Risk of very early recurrent cerebrovascular events in symptomatic carotid artery stenosis

Clinical article

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Object. The risk of recurrence of cerebrovascular events within the first 72 hours of admission in patients hospitalized with symptomatic carotid artery (CA) stenoses and the risks and benefits of emergency CA intervention within the first hours after the onset of symptoms are not well known. Therefore, the authors aimed to assess 1) the ipsilateral recurrence rate within 72 hours of admission, in the period from 72 hours to 7 days, and after 7 days in patients presenting with nondisabling stroke, transient ischemic attack (TIA), or amaurosis fugax (AF), and with an ipsilateral symptomatic CA stenosis of 50% or more, and 2) the risk of stroke in CA interventions within 48 hours of admission versus the risk in interventions performed after 48 hours.

Methods. Ninety-four patients were included in this study. These patients were admitted to hospital within 48 hours of a nondisabling stroke, TIA, or AF resulting from a symptomatic CA stenosis of 50% or more. The patients underwent carotid endarterectomy (85 patients) or CA stenting (9 patients). At baseline, the cardiovascular risk factors of the patients, the degree of symptomatic CA stenosis, and the type of secondary preventive treatment were assessed. The in-hospital recurrence rate of stroke, TIA, or AF ipsilateral to the symptomatic CA stenosis was determined for the first 72 hours after admission, from 72 hours to 7 days, and after 7 days. Procedure-related cerebrovascular events were also recorded.

Results. The median time from symptom onset to CA intervention was 5 days (interquartile range 3.00–9.25 days). Twenty-one patients (22.3%) underwent CA intervention within 48 hours after being admitted. Overall, 15 recurrent cerebrovascular events were observed in 12 patients (12.8%) in the period between admission and CA intervention: 3 strokes (2 strokes in progress and 1 stroke) (3.2%), 5 TIAs (5.3%), and 1 AF (1.1%) occurred within the first 72 hours (total 9.6%) of admission; 1 TIA (1.1%) occurred between 72 hours and 7 days, and 5 TIAs (5.3%) occurred after more than 7 days. The corresponding actuarial cerebrovascular recurrence rates were 11.4% (within 72 hours of admission), 2.4% (between 72 hours and 7 days), and 7.9% (after 7 days). Among baseline characteristics, no predictive factors for cerebrovascular recurrence were identified.

Procedure-related cerebrovascular events occurred at a rate of 4.3% (3 strokes and 1 TIA), and procedures performed within the first 48 hours and procedures performed after 48 hours had a similar frequency of these events (4.5% vs 4.1%, respectively; p = 0.896).

Conclusions. The in-hospital recurrence of cerebrovascular events was quite low, but all recurrent strokes occurred within 72 hours. The risk of stroke associated with a CA intervention performed within the first 48 hours was not increased compared with that for later interventions. This raises the question of the optimal timing of CA intervention in symptomatic CA stenosis. To answer this question, more data are needed, preferably from large randomized trials.

(key words) • symptomatic carotid stenosis • recurrent cerebrovascular events • carotid artery intervention • vascular disorders

Abbreviations used in this paper: AF = amaurosis fugax; CA = carotid artery; CAS = CA stenting; CEA = carotid endarterectomy; ECST = European Carotid Surgery Trial; NASCET = North American Symptomatic Carotid Endarterectomy Trial; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

The risk of recurrent stroke after transient ischemic attack (TIA) or minor stroke is highest within the first 7–14 days after the onset of symptoms, especially in patients with large-artery disease.4,12,14,22,26,35 Pooled data from the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid End-
arterectomy Trial (NASCET), and the Veterans Affair Trial show that the benefit from carotid endarterectomy (CEA) depends on the degree of stenosis and also on the time to surgery after the index event. Patients benefit most from CEA performed within 14 days after the onset of symptoms. Accordingly, current guidelines of the European Vascular Surgery Society and the American Heart Association recommend that CEA should be performed within 14 days after the index event. Other guidelines, such as the United Kingdom National Stroke Strategy, even suggest that the operation should be performed within 48 hours after a TIA or minor stroke. It is of note that this applies only to patients presenting with a nondisabling stroke, a TIA, or an amaurosis fugax (AF), but not to patients with major disabling strokes. However, in many hospitals it might be difficult to plan for very early CEAs, and the periprocedural risk of adverse events in such early operations is largely unknown. Furthermore, data to estimate the risk of cerebrovascular events within the first 72 hours after symptom onset are scarce, and only 1 of these studies has analyzed the recurrence of ipsilateral ischemic strokes.

Therefore, we aimed to assess the following: 1) the ipsilateral recurrence rate within 72 hours of admission, in the period from 72 hours to 7 days, and after 7 days in patients presenting with nondisabling stroke, TIA, or AF, and an ipsilateral symptomatic CA stenosis of 50% or more, and 2) the risk of stroke in CA interventions performed within 48 hours of admission compared with the risk in later interventions.

