Lecture outline

• Symptoms of carotid stenosis
• Indications for carotid endarterectomy
  • Symptomatic stenosis
  • Asymptomatic stenosis
• Is angioplasty or stenting an alternative?
  • Meta-analysis of endovascular treatment versus surgery for carotid stenosis
• Conclusions
Symptoms of carotid stenosis 1

- Embolic TIA or stroke
  - Retinal
  - MCA territory (arm > leg)
  - ACA territory (leg > arm)
  - Combined ipsilateral retinal & contralateral hemiparesis
- Occasionally
  - PCA territory (hemianopia)

Intracranial angiogram showing anterior cerebral artery (ACA), an occluded middle cerebral artery (MCA) and a prominent posterior communicating artery (PCoA)

Symptoms of carotid stenosis 2

- Haemodynamic TIA
  - Hypotensive / vasodilatory stimuli
  - Atypical TIAs e.g. "shaking TIAs"
  - Haemodynamic TMB (ischaemic retinopathy)
- Haemodynamic stroke
  - Borderzone infarction
Carotid endarterectomy, angioplasty and stenting

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Superficial borderzone infarction: uncommon in carotid stenosis but may be seen with carotid occlusion

Carotid stenosis
Deep borderzone infarction: string of beads sign

Perfusion MR: Mean Transit Time maps showing impaired perfusion in deep borderzones in a patient with severe left carotid stenosis
Other symptoms of carotid artery disease

- Pulsatile tinnitus (usually distal stenosis)
- Non-specific features (usually dissection)
  - Carotidodynia
  - Migraine with aura
- Lower cranial nerve palsies (dissection)

Signs of carotid artery disease

- Bruit
  - NB sometimes external carotid artery
  - Stenosis not always present
  - Often absent if severe stenosis
- Absent/reduced carotid pulsation
  (common carotid occlusion)
- Horner’s syndrome (usually dissection)
- Unilateral low flow retinopathy
- Cholesterol retinal emboli (Hollenhorst plaque)

Examination

Low flow retinopathy

- Blot haemorrhages
- Dilated veins
- Retinal arteries pulsate with ocular pressure
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Optimum management of carotid stenosis: treatment should be evidence based

Cholesterol embolus with retinal infarction secondary to carotid stenosis
Mechanisms of ischaemic stroke
(Lausanne Stroke Registry, n=891)

- Large artery atherosclerosis (44%)
- Surgical carotid stenosis (5%)
- Lacunar (15%)
- Cardiac (18%)
- Mixed (5%)
- Dissection (5%)
- Other (6%)
- Unknown (8%)


Combined analysis of the major symptomatic carotid surgery trials

- European Carotid Surgery Trial - ECST
- North American Symptomatic Carotid Endarterectomy Trial - NASCET
- Veterans Affairs Symptomatic Carotid Artery Surgery Trial - VA

Medical arm (N) 1,213 1,449 101
Surgical arm (N) 1,811 1,436 92

Stenosis severity (%)
0 - 99
30 - 99
50 - 99

- Outcomes: 1710 strokes and 1492 deaths
- Total follow-up: 35,000 patient years


NASCET % stenosis = (1-A/B) x 100

ECST % stenosis = (1-A/C) x 100

CC % stenosis = (1-A/D) x 100

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Stenosis 70-99% (excluding near occlusions)
Ipsilateral carotid territory ischemic stroke plus any surgical stroke or surgical death

- Surgical treatment was better than medical treatment
- Surgery is highly effective at reducing the number of events
- In patients treated medically, the biggest benefit occurs in the first few years
- Surgery is only beneficial if performed soon after symptoms

Patients
Surgery: 573 487 454 427 404 374 315 237 157 86 20
No surgery: 498 393 332 299 284 254 218 166 90 36 10

