Pool data and the subgroup analysis from the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and Veterans Affairs (VA) trials suggest that patients undergoing subacute carotid endarterectomy (CEA) gained greater benefit than patients with significant delays in surgery.1,2 Performing subacute CEA within 2 weeks in patients with a 50% to 99% stenosis (NASCET) and 70% to 99% stenosis (ECST) will prevent 185 ipsilateral disabling strokes at 5 years per 1000 CEAs (numbers needed to treat=6), whereas only 8 strokes will be prevented at 5 years if surgery is delayed by >12 weeks (numbers needed to treat=125).2–4

Accordingly, guidelines from the European Vascular Surgery Society and the UK National Institute for Clinical Excellence now recommend that CEA should be performed within 14 days of onset of symptoms.5 The UK National Stroke Strategy and the Danish Carotid guidelines recommend that CEA should be performed within 48 hours of transient ischemic attack (TIA) or minor stroke.3–6 The impetus for undertaking more rapid intervention after index event came from 2 recently published meta-analyses by Giles and Wu.7,8 These meta-analyses showed that the pooled risk of stroke after a TIA was highest in the first 7 days (5.2%). The lowest risks were seen in studies of emergency treatment in specialist stroke services (0.9%) and the highest risks in population-based studies without urgent treatment (11%). These and other natural history studies have driven the move toward urgent intervention/surgery (<48 hours). Current American Heart Association guidelines state that when CEA is indicated for patients with TIA or stroke, surgery should be performed within 2 weeks.9 American Heart Association guidelines also recommend that the combined risk of stroke and death resulting from CEA should not exceed 5% in symptomatic carotid stenosis (SCS) with TIA, and 7% for those with stroke.

Despite evidence suggesting the benefit of early intervention9 a prerequisite is urgent access to high-quality surgical services. There is also uncertainty on the role of modern medical therapies in secondary stroke prevention in patients awaiting CEA after an index event. This study examines the effect of introducing a new rapid access carotid surgery service with specific regard to delays to surgery and also the
effect of best medical treatment (BMT) on recurrent TIA/ischemic stroke and the procedural risk.

The Carotid Readmission Project and urgent BMT from October 2010 to October 2012 in our region is summarized below.

Materials and Methods

Data were collected prospectively by a single investigator through direct face-to-face contact with patients and by analysis of clinical case records. Patients were referred by our emergency specialist stroke clinics, regional stroke physicians, department of general medicine, or eye specialists.

The Zealand region in Denmark has only 1 vascular surgery unit but 4 hospitals with emergency specialist stroke services. The vascular surgery unit covers the vascular service, including carotid surgery for a population of 820,000 (15% of the Danish population).

Cases were diagnosed on hospital admission by a neurologist or a specialist in internal medicine, who established the initial neurological severity. Time of stroke onset was registered in all patients. When the onset of the neurological symptoms was unknown or occurred while sleeping, the stroke onset was established as the last time that the patient was seen free of symptoms. Candidates for thrombolysis were transferred rapidly for emergency treatment to the Department of Neurology at Roskilde Hospital. Patients, who were not candidates for thrombolysis, were treated according to guidelines established by the Danish National Standard Indicator Project for stroke (NIP).11 BMT started with stabilization of acute cardiorespiratory, metabolic, infectious, nutritional, or gastrointestinal issues. Patients whose emergency computed tomography (CT) revealed absence of hemorrhage and patients who presented with TIA or stroke received a loading dose of aspirin (300 mg) and clopidogrel (300 mg) plus simvastatin (40 mg) in the clinic plus a prescription for aspirin and clopidogrel (75 mg) within 6 hours after admission. This therapy was continued pre- and postoperatively, although aspirin (75 mg) was stopped after 7 days in low degree and non carotid stenosis patients.

Consistent with NIP, all patients were investigated by urgent echocardiogram. Holter monitoring and cardiology assessment were obtained before referral to surgical unit if indicated.

Denmark has a national standard (NIP) of providing primary duplex ultrasound within 4 days of admission for carotid distribution (TIA or stroke) with rapid CEA in appropriate patients. Because of weekends and our limited resources, carotid ultrasound was obtained in our study. Patients with a primary duplex ultrasound showing carotid disease/stenosis were referred by fax to our vascular surgery unit and were admitted within 72 hours of receiving the fax. There was no emergency consultation and no emergency surgery during weekends. There was an agreement that patients with crescendo TIA who needed emergency CEA could be transferred to another hospital (Odense University Hospital).