Methods

Patients

From January 2000 to November 2010, 2034 patients with acute ischemic stroke or TIA with an onset of symptoms within less than 48 hours were admitted to our university-based stroke center. The patient data were prospectively recorded in our database. Of these patients, 94 had a nondisabling ischemic stroke (with a score on the modified Rankin Scale score of ≥2), TIA, or AF resulting from an ipsilateral symptomatic CA stenosis of 50% or more and were considered suitable for CA intervention within 14 days of the onset of symptoms. These 94 patients were included in this study. Approval for the study was obtained from Cantonal Ethics Committee Bern.

Baseline investigations consisted of neurological and physical examinations, assessment of stroke severity using the National Institutes of Health Stroke Scale (NIHSS), routine blood analysis, 12-lead electrocardiography, and brain imaging with MRI or CT. The degree of CA stenosis was quantified by concordance of color-coded duplex sonography (with a 7.5-MHz linear-array transducer, Acuson Sequoia) and CT or MR angiography of the extracranial CAs. Carotid artery stenoses were categorized into high grade (≥70%) and moderate grade (50%–69%) according to the criteria of NASCET. When necessary, angiography was performed to determine the exact degree of the stenosis or to carry out intraarterial thrombolysis.

Risk Factors

The following vascular risk factors were assessed: history of coronary artery disease, previous TIA or ischemic stroke, hypertension (treated hypertension or a systolic and diastolic blood pressure of >140 mm Hg and >90 mm Hg, respectively, measured on 2 different occasions), diabetes mellitus (symptoms of diabetes and blood glucose concentration >11 mmol/L or fasting glucose >7 mmol/L), current cigarette smoking, hypercholesterolemia (assessed as a total venous plasma cholesterol concentration of >5 mmol/L), and atrial fibrillation.

Treatment

At admission, 41 patients (43.6%) were treated with antithrombotic agents (aspirin in 36 [38.3%], aspirin with clopidogrel in 1 [1%], anticoagulants in 3 [3.2%], and anticoagulants with aspirin in 1 [1%]). In the remaining 53 patients (56.4%), antithrombotic treatment was started immediately after admission. The secondary preventive treatment after the index event was aspirin in 45 patients (47.9%), clopidogrel in 10 (10.6%), and aspirin and clopidogrel in 23 (24.5%), full-dose intravenous heparin in 4 (4.3%), full-dose intravenous heparin and aspirin in 9 (9.6%), full-dose intravenous heparin and aspirin plus clopidogrel in 2 (2.1%), and oral anticoagulants in 2 (2.1%). Sixty-five patients (69.1%) received statins (mostly as atorvastatin). Patients on antiplatelet medications were also given low-dose heparin for the prophylaxis against venous thrombosis.

All patients were treated according to our institutional guideline with bed rest immediately after admission and a stepwise mobilization during 3–7 days. Blood pressure was monitored at least 4 times a day.

Up to 4.5 hours after stroke onset, intravenous thrombolysis with recombinant tissue plasminogen activator and up to 6 hours intraarterial thrombolysis with urokinase, mechanical thrombolysis, or both was performed if the NIHSS score was 4 or more or if severe aphasia or complete hemianopia was present. All patients underwent carotid artery stenting (CAS) or CEA during follow-up. The decision whether to choose CEA or CAS was usually based on an interdisciplinary consensus but eventually left to the discretion of the treating physician. Anesthesia, interventional and operative techniques, and intraoperative monitoring procedures for CAS and CEA were performed as reported previously.

Recurrent Events

Recurrent events were assessed retrospectively by reviewing the medical reports and nurses’ records. The in-hospital recurrence was assessed at 3 different time points: within 72 hours of admission, in the period from 72 hours to 7 days, and after 7 days. Cerebrovascular recurrence was assumed if a new focal neurological deficit occurred in the territory of the stenosed CA. A TIA was defined as a focal neurological deficit that resolved within 24 hours and AF as a transient monocular visual loss lasting less than 24 hours. Stroke was defined as a focal neurological deficit lasting longer than 24 hours with corresponding findings on CT or MRI.
with nondisabling stroke, a recurrent event was assumed if the new focal neurological deficit resulted in worsening of the NIHSS score by 4 or more points compared with the NIHSS score at admission or if a patient showed new signs and symptoms. Stroke in progress was defined as progressive neurological deficit for more than 24 hours including fluctuating symptoms with progressive worsening or gradually increasing deficits.