Years from randomization
0 1 2 3 4 5 6 7 8 9 10
0.5 1.0

Proportion free of event
0.5 0.6 0.7 0.8 0.9 1.0

Log Rank = 30.7
p < 0.00001

85% stenosis Near-occlusion
NASCET method

Near occlusion
Ipsilateral carotid territory ischemic stroke plus any surgical stroke or surgical death

Patients
Surgery: 164 148 138 130 106 92 72 43 21 5
No surgery: 122 105 93 92 80 66 47 26 11 3

Years from randomization
0 1 2 3 4 5 6 7 8 9 10
0.5 1.0

Proportion free of event
0.5 0.6 0.7 0.8 0.9 1.0

Log Rank = 0.0006
p = 0.98
Absolute risk reduction with surgery at different degrees of stenosis:

Ipsilateral stroke and any operative stroke or death

Negligible risk <30%
30-49%
50-69% small benefit
60-99% moderate benefit
Near inevitable

The effect of surgery by time since last event in patients with 50-99% stenosis

Slope = 2.9% per month, P<0.01

Male
Female

Rothwell PM et al, Lancet 2005; 366:256-265
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Risk of recurrent stroke prior to endarterectomy in Oxford Vascular Study:
85 patients with prior TIA/non-disabling stroke and >50% carotid stenosis on ultrasound

Fairhead JF et al., Neurology 2005; 65:371-375

Lecture outline

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Asymptomatic carotid surgery trial

Entry 1993 – 2003

3120 patients with asymptomatic stenosis randomised

Immediate CEA vs. Deferral CEA

Lancet 2004;363:1491-1502
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ACST: 5-year risk of any type of STROKE or perioperative DEATH

\[ z = 4.38, p = 0.00001 \]

Combined analysis of ACST & ACAS trials: no apparent benefit on stroke or death during a mean follow up of 2-3 years in women

Rothwell PM. Lancet 2004; 364: 1122–1123
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Benefit from surgery for asymptomatic patients, calculated from ACST 5 year result

- NNT to prevent one stroke in 5 years = 17
- Of 100 asymptomatic patients operated
  - 9 benefit from avoiding stroke
  - 3 harmed by perioperative stroke or death
  - 88 unnecessary surgery without harm
    - 6 have a stroke not prevented by surgery
    - 82 would have been free of stroke anyway

HPS: benefit of simvastatin on rate of carotid endarterectomy or angioplasty

- All patients
  - Statin 0.4% vs. placebo 0.8%, p<0.0003
- Patients with prior cerebrovascular disease
  - Statin 1.0% vs. placebo 2.3%, p<0.002

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Endovascular treatment – an alternative to surgery?

Against surgery
- Risk of MI and PE
- Incision in the neck
  - Haematoma
  - Cranial nerve palsy
  - Permanent scar
- General anaesthesia
- Expensive

Carotid endarterectomy specimen: thrombus within ulcerated plaque

What have we learnt from CAVATAS?
Carotid and Vertebral Artery Transluminal Angioplasty Study
International multicentre randomised trial of endovascular treatment for extracranial cerebrovascular disease
Randomisation started in 1992
Randomisation completed 1997
Follow up completed 2008

Lancet 2001; 357: 1729-1737
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**Inflated angioplasty balloon**

**CAVATAS intention to treat analysis**
Carotids fit for surgery (n=504)
Events within 30 days of treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Endovascular treatment</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes/death</td>
<td>10.0%</td>
<td>9.9%</td>
</tr>
<tr>
<td>* More than 7 days duration</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>0%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Haematoma†</td>
<td>1.2%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

† requiring surgery or prolonging stay

**CAVATAS: 5 year risks of disabling or fatal stroke or procedural death/MI**

- Surgical 11.6%
- Endovascular 11.5%

Incomplete unaudited data

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Conclusions from CAVATAS

- In favour of endovascular treatment
  - No difference in early risk of stroke or death
  - Less minor complications
- Against endovascular treatment
  - 10% risk of stroke or death too high
  - Greater risk of restenosis
  - Not enough long term follow up
- Safety needs to be improved
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and stenting
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Evolution of endovascular treatment since first trials

