Clinical Decision Making: Hyperacute Management of Symptomatic Carotid Artery Disease

Tarvinder Singh, MS, MD
Neurohospitalist
Swedish Neuroscience Institute
Objectives

• Definition
• Why the urgency?
• Evidence/Guidelines for symptomatic carotid disease (BP, anti-thrombotics, CEA/CUS)
• Special situations:
  • Role of heparin
  • Role of acute endovascular management
  • CEA/CUS in – women, elderly, while on DAP, with disabling stroke, timing
Case

58 year-old right-handed woman woke up with new left-sided weakness.
PMHX: Diabetes, Hypertension, Hyperlipidemia, TIA 2 years ago.
SHX: No bad habits.
Home Meds: ASA 81mg daily. No statin.
Exam: BP 160/90, CN intact. Left hand and entire leg strength 4/5. Walks without support.
Labs: LDL 122, A1c 7.0
Case: 58yo with left-sided weakness

- CT/H without acute changes
- CTA with R ICA 80% stenosis (NASCET criteria), L ICA < 50%, and diffuse mild atherosclerotic disease.

- Next steps?
Case: 58yo with left-sided weakness

- MRI with peri-rolandic R frontal ischemic stroke, about 10 cc in volume.
- Started on aspirin 81mg daily and clopidogrel 75mg daily
- Admitted to the neurology floor with acute ischemic stroke order set and frequent neuro checks.

- Next steps?
What is the urgency?

Why close monitoring, further diagnostics and urgency of intervention?
Risk of recurrent TIA/stroke after event is **front loaded**.

- > 2000 pts with ischemic stroke. Of those, > 500 with prior TIA events.
- Of strokes preceded by TIA, 43% of strokes happened in first 7 days after TIA.
- Third of those happened on the day of stroke!

The second event was disabling or fatal in half of these patients.

Risk of stroke in the hyperacute period after the index TIA in patients with 50–99% carotid stenosis compared with pooled data from the randomized trials.

<table>
<thead>
<tr>
<th>Study Description</th>
<th>48 h</th>
<th>72 h</th>
<th>7 d</th>
<th>14 d</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCT + NASCET + VA (medical therapy)²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>Fairhead et al. (2005)²⁹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>Purroy et al. (2007)³⁰</td>
<td></td>
<td></td>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Ois et al. (2009)³¹</td>
<td></td>
<td>17%</td>
<td>22%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Bonifati et al. (2011)³²</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johansson et al. (2013)³³</td>
<td>5%</td>
<td>8%</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merwick et al. (2013)³⁴</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marnane et al. (2014)³⁵</td>
<td>5%</td>
<td>9%</td>
<td>9%</td>
<td>16%b</td>
<td></td>
</tr>
</tbody>
</table>

Why is early stroke risk high?

<table>
<thead>
<tr>
<th>CEA performed</th>
<th>&lt; 4 weeks of index TIA</th>
<th>&gt; 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus overlying plaque</td>
<td>66%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Naylor, Review Time is Brain 2015; [Harrison, Marshall 1977]
• However, not everyone with TIA or minor stroke ends up with a stroke.

• Can high-risk patients be identified?

• Would they be treated differently?
Transcranial doppler

• Prevalence of spontaneous emboli on TCD after symptom onset:
  • 42% of patients in < 7 days
  • 22% 8-14 days
  • 16% > 14 days

MRI of carotid plaque

**Carotid Plaque Hemorrhage on Magnetic Resonance Imaging Strongly Predicts Recurrent Ischemia and Stroke**

Akram A. Hosseini, MRCP, MD, Neghal Kandiyili, MRCS, Shane T. S. MacSweeney, FRCS, MChir, Nishath Altaf, FRCS, PhD, and Dorothee P. Auer, FRCP, PhD

**Objective:** There is a recognized need to improve selection of patients with carotid artery stenosis for carotid endarterectomy (CEA). We assessed the value of magnetic resonance imaging (MRI)-defined carotid plaque hemorrhage (MRIPH) to predict recurrent ipsilateral cerebral ischemic events, and stroke in symptomatic carotid stenosis.

