CAROTID INTERVENTION IS INDICATED FOR ASYMPTOMATIC CAROTID OCCLUSIVE DISEASE

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DISCLOSURES

I have no financial disclosures.

TO OPERATE OR NOT... THAT IS THE QUESTION

What is the modern benefit of performing carotid endarterectomy for patients with high-grade asymptomatic disease?
THE CRUX OF THE ISSUE

Data from ACAS, NASCET and the VA Study were collected nearly 25 years ago.

Things have changed...

- Statins
- Clopidogrel

Modern maximal medical therapy has reduced risk of stroke from asymptomatic carotid stenosis to rates equivalent to that obtained from CEA (Abbott et al 2009).

Lifetime risk of stroke in a 65-year-old male has decreased from 19.3% in the 1970s to 14.5% today.

THE REAL ISSUE

HISTORICAL PERSPECTIVE OF RCTS

<table>
<thead>
<tr>
<th>Year</th>
<th>VA Study</th>
<th>ACAS</th>
<th>ACST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Asymp &gt; 50% stenosis</td>
<td>Asymp &gt; 60% stenosis</td>
<td>Asymp (mainly) &gt; 60% stenosis</td>
</tr>
<tr>
<td>1995</td>
<td>Asymp &gt; 60% stenosis</td>
<td>Asymp &gt; 60% stenosis</td>
<td>Asymp &gt; 60% stenosis</td>
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<tr>
<td>2004</td>
<td>Asymp &gt; 60% stenosis</td>
<td>Asymp &gt; 60% stenosis</td>
<td>Asymp &gt; 60% stenosis</td>
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</tbody>
</table>

Comparison:

- CEA vs aspirin vs. medical treatment alone
- CEA vs aspirin vs. Aspirin and risk factor modification
- CEA vs medical tx (or until CEA necessary) vs aspirin and risk factor modification

Results:

- 5 year risk of ipsi stroke and perioperative stroke or death was 5.1% for CEA, 8.1% for medical tx
- 5 year risk of stroke or death was 6.4% for CEA, 11.8% for medical tx

The “winner”:

- CEA
- CEA
- CEA
IN A NEW ERA, WHAT IS THE BENEFIT?

What is the impact of modern maximal medical therapy?

Does this impact stroke risk reduction in ACAS?

What are the costs of medical treatment vs CAS/CEA?

MODERN MAXIMAL MEDICAL THERAPY

- Smoking cessation
- Anti-hypertensives
- Diabetes control
- Anti-platelets
- Statins

MAXIMAL MEDICAL THERAPY
MAXIMAL MEDICAL THERAPY

**Statins**
- 1987: lovastatin
  - Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin, Simvastatin, Pitavastatin
  - $29 billion in global sales in 2012

**Plavix**
- 1998: clopidogrel
  - $9 billion in global sales in 2010

IMPACT OF THESE DRUGS:

**STATIN**
- Cholesterol Treatment Trials' Collaboration
- Reducing LDL by 1 mmol/L decreases the incidence of major vascular events (non-fatal myocardial infarction, coronary death, any stroke, or coronary revascularization procedure) by ~1/5
- Further reductions in LDL cholesterol with more intensive statin regimens yielded further reductions in risk

**CLOPIDOGREL**
- CAPRIE Trial: reduction of cardiovascular events in patients with recent stroke, MI, or peripheral artery disease
- Expanded indications to include ACS, NSTEAMI, STEAMI, coronary stent

BUT...

**CAPRIE Trial**
- No difference in clopidogrel vs aspirin in > 6000 with recent ischemic stroke

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial
- Requires dual antiplatelet therapy in patients with a prior stroke, TIA, or other atherosclerotic disease or in patients with high risk for cardiovascular disease.
AND...

STATINS FOR STROKE PREVENTION: DISAPPOINTMENT AND HOPE

The number of strokes prevented per 1000 patients treated for 5 years in patients with CHD is 9 for statins, compared with 17.3 for antiplatelet agents.

Statins do not prevent recurrent stroke in patients with prior stroke.

Statins may increase the risk of hemorrhagic stroke.


META-ANALYSIS OF 9 MAJOR LONG-TERM STATIN TRIALS

70,070 patients with known CHD or considered at increased risk.

- 4.3% (1501 of 34,739 patients) risk of stroke in control group
- 3.4% (1215 of 35,331 patients) risk of stroke with statin therapy
- 21% relative risk reduction in stroke
- 0.9% absolute risk reduction
- 9 strokes prevented per 1000 patients treated for 5 years.

By comparison, meta analyses have shown that, in similar patients with known CHD:

- 17 strokes per 1000 patients prevented with Ramipril treatment for 5 years
- 17.3 strokes per 1000 patients prevented with antiplatelet agents
- 45 strokes prevented per 1000 patients treated for 5 years in patients with prior stroke.