- Stenting now technique of choice
- New stents, guide-wires & delivery systems designed for carotid arteries
- Technique and patient selection improved
- Aspirin plus clopidogrel during stenting
- Carotid stenting training courses and proctoring mandatory
- Protection devices introduced

Self expanding nitinol stent

Cerebral protection devices
Carotid endarterectomy, angioplasty and stenting
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Parodi anti-embolism system

Disadvantages of protection devices
- Increased complexity of procedure
- Distal protection devices
  - May get stuck or injure wall
  - Pre-dilation or insertion of filter across the stenosis may cause emboli
- Proximal balloon devices
  - No imaging of the stenosis during reverse flow
  - May cause ischaemia during flow reversal
- Do not protect against stroke after stenting

CAVATAS: timing of strokes after treatment

One third of treatment related stroke delayed
Examples of recent prospective case series and registries

- Industry sponsored case series - single design of stent with protection device
  - ARCHER BEACH
  - CABERNET SECURITY
  - MAVERIC SAPPHIRE (registry)

- Large European registries
  - German registry
  - Italian/German registry

Problems with case series and registry data

- Uncertainty about quality of data and completeness of neurological follow up
- Symptomatic and asymptomatic often mixed together
- Selection bias
- No comparison group
  - e.g. Reimers et al.,* (n=750) 67% ineligible for surgery in NASCET

Accuracy of outcome event assessment in German Carotid Stenting Registry

- 30 day stroke & death rate
  - Not seen by a neurologist at all: 1.3%
  - Seen by a neurologist before and after the event: 3.5%
  - Seen after the event by a neurologist: 9.3%


Stroke 2004; 35(5):2134-2139
Randomised control trials provide best data to assess effects of treatment.

Randomised trials of carotid angioplasty and stenting vs. surgery for predominantly symptomatic carotid stenosis:
- Leicester 1996, n=23
- Wallstent 1997, n=219
- Kentucky 2001, n=104
- BACASS unpublished, n=20
- CAVATAS 2001, n=504
- SAPPHIRE 2004, n=307
- SPACE 2006, n=1,200
- EVA-3S 2006, n=527

Stenting and angioplasty with protection in patients at high risk for endarterectomy (SAPPHIRE) trial:
- Stenting (Smart or Precise) plus protection (Angioguard or Angioguard XP) versus carotid endarterectomy
- Inclusion criteria:
  - Co-existing conditions which potentially increased risk of surgery
  - Symptomatic stenosis >50%
  - Asymptomatic stenosis >80%

Yadav JS et al., NEJM 2004; 351:1493-1501
Carotid endarterectomy, angioplasty and stenting

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SAPPHIRE Trial: 30 day outcome data (Intention to treat analysis)

<table>
<thead>
<tr>
<th></th>
<th>Stenting</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomised</td>
<td>167</td>
<td>167</td>
</tr>
<tr>
<td>Stroke, MI or death (%)</td>
<td>4.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Q wave MI (%)</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>Non-Q wave MI (%)</td>
<td>3.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Stroke or death (%)</td>
<td>4.8</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Yadav JS et al., NEJM 2004; 351:1493-1501

SAPPHIRE: primary analysis stroke, MI or death within 30 days, plus ipsilateral stroke or death up to one year

Days after procedure

Freedom from major adverse events (%)

Stent 12.2
Surgery 20.1
p=0.053

SAPPHIRE trial: notable features

- Single stent and protection device only
- Inclusion criteria required increased risk from surgery e.g. ischaemic heart disease
- N=334, only 83 symptomatic
- Declared benefit of stenting weighted by including non-Q wave myocardial infarction
- Trial stopped because of declining recruitment

Yadav JS et al., NEJM 2004; 351:1493-1501
EVA-3S trial
30 day safety data

- Stopped early by DMC (n=527):
- Rate of stroke or death
  - Endarterectomy 3.9%
  - Stenting 9.6% (p = 0.01)