**Methods:** One hundred seventy-nine symptomatic patients with ≥50% stenosis were prospectively recruited, underwent carotid MRI, and were clinically followed up until CEA, death, or ischemic event. MRIPH was diagnosed if the plaque signal intensity was >150% of the adjacent muscle. Event-free survival analysis was done using Kaplan-Meier plots and Cox regression models controlling for known vascular risk factors. We also undertook a meta-analysis of reported data on MRIPH and recurrent events.

**Results:** One hundred fourteen patients (63.7%) showed MRIPH, suffering 92% (57 of 62) of all recurrent ipsilateral events and all but 1 (25 of 26) future strokes. Patients without MRIPH had an estimated annual absolute stroke risk of only 0.6%. Cox multivariate regression analysis proved MRIPH as a strong predictor of recurrent ischemic events (hazard ratio [HR] = 12.0, 95% confidence interval [CI] = 4.8-30.1, p < 0.001) and stroke alone (HR = 35.0, 95% CI = 4.7-261.6, p = 0.001). Meta-analysis of published data confirmed this association between MRIPH and recurrent cerebral ischemic events in symptomatic carotid artery stenosis (odds ratio = 12.2, 95% CI = 5.5-27.1, p = 0.0001).

**Interpretation:** MRIPH independently and strongly predicts recurrent ipsilateral ischemic events, and stroke alone, in symptomatic ≥50% carotid artery stenosis. The very low stroke risk in patients without MRIPH puts into question current risk-benefit assessment for CEA in this subgroup.

**Ann Neurol 2012;72:714-784**

Axial views of T1-weighted water-selective magnetic resonance imaging to detect plaque hemorrhage of carotid arteries. Hyperintense signals (B-D, white arrows) reflect plaque hemorrhage in carotid arteries, black arrows (A) show absence of plaque hemorrhage, and asterisks indicate the lumen of internal carotid artery. (A) No signal hyperintensity. (B) Large moderately hyperintense plaque. (C) Small strongly hyperintense plaque. (D) Large strongly hyperintense plaque.
Intraplaque hemorrhage predicts outcome

| TABLE 2. Analysis of Recurrent Cerebral Ischemic Events in Symptomatic Patients with ≥50% Carotid Artery Stenosis |
|-------------------------------------------------|------------------|------------------|------------------|------------------|
| Events, No. | PY     | Event Rate per 100 PY | Annual Risk | Adjusted for Risk Factorsa Hazard Ratio (95% CI) | p        |
|---------------------------------|------------------|------------------|------------------|------------------|
| Ipsilateral recurrent stroke, TIA or AmF |                   |                   |                 |                   |         |
| MRIPH+  | 57          | 94.6             | 60.2             | 45.2%             | 11.95 (4.8−30.1) | <0.001 |
| MRIPH−  | 5           | 156.7            | 3.2              | 3.1%              | 1.0               |         |
| Ipsilateral recurrent stroke    |                   |                   |                 |                   |         |
| MRIPH+  | 25          | 94.6             | 26.4             | 23.2%             | 35.0 (4.7−261.6) | 0.001  |
| MRIPH−  | 1           | 156.7            | 0.64             | 0.6%              | 1.0               |         |

*aAdjusted for age, sex, degree of carotid stenosis, and known vascular risk factors as described in Patients and Methods. AmF = amaurosis fugax; CI = confidence interval; MRI = magnetic resonance imaging; MRIPH− = absence of hyperintense signal on MRI; MRIPH+ = presence of hyperintense signal on MRI; PY = person years; TIA = transient ischemic attack."
Management
Blood pressure

- Current consensus guidelines recommend treating BP > 220/120 mmHg unless patient has received thrombolytic therapy in which case the maximum permitted BP is 185/110 mmHg.
- However, hyperacute post-stroke BP often has to be individualized.
Anti-platelet therapy

- ASA + Clopidogrel
  - > 50% reduction in microemboli
  - POINT trial ongoing.
- SOCRATES trial ticagrelor 90mg BID vs ASA 100mg QD after stroke/TIA with no significant benefit.
  - However, subgroup analysis showed benefit if ipsilateral carotid disease.

