome data.
for these patients; we presume that such patients were subsequently referred for outpatient vascular imaging, but the results of these tests could not be tracked by our registry or provincial administrative databases. We recognize that the exclusion of this outpatient component likely introduces a selection bias in our study. We speculate that for some patients discharged without carotid imaging, the additional wait for outpatient imaging may result in longer delays to surgical referral and endarterectomy; conversely, it is possible that outpatient clinic management at some centers may enable quicker access to surgery. Conclusions drawn from this hospital-based study, therefore, cannot be generalized to the entire population of patients with symptomatic carotid stenosis.

This study has implications for improving adherence to best practice guidelines for stroke prevention. Expediting the diagnosis and treatment of symptomatic carotid disease must become a priority for all hospitals that care for patients with acute stroke and TIA. For patients with acute high-risk TIAs and minor strokes, carotid imaging should be performed ideally within 24 hours, which can be accomplished rapidly and noninvasively in most emergency departments using CT angiography when carotid ultrasound is unavailable; MR angiography is another option where available. An online calculator can be helpful in predicting stroke risk for individual patients with carotid stenosis (www.stroke.ox.ac.uk/). The creation of dedicated, rapid-response outpatient stroke/TIA clinics is one way to fast-track the diagnosis and management of patients with symptomatic carotid disease. For example, a recent study demonstrated the feasibility and effectiveness of urgent, aggressive outpatient management of patients with TIA and minor stroke with an increase in the proportion of patients receiving early carotid endarterectomy (within 30 days) from 12% to 67% and a decrease in 90-day stroke risk from 10% to 2%. In another recent study demonstrating the effectiveness of a dedicated TIA clinic, expedited carotid revascularization was able to be achieved within a median time of 6 days.

In conclusion, stroke prevention surgery with carotid endarterectomy should be performed early after a cerebral ischemic event to be most effective. Clinicians and administrators must be aware that carotid endarterectomy for symptomatic stenosis is a time-sensitive treatment, and hospital protocols should aim to streamline diagnostic imaging for high-risk patients with stroke/TIA and provide urgent operating room availability for suitable candidates. The “onset-to-endarterectomy” time should be monitored as a key performance indicator for stroke prevention.13a Wait time coalitions have been established for other medical and surgical procedures, and it is hoped that carotid endarterectomy will join the list of procedures that are being tracked regionally and nationally.

**Sources of Funding**

The Registry of the Canadian Stroke Network is funded by an operating grant from the Canadian Stroke Network. The Institute for Clinical Evaluative Sciences is supported by an operating grant from the Ontario Ministry of Health and Long-Term Care. D.J.G. received a Clinician-Scientist Award from the Heart and Stroke Foundation of Ontario and is supported by the Heart and Stroke Foundation Centre for Stroke Recovery and the Department of Medicine (Sunnybrook Health Sciences Centre and University of Toronto). M.K.K. is funded by a New Investigator Award from the Canadian Institutes for Health Research and also receives funding from the University Health Network Women’s Health Program and the Canadian Stroke Network. J.V.T. is supported by a Canada Research Chair in Health Services Research and a Career Investigator Award from the Heart and Stroke Foundation of Ontario.

The results and conclusions are those of the authors and should not be attributed to any of the sponsoring or funding agencies. The funding agencies had no role in the design or conduct of the study or the collection, management, analysis, and interpretation of the data. The project was reviewed and approved by the Publications Committee of the Registry of the Canadian Stroke Network.

**Disclosures**

None.

**References**


Urgency of Carotid Endarterectomy for Secondary Stroke Prevention. Results From the Registry of the Canadian Stroke Network

David J. Gladstone, Jiwon Oh, Jiming Fang, Patty Lindsay, Jack V. Tu, Frank L. Silver and Moira K. Kapral

Stroke. published online June 18, 2009;

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/early/2009/06/18/STROKEAHA.109.547497.citation

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/