Vascular Surgery Unit

All patients underwent a secondary duplex assessment (in line with Danish Carotid guidelines) and were evaluated by the carotid surgeon. The secondary duplex was taken to be representative of the degree of stenosis. All patients who initially had been treated by thrombolysis and the patients where the flow in the distal internal carotid artery (ICA) was not easy to find by duplex ultrasound, as well as those patients in whom near occlusion/occlusion of the ipsilateral ICA was suspected, had a subacute CT angiogram before CEA. The risk of stroke after TIA or minor stroke during the first 7 to 14 days was estimated by ABCD2 score.12 Indication for fast-track CEA in our study was recent SCS as TIA, ischemic stroke Rankin score 0–3, and relevant ICA stenosis of 50% to 99%. If surgery was indicated, patients were booked for CEA with the aim of surgery within 2 to 7 days, including weekends. The unit also aimed to offer rapid CEA to all patients who presented with amaurosis fugax (AFx) and major stroke (Rankin score >3), provided they fulfilled the following criteria: no ICA occlusion, no evidence of hemorrhage or tumors on CT/MRI, and infarction less than one third of the middle cerebral artery territory. Patients with major stroke could rerefer during phase II rehabilitation, if there was considerable progress in their walking function <90 days from index event.

The vascular surgery unit maintains 2 half-day operating lists (Monday/Wednesday) for performing expedited CEA. We did not have an emergency theater for performing emergency CEA within 24 hours and our unit did not perform emergency CEA during weekends. All patients continued their triple medical treatment with aspirin (75 mg), clopidogrel (75 mg), and simvastatin (40 mg) until the day of surgery and continued with clopidogrel and simvastatin after surgery.

Exclusion Criteria

Patients with major stroke, severe comorbidity, dementia, or advanced malignancy were excluded.

After surgery, the patients recovered in the high dependency unit with continuous blood pressure monitoring for 8 to 12 hours. Our neurological assessment protocol required preoperative assessment by the anesthesiologist and frequent postoperative assessment by nurses or doctors during the first 24 hours after surgery. Twenty-four hours after CEA, patients were transferred back to the vascular ward pending discharge 2 to 3 days after surgery.

All CEA patients were assessed in the vascular unit 6 to 8 weeks and 1 year postoperatively. TIA, stroke, and thrombolysis patients were seen routinely by a neurologist after discharge from the vascular unit and 12 weeks after surgery. Subacute carotid surgery was defined as surgery (>2 to ≤30 days) after the index event.

Statistics

Data were collected by a single investigator (S.S.H.). Statistical analysis was performed using statistical Package for Social Science (SPSS; version 22) and P values were calculated by Fisher test.

Results

Overall, 4905 (300/100,000 inhabitant/y) patients between October 1, 2010, and October 1, 2012, were registered as emergencies in our 4 stroke clinics during this study. Figure 1 shows that, of 4905 patients, there were 315 patients (7%) where the primary duplex ultrasound showed carotid disease/stenosis or near occlusion/occlusion, and these were referred to the vascular surgery unit. Of these 315 patients, we found indication for CEA in 115 SCS patients, n=7 to 7.5 CEA/100,000/y in our region. All patients were symptomatic (stroke, n=65 [56%]; TIA, n=39 [34%]; and AFx, n=11 [10%]).

Figure 2 details the median times from the index event to evaluation at vascular unit and from the date of surgical referral to surgery. The median delay, including weekends from index event to CEA, was 26 (range, 3–90) days, whereas the median delay, including weekends from surgical referral to CEA, was 6 (range, 1–22) days. There was no significant difference in delay from referral to CEA related to mode of presentation (stroke, TIA, and AFx). There were no significant differences in the group of thrombolysis patients from index event to CEA, 14 (range, 7–22) days. There were no significant delays with related to age, sex, or diabetes mellitus.

After the total reconfiguration of services there was a dramatic reduction in the median delay (16–6 days) from referral to surgery. A total of 18% were operated on within 2 days, 65% were operated on in the interval from 3 to 7 days, and another 17% were operated on in the interval from 8 to 14 days. Overall, 42% of patients underwent CEA within 14 days of the index event, whereas 99% underwent CEA within 14 days of surgical referral. None of the patients underwent surgery within 48 hours of the index event, whereas 15%...
underwent CEA within 7 days of the index event. The mean length of hospital stay preoperatively was 3 (range, 2–5) days.