SOCRATES, Lancet 2017
TARDIS

• Anti-platelet triple therapy no benefit over dual therapy
  • More bleeding
  • POINT trial for further data on DAPT

The Triple Antiplatelets for Reducing Dependency in Ischemic Stroke (TARDIS) trial, 2017
Case: 58yo with left-sided weakness

• Additional diagnostics
  • TCD w/ emboli monitoring
  • Carotid ultrasound/MRI to characterize the carotid plaque

• Additional management
  • CEA/CAS
  • Heparin gtt
CEA
CEA - Timing

Figure 1. Number of ipsilateral strokes prevented at 5 years by performing 1000 CEAs in symptomatic patients with 50–69% and 70–99% carotid stenoses relative to interval from randomization to undergoing surgery.

Based on a reanalysis of Carotid Endarterectomy Trialists Collaboration data [8].

CEA: Carotid endarterectomy.

Naylor, Review Time is Brain
CEA - Gender

Figure 2. Number of ipsilateral strokes prevented at 5 years by performing 1000 CEs in symptomatic male patients with 50–69% and 70–99% carotid stenoses, relative to interval from randomization to undergoing surgery. Based on a reanalysis of Carotid Endarterectomy Trialists Collaboration data [8] and reproduced with permission from Naylor AR, Time is Brain, The Surgeon 2007;5:23-30. CEA: Carotid endarterectomy.

Figure 3. Number of ipsilateral strokes prevented at 5 years by performing 1000 CEs in symptomatic female patients with 50–69% and 70–99% carotid stenoses, relative to interval from randomization to undergoing surgery. Based on a reanalysis of Carotid Endarterectomy Trialists Collaboration data [9] and reproduced with permission from Naylor AR, Time is Brain, The Surgeon 2007;5:23-30. CEA: Carotid endarterectomy.

Naylor, Review Time is Brain
CEA

- Most of the data is based on old medical therapy, TIA/minor stroke and high peri-procedural risk.
- Current guidelines recommend periprocedural risk of stroke/death < 6% for symptomatic carotid stenosis.
- Suggested that this be lowered to < 2%.

<table>
<thead>
<tr>
<th></th>
<th>Favors medical mgmt.</th>
<th>Favors surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Lesion</td>
<td>Smooth</td>
<td>Ulcerated</td>
</tr>
<tr>
<td>Sx type</td>
<td>Retinal</td>
<td>Hemispheric</td>
</tr>
<tr>
<td>Collaterals</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Chaturvedi S, Emergency Medicine 2000
Hyperacute CEA

• How early can we safely do CEA?
Procedural risk of CEA w.r.t. to timing

Table 2. Thirty-day death/stroke after carotid endarterectomy stratified for delay from index symptom to surgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>0–48 h (Procedural Risk)</th>
<th>3–7 d (Procedural Risk)</th>
<th>8–14 d (Procedural Risk)</th>
<th>&gt;14 d (Procedural Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromberg et al. (2012)</td>
<td>17/148 (11.5%)</td>
<td>29/894 (3.6%)</td>
<td>26/677 (4.0%)</td>
<td>52/967 (5.4%)</td>
</tr>
<tr>
<td>Sharpe et al. (2013)</td>
<td>1/41 (2.4%)</td>
<td>3/167 (1.8%)</td>
<td>1/133 (0.8%)</td>
<td>1/134 (0.7%)</td>
</tr>
<tr>
<td>Rantner et al. (2015)</td>
<td>9/206 (4.4%)</td>
<td>4/219 (1.8%)</td>
<td>6/136 (4.4%)</td>
<td>5/200 (2.5%)</td>
</tr>
</tbody>
</table>