Procedure-Related Complications

All patients underwent a neurological examination before and immediately after the CA intervention, at discharge, and after 6 weeks. The following complications were assessed: TIA, ischemic stroke, intracerebral hemorrhage (defined as any intracerebral hemorrhage documented on postprocedural brain imaging), myocardial infarction (defined as a combination of clinical symptoms, electrocardiographic criteria, and elevation of cardiac enzymes), in-stent thrombosis, cranial nerve palsies, and local hematoma (defined as hematoma requiring surgical evaluation). All of these complications were assumed to be related to the procedure if they occurred within 6 weeks of the CA intervention.

Statistical Analysis

Continuous variables are expressed as the mean ± 1 SD. Recurrence-free survival time was assessed by life-table analysis with censoring of patients at the time of CA intervention. Risk factors for recurrent events and risk factors for procedure-related complications were identified using the $\chi^2$ test for contingency tables for nominal variables and the Mann-Whitney U-test and Student t-test for continuous variables. Variables with a $p < 0.10$ were subsequently entered into a logistic regression model with a backward selection process using all recurrent events and recurrent events within 72 hours as dependent variables. Statistical significance was assumed at a 2-sided $p$ value of $< 0.05$.

Results

Demographic, Baseline Characteristics, and Time Delay

Demographic and baseline clinical characteristics are summarized in Table 1. The index event was a stroke in 60%, a TIA in 34%, and an AF in 6% of the patients. Seven patients (7%) were treated with intravenous and 1 (1%) with intraarterial thrombolysis. In 30 patients (32%), the event leading to admission was preceded by 1 or more cerebrovascular events within 14 days before the admission. These were strokes in 3 patients (3%), TIAs in 27 (29%), and AF in 3 (3%). The median delay from symptom onset to CA intervention was 5 days (interquartile range 3.00–9.25 days). Twenty-one patients (22%) were treated within 48 hours of the admission.

Recurrent Events

Twelve patients (12.8%) experienced ipsilateral recurrent cerebrovascular events between admission and CA intervention. There were 15 recurrent cerebrovascular events in these 12 patients: 2 strokes in progress, 1 stroke, 1 AF, and 11 TIAs. All 3 patients with more than 1 recurrent event had a TIA after 7 days after the admission. Table 2 shows the distribution of the recurrent events depending on the interval from admission and the actuarial recurrence rates at 72 hours, between 72 hours and 7 days, and after 7 days. All recurrent strokes (2 strokes in progress and 1 stroke [3%]) occurred within 72 hours of admission; later symptoms were only transient.

Univariate analysis indicated that age, sex, cardiovascular risk factors, the degree of the CA stenosis, the kind
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**TABLE 2: Recurrent ipsilateral cerebrovascular events in the 94 patients of this study**

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Events (%)</th>
<th>% Actuarial Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Stroke in Progress</td>
</tr>
<tr>
<td>overall</td>
<td>15 (16.0)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>≤72 hrs from symptom onset</td>
<td>9 (9.6)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>72 hrs to 7 days from symptom onset</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>7–14 days from symptom onset</td>
<td>5 (5.3)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**TABLE 3: Frequency of procedure-related complications in 85 CEA and 9 CAS patients**

<table>
<thead>
<tr>
<th>Event</th>
<th>CEA</th>
<th>CAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerebrovascular events</td>
<td>4 (7.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>TIA</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>stroke</td>
<td>3 (5.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>in-stent thrombosis/occlusion</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>cranial nerve paresis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>hematoma requiring surgical evaluation</td>
<td>2 (2.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>total no.</td>
<td>7 (8.2)</td>
<td>1 (11.1)</td>
</tr>
</tbody>
</table>

of index event, thrombolysis, or the type of the secondary preventive treatment was not significantly associated with an increased risk for cerebrovascular recurrence.

Patients with recurrent stroke or stroke in progress still underwent CA intervention. Carotid endarterectomy was performed in 85 patients (90%) and CAS was performed in 9 patients (10%) (Table 3). The CAS group had a higher rate of recurrence of cerebrovascular events (44%) than the CEA group (10.4%) (p = 0.003), but there was no significant difference between the 2 groups in the time from the index event to intervention or in the type of secondary prevention. Table 3 shows the frequency of procedure-related complications in the CEA and the CAS groups. The overall risk of procedure-related cerebrovascular events was 4.3% (3 strokes and 1 TIA). One stroke occurred in a patient treated within 48 hours, and 2 strokes and 1 TIA occurred in patients treated after 48 hours. One patient in the CAS group had an asymptomatic in-stent thrombosis, which was successfully recanalized with abciximab, whereas no early reocclusion occurred in the CEA group. The stroke risk was similar in interventions performed within or after 48 hours after admission (4.5% vs 4.1%, p = 0.896).