Mas JL et al., NEJM 2006; 355:1660-1671

Explanations for the difference in EVA-3S

- Surgery safer than in previous carotid surgery & other stenting trials
- EVA-3S centre requirements
  - Interventionists: 5 carotid stents
  - Surgeons: 25 carotid endarterectomy operations in previous year
- Variety of stents and protection devices
- Inverse learning curve

Effect of carotid angioplasty/stenting experience in CAVATAS

- Rate of stroke within 30 days of angioplasty/stenting
  - First 30 patients = 11.1% (n=180)
  - Next 20 patients = 7.5% (n=40)
  - Next 50 patients = 4.0% (n=50)
  (average of all centres combined)

Lancet 2001; 358:1999
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SPACE
30 day safety data

- n=1,183
- Rate of stroke or death
  - Endarterectomy 6.5%
  - Stenting 7.7%
  - (OR 1.19, 95% CI 0.75-1.92)

Lancet 2006; 368:1239-1247

SPACE: notable features

- Myocardial infarct not included as an outcome event
- Age and rate of ipsilateral stroke or death
  - Age < 76 years: CEA 5.9%, CAS 5.9%
  - Age > 76 years: CEA 7.5%, CAS 11.1%
- Variety of stents & devices approved
- Use of protection devices
  - No protection: 73% Risk: 7%
  - Protection: 27% Risk: 7%

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Carotid endarterectomy, angioplasty and stenting

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Endovascular vs. surgical treatment of carotid stenosis: any stroke or death at 30 days – fixed effects method

<table>
<thead>
<tr>
<th>Study or Procedure</th>
<th>Endovascular</th>
<th>Surgical</th>
<th>Total Events</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVATRS 2001</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td>1.0 (0.56, 1.81)</td>
</tr>
<tr>
<td>Lecouer 2001</td>
<td>10</td>
<td>11</td>
<td>21</td>
<td>2.1 (0.85, 5.91)</td>
</tr>
<tr>
<td>Kastally 2004</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.1 (0.03, 0.65)</td>
</tr>
<tr>
<td>Helzberg 2004</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1.1 (0.09, 12.7)</td>
</tr>
<tr>
<td>SPACE 2006</td>
<td>46</td>
<td>53</td>
<td>199</td>
<td>1.8 (0.80, 4.1)</td>
</tr>
<tr>
<td>ENY-22000</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td>1.0 (0.56, 1.81)</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>210</strong></td>
<td></td>
<td><strong>1.40 (1.05, 1.85)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: (P = 0.04)

Fixed effects: OR 1.40; CI 1.05 – 1.85 favours surgery

Total events = 210, Test for heterogeneity significant

Ederle J et al., Cochrane Database of Systematic Reviews: 2007

Endovascular vs. surgical treatment of carotid stenosis: MI, death or stroke within 30 days of treatment

<table>
<thead>
<tr>
<th>Study or Procedure</th>
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<th>Surgical</th>
<th>Total Events</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVEATR-2001</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td>2.0 (0.91, 4.4)</td>
</tr>
<tr>
<td>Lecouer 2001</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1.0 (0.19, 4.5)</td>
</tr>
<tr>
<td>Kastally 2004</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Helzberg 2004</td>
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<td>1</td>
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<tr>
<td>ENY-22000</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td>1.0 (0.56, 1.81)</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>210</strong></td>
<td></td>
<td><strong>1.11 (0.77 – 1.6)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: OR = 1.11; 95% CI = 0.77 – 1.6; p = 0.6