[16] Procedural risk following carotid endarterectomy in the hyperacute period after onset of symptoms Eur J Vasc Endovasc Surg, 46 (2013), pp. 519–524
Procedural Risk Following Carotid Endarterectomy in the Hyperacute Period after Onset of Symptoms


*The Vascular Studies Unit, Leicester Royal Infirmary, Leicester, UK
b The Department of Vascular Surgery, Leicester Royal Infirmary, Leicester, UK

WHAT THIS PAPER ADDS
Performing carotid endarterectomy within the hyperacute period after a transient ischaemic attack or minor stroke (whether this time period was defined as <48 hours, <7 days, or <14 days) was not associated with a significant increase in the procedural risk.

Objectives: There have been concerns that performing carotid endarterectomy (CEA) in the hyperacute period after onset of a transient ischaemic attack (TIA) or stroke may be associated with a significant increase in the procedural risk that could offset any long-term benefit to the patient. The aim of this audit was to determine the 30-day risk of stroke/death after CEA in symptomatic patients, stratified for delay from the most recent neurological event, mode of presentation, and age.

Methods: Retrospective audit in 475 recently symptomatic patients between October 1, 2008, and April 24, 2013.

Results: Forty-one patients (9%) underwent surgery <48 hours of their most recent event, with a 30-day death/stroke rate of 2.4% (1/41). The procedural risk was 1.8% in 167 patients who underwent surgery within 3–7 days (3/167), falling to 0.8% in 133 patients who underwent surgery between 8 and 14 days (1/133) and 0.8% in 134 patients whose surgery took place after >14 days had elapsed (1/134). Overall, 208 (44%) underwent surgery within 7 days of their most recent neurological event (30-day risk = 1.9%), while 341 (72%) underwent CEA within 14 days (30 day risk = 1.5%). There was no evidence of any systematic differences in procedural risk by operating in the hyperacute period relating to mode of presentation (TIA, stroke, amaurosis) or age (<80 years; >80 years).

Conclusions: This audit found no evidence that the procedural risk was increased when CEA was performed in the hyperacute period whether this time period was defined as <48 hours, <7 days, or <14 days.

© 2013 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.

Article history: Received 26 July 2013, Accepted 27 August 2013, Available online 5 September 2013

Keywords: Carotid endarterectomy, Transient ischaemic attack, Stroke, Rapid treatment
Why lower procedural risk in Leicester study?

“...we attributed our very low procedural risks to an obsessional attention to surgical technique, completion angioscopy/intraoperative TCD, peri-operative dual antiplatelet therapy and written guidelines for treating post-CEA hypertension.”
CEA - Elderly

• Depends on life expectancy.
• There is post-operative risk and that benefit recouped over the years.
• However, if they are not alive long, then that benefit cannot be recuperated.
Debatable

- Heparin for acute ischemic stroke
- Severe stroke patients excluded from trials. Would they benefit from intervention?
Case

• 75 year old woman with no PMHx woke up with left side weakness.
• On exam: Left hemiparesis and neglect
• EKG: normal
• Symptoms: progressing

• What antithrombotic medication would you want to use acutely?
Aspirin
Heparin
Acute Basilar Artery Occlusive Disease

To the Editor:

Current treatment of basilar artery occlusion is unconventional, with an unpredictable mortality and morbidity approaching 70%. Thrombolytic therapy is an emerging approach and has been shown promisingly to help, but it is still experimental and therefore of unproved value. Heptapela has recently been described in improving basilar artery occlusion. C. Miller Fisher has described two patients with presumed basilar artery occlusion who improved after being treated with argon laser and given heparin as an intravenous bolus. We recently had the opportunity of implementing Fisher's novel approach, with a new twist and a surprisingly good outcome.