Figure 3 shows that 29% (95% confidence interval, 20%–37%) of patients had experienced ≥1 recent neurological recurrence (NR) in a period of 90 days before their index event and first admission to stroke clinics. After the first contact to stroke clinics and initiation of BMT, only 2.5% (95% confidence interval, 1%–6%) of patients had ≥1 recurrent TIA before CEA.

Table 1 summarizes the mode of presentation in our cohort and the comparison of NR ≤90 days and after CEA. In the interval from surgical referral to surgery only 1 (0.8%) of all patients had a recurrent TIA (ABCD2=3). This case was the only crescendo TIA that we observed during our study. There were no strokes or mortalities from referral to CEA. Of 65 strokes and thrombolysis patients, 13 patients (20%) had ≥1 recent NR as TIA or AfX before their first contact to the stroke clinic. Seven of these patients (55%) experienced minor stroke and 6 (45%) experienced Rankin 2 to 3 stroke and were admitted to stroke clinics after the index event.

Reasons for Delay and the Consequences

Table 2 presents the reasons for delay for the 46 (40%) patients who underwent CEA within 14 to 30 days and 21 (18%) patients who underwent CEA >30 days after the index event. Our data show a long delay in the subgroup of TIA (ABCD2≤4) and AfX, the reasons being that the patients did not take their symptoms seriously or the family doctors and eye specialist had some diagnostic difficulty.

In the group of patients with delayed referral from our stroke clinics, 2 reasons were evident in that >40% of cases had long delays (>5 days) waiting for duplex ultrasound or the consulting cardiologist. After referral to our vascular unit some patients waited >2 days for CT angiography and anti-hypertensive treatment. A few patients were not psychologically ready for CEA or had Rankin >3 at first contact with carotid surgeon.

There was a discrepancy of ≈60% (95% confidence interval, 50%–70%) between primary and secondary duplex ultrasound. In most cases there was an overestimation of stenosis degree or difficulty in verifying near occlusion/occlusion of ICA. It was agreed from the beginning of the project that in cases of doubt with regard to the primary duplex scanning, a new scanning was undertaken in the vascular unit. In patients with possible distal problems in ICA identified by ultrasound, we performed 12 (10%) subacute CT angiographies, all patients proceeded to surgery.
After CEA

There were no deaths, no strokes, and no myocardial infarction within the 30-day postoperative period. Two patients (1.85%) experienced an ipsilateral TIA (ABCD2≤4) and occluded ICA, 2 and 3 days after discharge.

Discussion

The optimal timing of CEA after TIA or stroke remains an important and controversial issue. Pooled data and subgroup analysis from the ECST and NASCET showed that performing CEA within 2 weeks after TIA or minor stroke gave optimal results.2,3 It is well known that the risk of recurrence of events after stroke or TIA has been traditionally underestimated.7,8 Natural history studies have driven the move toward urgent intervention/surgery ≤48 hours, as recommended by the latest European Vascular Society and the UK National Stroke Strategy guidelines.3,5 All the above natural history studies focused on TIA/minor stroke patients irrespective of the extent of disease or the suspected source of the event.

A number of trials13–16 and individual investigators have reported no differences in outcome based on timing of CEA after stroke. Paty et al16 found no difference when stroke patients underwent CEA 1, 2, 3, or 6 weeks after the acute event. A prospective study from Ballotta et al15 reported no significant differences in outcome between 45 patients randomized to early and 41 patients to delayed >30 days CEA, and no recurrent stroke occurred during the waiting period in the delayed group.

The 30-day stroke and death rate after CEA in published series where patients presented with crescendo TIA or a non-disabling stroke and then underwent CEA within 14 days found the periprocedural risk to be ≈8%.13 This level of procedural risk has been seen by some to be too high. A recent large prospective Swedish study showed that urgent CEA (0–3 days) confers 4-fold increase in procedural risk.17

The Carotid Endarterectomy Trialists Collaboration (CETC) data have allowed researchers to model the number of strokes prevented per 1000 CEAs at 5 years in relation to the procedural risk and delay in surgery. At present a high recurrence risk is widely accepted in stroke patients with large artery atherosclerosis. A single-center study by Ois et al18 evaluated the hyperacute risk of stroke after TIA/minor stroke in patients with SCS. Ois found that in SCS patients with 50% to 99% stenosis, the risk of stroke was 17% at 72 hours, 22% at 7 days, and 25% at 14 days, concluding that patients with

Table 1. Subgroups and the Incidence of Neurological Recurrence up to and After Carotid Endarterectomy in our Cohort