**Discussion**

Both NASCET and ECST have demonstrated a benefit of surgical treatment for patients with symptomatic extracranial CA stenosis, provided that the symptoms had occurred within the preceding 6 months and that the stenosis was 50%–99% according to NASCET or 70%–99% according to ECST criteria. However, the optimal timing of CA intervention in patients with symptomatic CA stenosis is unknown. A meta-analysis indicated that CEA is most effective when performed within 2 weeks of a TIA or nondisabling stroke and that the absolute benefit declines rapidly thereafter.

According to 2 recent meta-analyses, the risk of stroke after TIA is 6.7% at 48 hours and 10% at 7 days. After a TIA, patients with large-artery disease (predominantly CA stenosis) showed the highest rate of stroke (4.0% at 7 days, 12.6% at 30 days, and 19.2% at 3 months). Moreover, almost half of all strokes occurring within 7 days do so within the first 24 hours. Expert opinions expressed in the most recent guidelines of the European Vascular Society recommend early CA interventions, and the United Kingdom National Stroke Strategy guideline advocates interventions within 48 hours of the onset of symptoms.

In patients with minor strokes and symptomatic CA stenosis, few data on early recurrence of cerebrovascular events exist. Ois and colleagues determined the rate of recurrent stroke and TIA in 163 patients with symptomatic CA stenosis of 50% or more and with nondisabling stroke or TIA who were evaluated within 6 hours of symptom onset. The authors reported a recurrence rate of 20.9% in the first 72 hours (stroke rate 17.2%), of 6.7% between 72 hours and 7 days, and of 3.7% between 7 and 14 days. Marnane and colleagues reported data from a population-based study in 314 patients with anterior circulation strokes; 36 patients had an ipsilateral symptomatic CA stenosis of 50% or more. Recurrent strokes occurred in 2 patients with symptomatic CA stenosis (5.6%) within 72 hours and in 1 additional patient (2.8%) between 72 hours and 14 days of the onset of symptoms. Patients with stroke in progress and patients with a TIA as an index event were not included in this analysis. The only study that has analyzed recurrence of ipsilateral ischemic stroke reported a stroke recurrence risk of 5.2% within 2 days, 7.9% within 7 days, and 11.2% within 14 days.

Table 4 summarizes the risk of early recurrent strokes in patients with symptomatic CA stenosis reported by various authors and observed in our patients. The stroke risks observed by the various studies were quite variable, most likely because of differences in patient characteristics and management. Unlike in most other series, our patients had CA interventions rather early after symptom onset and admission. It is of note that all recurrent strokes in our series occurred within 72 hours and none thereafter. Furthermore, the risk of procedure-related cerebrovascular events in procedures performed within the first 48 hours was similar to that in later interventions.
This raises the question whether interventions in symptomatic CA stenosis should be performed very early after patient admission. However, this is a highly controversial issue. If surgery is performed immediately or within the first days of the onset of symptoms, the risk of stroke in the natural history has to be weighed against the risk of very early surgery, and the risk of very early surgery might differ from that of surgery at a later time. Carotid endarterectomy for stroke in progress carries a high operative risk, but as soon as a patient with stroke or TIA is stable, very early CA intervention might be beneficial (JF Meschia, et al., presentation to the American Academy of Neurology Annual Meeting, 2011). However, data from the Swedish Vascular Registry on 2596 CEA patients with symptomatic CA disease show that patients treated within 0–2 days after the qualifying neurological event have a significantly increased perioperative risk compared with patients treated after 3–7 days, 8–14 days, or 15–180 days (11.5% vs 3.6%, 4.0%, or 5.4%, respectively; p < 0.001).

With the current data, the question of the optimal timing of CA interventions in symptomatic CA stenosis cannot be answered. Further studies are needed to determine whether very early carotid intervention may further decrease the rate of recurrent strokes without increasing periprocedural complications. The studies published to date indicate that the question of the optimal timing of surgery in symptomatic CA stenosis needs to be addressed with much more solid data, preferentially from a randomized trial.

Our study has several limitations. First, it represents a retrospective analysis of prospectively collected data. Second, the absolute numbers of recurrent events was rather low, which may be the reason why no significant predictors of recurrence could be identified. Third, all of our patients underwent CA intervention during follow-up, which may have resulted in an underestimation of the cerebrovascular recurrence rate. Finally, the decision on the time point of CA intervention was taken individually, which may have led to a bias when comparing procedure-related complications of CA intervention within 48 hours to those at a later time point.

**Conclusions**

The in-hospital recurrence of cerebrovascular events in our study was quite low, especially for strokes. However, all recurrent strokes occurred within 72 hours of patient admission. The risk of stroke associated with CA intervention performed within 48 hours of admission was not higher than that in later interventions. This raises the question whether CA intervention in patients with symptomatic CA stenosis should be performed on an emergency basis immediately after admission. However, to answer the question of the optimal timing of CA intervention in symptomatic CA stenosis, more data are needed, preferably from a randomized trial.

**Disclosure**

The authors report no conflict of interest concerning the mat-
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