A 75-year-old male was a history of heavy cigarette and alcohol use, no history of illicit drug use including cocaine, arrived at the emergency room in the evening complaining of bitemporal and partial headache, which first appeared upon awakening that morning and continued steadily for several hours. Early in the afternoon while at work, he had felt a sense of yawning and contractions of jaw, with subsequent difficulty and blurred vision. He felt weak on both sides, but more so on the right. These symptoms fluctuated prior to his arrival at the emergency room, but had been present for longer than 1 hour at the time of this evaluation.

Initial neurologic examination revealed the patient to be alert and oriented. He had severe dysmetria. A left hemiparesis path and left internuclear ophthalmoplegia, as well as a right facial weakness and decreased hearing in the right ear, were present. The gag reflex was diminished. Motor examination revealed a flaccid, flaccid right upper extremity and a paretic right upper extremity. Sensation was preserved in the left upper extremity and diminished in the right upper extremity. The remainder of his neurologic examination was normal, with no evidence of hemianopia, dysphasia, or other bilateral clinical features. The patient had no nystagmus, and his pupils were equal and reacting to light.

Acute basilar artery occlusive disease.

P Mitsias, S R Levine and J Lozon

Stroke. 1990;21:503-504

as well as a questionable left dorsomedial pontine infarct (Figure 1). Because of the suspicion of basilar artery occlusion, the patient was initially hydrated and held upside down and shaken for about 5 minutes. He was then started on heparin (intravenous drip), without bolus, and phlebotomized. In about 5 minutes his neurologic deficit resolved with the exception of the left sixth nerve paresis and internuclear ophthalmoplegia.

Transcranial Doppler performed the following day negated basilar stenosis. The patient's condition remained unchanged, and no further imaging was performed. He returned to his normal work schedule, which demonstrated a 23/30H left medullary syndrome (Figures 2 and 3), as well as filming deficits in the hands intermittently, probably due to clot. The patient continued on heparin and then transitioned to warfarin. Permanent search for angiography was not performed. Follow-up at 2 and 6 weeks revealed an intact neurologic examination with the exception of a mild left internuclear ophthalmoplegia.

Our initial clinical impression was that the patient had impending basilar artery occlusion based on fluctuating bilateral findings.
Miller Fisher: The Master of Clinicopathologic Correlation. Interview Trobe, Jonathan D. MD

• **JDT:** And weren’t you responsible for introducing the idea of anticoagulation in TIAs and large extracranial artery stenosis?

• **CMF:** Yes. The first patient I anticoagulated with heparin had basilar TIAs. We’d turn on the heparin and the TIAs would stop, turn it off and they’d start up again. I set up the first anticoagulation trial. Seven centers cooperated. *We had so many fatal bleeding accidents that it appeared unlikely that a benefit could be shown.*

Multiple trials in use of heparin

- IST (unfractionated sq heparin)
- TOAST (danaproid)
- FisBis (fraxiparin)
- HAEST (dalteparin)

NO overall benefit.
Anticoagulation for acute ischemic stroke

Guidelines do not support “routine” use of anticoagulation post-stroke. However, experts consider it in:

• Conditions with potential high risk of early cardiogenic reembolization
• Symptomatic dissection of the arteries supplying the brain
• Symptomatic extracranial or intracranial arteriosclerotic stenosis with crescendo TIAs or early progressive stroke
• TCDs with embolization/Stump
• Basilar artery occlusion before or after intra-arterial pharmacological or mechanical thrombolysis.
• Known hypercoagulable states
• Cerebral venous sinus thrombosis
Conclusion

• Post-stroke/TIA recurrence stroke rate is high.
• Evidence/Guidelines exist for symptomatic carotid disease (BP, anti-thrombotics, CEA/CUS)
• Identification of high-risk patients can allow targeted therapies such as hyperacute CEA and anticoagulation.
• Women have a different risk/benefit profile.
Extra slides