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>TIA</th>
<th>Minor Stroke</th>
<th>Stroke Rankin 2–3</th>
<th>Ocular events</th>
<th>Total, %</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subgroups underwent CEA in our study, %</td>
<td>39 (34)</td>
<td>22 (19)</td>
<td>43 (38)</td>
<td>11 (9)</td>
<td>115 (100)</td>
<td>(97–100)</td>
</tr>
<tr>
<td>No. of patients with ≥1 NR before admission, %</td>
<td>13 (33)</td>
<td>7 (33)</td>
<td>6 (14)</td>
<td>8 (73)</td>
<td>34 (29)</td>
<td>(20–37)</td>
</tr>
<tr>
<td>No. of patients with ≥1 NR after admission, %</td>
<td>3 (7)</td>
<td>0</td>
<td>0</td>
<td>3 (2.5)</td>
<td>1 (0.8)</td>
<td>(1–6)</td>
</tr>
<tr>
<td>≥1 NR after admission to vascular unit</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td>(0–5)</td>
</tr>
<tr>
<td>No further events after BMT until CEA, %</td>
<td>36 (92)</td>
<td>22 (100)</td>
<td>43 (100)</td>
<td>11 (100)</td>
<td>112 (97)</td>
<td>(93–99)</td>
</tr>
<tr>
<td>30-day stroke, AMI, and death rate pre/post CEA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(0–3)</td>
</tr>
<tr>
<td>Reduction of NR before versus after admission and BMT (P value)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0025</td>
<td>0.0003</td>
<td>0.00001</td>
<td></td>
</tr>
</tbody>
</table>

ATE indicates amaurosis fugax; AMI, acute myocardial infarction; BMT, best medical treatment; CEA, carotid endarterectomy; Cl, confidence interval; NR, neurological recurrence; and TIA, transient ischemic attack.
first-ever mild stroke or TIA and carotid stenosis are at high risk for NR especially within the first 72 hours. They suggested testing pharmacological or interventional strategies for use during the hyperacute stroke phase in these patients.

Dual antiplatelet therapy has not been proven to reduce the risk of recurrent stroke. Combination of clopidogrel and aspirin versus mono clopidogrel failed in the Management of A Thrombosis with Clopidogrel in High-risk patients (MATCH) trial to show a benefit of the combination therapy. This trial, however, showed a possible benefit of dual therapy in patients randomized early after the qualifying event, whereas the differences in bleeding complications emerged only after 3 months. Theoretically this would indicate that there is a window of opportunity for short-term use of the combination therapy.19 The authors interpretation of the Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER) pilot study was “Immediately after TIA or minor stroke, patients are at high risk of stroke which might be reduced by using clopidogrel in addition to aspirin.”20 The Clopidogrel and Aspirin for Reduction of Embolic in Symptomatic Carotid Stenosis (CARESS) and Clopidogrel plus Aspirin for Infarction Reduction in acute stroke or TIA (CLAIR) trial showed that the combination treatment of clopidogrel and aspirin would reduce early embolic duplex signal in SCS patients.21,22 They concluded that clinical trials were warranted to investigate whether this combination dual therapy also would result in a reduction in recurrent stroke incidence.

Pharmacologically it takes 3 to 7 days before there is complete blockage of thrombocyte aggregation when starting clopidogrel and thus it needs to be complemented with aspirin in high-risk carotid patient. Danish guidelines11 allow the possibility of combination therapy in the early phase but discourages long term (>3-month treatment) with aspirin plus clopidogrel. Urgent combination dual treatment after emergency CT of brain up to fast-track CEA has been started as standard treatment for CEA candidates with carotid stenosis >50% in our region since October 2010.

Our data show a very low incidence (2.5%) of NR in patients receiving BMT while awaiting CEA. All 3 NRs after initiation BMT were seen in TIA subgroup (3/39 [7%]). Compared with historic rates of early recurrent stroke, it would seem that our acute admission and BMT have a protective effect on NR prior CEA and may obviate the need for urgent CEA.