Not statistically significant

Ederle J et al., Cochrane Database of Systematic Reviews: 2007

Endovascular vs. surgical treatment of carotid stenosis: cranial neuropathy

<table>
<thead>
<tr>
<th>Study or Procedure</th>
<th>Endovascular</th>
<th>Surgical</th>
<th>Total Events</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>CAVEATR-2001</td>
<td>3</td>
<td>7</td>
<td>10</td>
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<tr>
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<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>Kastally 2004</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.1 (0.03, 0.65)</td>
</tr>
<tr>
<td>Helzberg 2004</td>
<td>1</td>
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<td>2</td>
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<tr>
<td>ENY-22000</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td>1.0 (0.56, 1.81)</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>210</strong></td>
<td></td>
<td><strong>0.07 (0.03, 0.2)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: OR = 0.07; 95% CI = 0.03 – 0.2; p < 0.0001

Strongly favours endovascular treatment

Ederle J et al., Cochrane Database of Systematic Reviews: 2007

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Endovascular vs. surgical treatment of carotid stenosis: other comparisons (fixed effects analysis)

- Any stroke, cranial neuropathy or death at 30 days (n=166 events)
  - OR 0.63; CI 0.45 – 0.87 (favours endovascular)
- Disabling stroke or death at 30 days (n=109 events)
  - OR 1.22; CI 0.83 – 1.80 (no significant difference)
- Stroke during long-term follow up (n=154 events)
  - OR 1.18, CI 0.61 – 2.28 (no significant difference)

Numbers of patients included in the meta-analysis of symptomatic carotid surgery trials

- Ederle J et al., Cochrane Review: Carotid surgery vs. endovascular treatment
  - Safety outcomes: 210 strokes & deaths
  - Outcomes: 3202 strokes & deaths

Conclusions from systematic review of endovascular vs. surgical treatment

- Meta-analysis of 30 day safety data
  - Some analyses favour surgery, some stenting
  - Small number of outcome events
  - Wide confidence intervals
  - Significant statistical heterogeneity
  - Important clinical heterogeneity
  - Little long term effectiveness data: restenosis a concern
  - Data and trial results not sufficient to make decisions
  - Further evidence needed from on-going trials
Carotid endarterectomy, angioplasty and stenting
Prof. Martin M. Brown

On-going trials of carotid stenting

- Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) North America – symptomatic + asymptomatic stenosis
- International Carotid Stenting Study (ICSS) Europe/Australasia/Canada – symptomatic stenosis
- Several trials of stenting versus endarterectomy for asymptomatic carotid stenosis starting recruitment

Conclusions 1: Treatment of symptomatic carotid stenosis

- Patients with stroke or TIA should be investigated for carotid stenosis as soon as possible
- Patients with stenosis of 50-99% should be considered for carotid intervention
- Patients should be seen to ensure that symptoms relate to the stenosis before intervention and discussed with their imaging at a MDT
- Carotid endarterectomy should be performed as soon as the patient is fit for surgery

Conclusions 2: Endarterectomy after stroke or TIA

- Decisions should be made on the basis of individualised risk estimates, particularly if some weeks after symptoms
- Carotid stenosis of less than 50% according to the NASCET criteria should not undergo surgery
- Carotid endarterectomy should only be undertaken by a specialist surgeon in centres where outcomes of carotid surgery are routinely audited
Conclusions 3: Endarterectomy for asymptomatic stenosis

- Rate of stroke low in medically treated patients
- Surgery has small benefit in younger patients over long term follow up
- Cost effectiveness just not justify an active policy of endarterectomy for asymptomatic stenosis
- Individual risks and benefits should be discussed with patient
- Those that choose to avoid or delay surgery should have active medical therapy including statins

Conclusions 4: Carotid stenting

- Carotid angioplasty or stenting may be an alternative to surgery but more evidence is required
- It should only be carried out in specialist centres by experienced interventionalists
- Stenting should preferably be performed as part of a randomised clinical trial

Acknowledgements

- Trial staff and fellows at UCL
- R. Featherstone
- J. Ederle
- J. Dobson
- Collaborators & patients in trials
- Professor Peter Rothwell
- Funding: The Stroke Association, the Medical Research Council and the Reta Lila Weston Trust for Medical Research
Carotid endarterectomy, angioplasty and stenting

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