The loading and urgent dual antiplatelet therapy did not increase the risk of intracerebral hemorrhage or other pre-

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Table 2. Reasons for Delay for Symptomatic Patients Undergoing Carotid Surgery >14 days After Index Event

<table>
<thead>
<tr>
<th>Reason</th>
<th>Thrombolysed</th>
<th>TIA</th>
<th>Minor Stroke</th>
<th>Stroke Rankin (2–3)</th>
<th>Af</th>
<th>Total, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subgroups underwent CEA, %</td>
<td>17 (15)</td>
<td>39 (34)</td>
<td>20 (17.5)</td>
<td>28 (24)</td>
<td>11 (9.5)</td>
<td>115 (100)</td>
<td></td>
</tr>
<tr>
<td>Delay in referral from GP or eye specialist</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>15 (13)</td>
<td>(9–24)</td>
</tr>
<tr>
<td>Delay in duplex ultrasound from GP or eye specialist</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>14 (9–24)</td>
<td></td>
</tr>
<tr>
<td>Overall delay in referral from stroke units</td>
<td>3</td>
<td>19</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>38 (33)</td>
<td>(25–43)</td>
</tr>
<tr>
<td>Overall delay &gt;7 days of referral to vascular unit</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>27 (15–32)</td>
<td></td>
</tr>
<tr>
<td>Overall delay &gt;7 days of referral to vascular unit</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>15 (13)</td>
<td>(9–24)</td>
</tr>
<tr>
<td>Overall delay &gt;7 days of referral to vascular unit</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>15 (13)</td>
<td>(9–24)</td>
</tr>
<tr>
<td>Overall delay &gt;7 days of referral to vascular unit</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>15 (13)</td>
<td>(9–24)</td>
</tr>
<tr>
<td>Overall delay &gt;7 days of referral to vascular unit</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>15 (13)</td>
<td>(9–24)</td>
</tr>
<tr>
<td>Unfit for surgery Rankin &gt;3 in the first contact</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3 (1–8)</td>
<td></td>
</tr>
<tr>
<td>Unfit for anesthesia at the first contact</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (0–5)</td>
<td></td>
</tr>
<tr>
<td>Patient canceled or no surgeon available</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (0–5)</td>
<td></td>
</tr>
<tr>
<td>Patient needed time for reflection</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5 (1–11)</td>
<td></td>
</tr>
<tr>
<td>All other reasons</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4 (1–10)</td>
<td></td>
</tr>
</tbody>
</table>

AfX indicates amaurosis fugax; CEA, carotid endarterectomy; CI, confidence interval; CT, computed tomography; GP, general practitioner; and TIA, transient ischemic attack.
postoperative bleeding in CEA patients in our study. Our results are thus in accordance with the Early use of existing Preventive Strategies for Stroke (EXPRESS) study,23 which concluded that urgent medical treatment in specialist stroke services after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke. In our 2-year study there was no significant difference in outcome between 48 early CEA (<14 days), 46 intermediate (14–30 days), and 21 delayed (>30 days) CEAs. There are, however, several logistical issues that still need to be addressed to deliver optimal service. Of 315 patients who were referred to our unit, 60% (95% confidence interval, 50%–70%) were rejected from the vascular unit because of either an overestimation of degree of stenosis or difficulty in verifying occlusion/near occlusion of ICA in primary duplex ultrasound. Therefore, we think secondary duplex ultrasound is indispensable and must be done by the departments responsible for the CEA and should be validated.

Most of the delay is from the time of first symptom to referral to our vascular unit. This delay was because of lack of patient and family doctor awareness, especially in the cases of TIA and AfX, with fast remission of symptoms. Waiting time from first symptom to duplex ultrasound was also a factor. Thirteen (20%) of our CEA patients with stroke had ≥1 TIA or AfX before their first contact to our stroke clinics and BMT. A conservative estimate would mean that more education in the symptoms of TIA/AfX, with fast remission of symptoms is indispensable and must be done by the departments responsible for the CEA and should be validated.

Confounders

We may have overlooked a few patients with severe carotid stenosis who died immediately after admission to our stroke clinics. Patients with very poor general condition after stroke where primary duplex was not warranted were not referred to our unit. There may be a bias in our study because of the small number of patients with a recorded complication. Our results need to be tested and confirmed elsewhere.

Conclusions

An expedited CEA can be performed in the subacute period without significantly increasing the operative risk. The acute admission and urgent aggressive BMT in our cohort were associated with significant reduction (P<0.00001) in the risk of early NR in the CEA patient. It seems that in neurologically stable patients CEA can wait ≤30 days, provided urgent BMT has been started in specialized stroke/TIA clinics. Our study also adds to the data on the benefit of specialist TIA clinics.

Disclosures

None.

References

Urgent Best Medical Therapy May Obviate the Need for Urgent Surgery in Patients With Symptomatic Carotid Stenosis
Saeid Shahidi, Alan Owen-Falkenberg, Ulrik Hjerpsted, Amrit Rai and Karsten Ellemann

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