HOW DOES MAXIMAL MEDICAL THERAPY INFLUENCE STROKE RISK IN ACAS?
MEDICAL (NONSURGICAL) INTERVENTION ALONE IS NOW BEST FOR PREVENTION OF STROKE ASSOCIATED WITH ASYMPHOMATIC SEVERE CAROTID STENOSIS: RESULTS OF A SYSTEMATIC REVIEW AND ANALYSIS

1. Investigate temporal changes in reported stroke rate among patients with ACAS receiving MMT alone
2. Compare above stroke rate rates with those of patients who received CEA in major randomized surgical trials
3. Compare stroke-prevention cost effectiveness of medical intervention alone with MMT plus CEA.

ABBOTT, STROKE 2009

Author notes that no systematic analysis of reported stroke rate associated with isolated medical management of ACAS has been performed.

One of the author's arguments is that the low peri-operative risk associated with CEA in these trials is not comparable to the risk in the community at large.

The flip side to this argument is that in order to benefit from the reduced stroke risk associated with MMT, patients must be compliant. In the community at large, is compliance equivalent to that of trial patients?

THE EFFECT OF MEDICAL TREATMENTS ON STROKE RISK IN ASYMPTOMATIC CAROTID STENOSIS

ACES data
477 patients with ACES
Followed Q6mos for 2 yrs

King et al. 2013
SVS VASCULAR REGISTRY REVIEW 2015

Normal Risk patients
- Age < 80
- Absence of clinically significant cardiac disease
- Absence of severe pulmonary disease
- Absence of contralateral carotid occlusion
- Absence of contralateral laryngeal nerve palsy
- No history of radical neck surgery or radiation to neck
- No recurrent stenosis
MODERN DATA

ACST-1 10 YEAR FOLLOW UP DATA (2010)

Stroke rates were lower in those on lipid-lowering therapy, the absolute difference in the stroke incidence rate produced by allocation to immediate CEA was not as great (0.7 vs 1.3% per year \( p < 0.0001 \) for those on lipid-lowering therapy, and 1.8 vs 3.3% per year \( p < 0.0001 \) for those not.

The event rates in patients on lipid-lowering therapy suggest somewhat lower perioperative risks and lower absolute benefits, but still with a significant reduction in net risk at year 10.

In patients with effective antihypertensive, antithrombotic, and lipid-lowering therapy and with little likelihood of death from other causes within 10 years, the absolute 10-year stroke reduction would be about 2%. If so, the number needed to treat to avoid one stroke would be about 20. Allowance for non-compliance might reduce this number to about 15.

MODERN DATA

Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis (AMTEC) Study Group

Russia has higher rate of stroke and death than Western countries.

55 patients with 70–79% asymptomatic carotid stenosis randomized 2009–2013

- 24 MMT and 31 CEA + MMT

MMT defined as:
- Aspirin
- Statin
- Anti-hypertensives
### AMTEC

<table>
<thead>
<tr>
<th>Condition</th>
<th>CRA (%)</th>
<th>WIN (%)</th>
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</thead>
<tbody>
<tr>
<td>Nonfatal stroke and death</td>
<td>6.5</td>
<td>37.5</td>
</tr>
<tr>
<td>Nonfatal stroke, carotid revascularization, and death</td>
<td>12.9</td>
<td>50</td>
</tr>
<tr>
<td>Major adverse cardiovascular event</td>
<td>12.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>3.2</td>
<td>20.8</td>
</tr>
<tr>
<td>Death</td>
<td>3.2</td>
<td>16.7</td>
</tr>
</tbody>
</table>

*Endpoints: nonfatal stroke, death, nonfatal myocardial infarction, and stroke.*

### CONRAD ET AL

900 carotid arteries in 794 patients

87.1% were on a statin throughout the study

Low-density lipoprotein cholesterol level was always normal (<100 mg/dL) in 37.8% and accordingly, 241 (30.3%) had OMT

The 5-year freedom from plaque progression was 61.3% vs 63.1% with no benefit from OMT vs the control group.

11.3% patients developed INS during follow-up (58% of these were strokes)

**Conclusions:** At the 5-year of follow-up, OMT failed to prevent carotid disease progression or development of ipsilateral symptoms in 45% of patients with ACAS.


### CONRAD ONE YEAR LATER

126 asymptomatic but severely stenotic (> 70%) carotid arteries

86% on statin

24.6% developed ipsilateral event during mean of 27 month follow-up

Statins not protective against ipsilateral events or death
ASYMPTOMATIC CAROTID STENOSIS: RISK OF PROGRESSION AND DEVELOPMENT OF SYMPTOMS

Retrospective review of 214 consecutive patients:
- 97% statins
- 95% antihypertensives
- 99% aspirin

68% progression of stenosis
21% develop ipsilateral symptoms in long term follow up
Mean of 6 years to development of symptoms

Risk factors for symptom development:
- Degree of stenosis at diagnosis
- Intracranial stenosis
- Plaque ulceration
- Silent infarction
- Prior history of TIA/stroke

Cerebrovasc Dis 2015;40:236–243

WHAT IS GOING ON?

DEFINITION OF SEVERE CAROTID STENOSIS

Abbott et al: > 50%
ACAS: > 60% by either angio or duplex
VA: >50% by angio

SVS guidelines ≥60%
Common practice ≥70%
SMOKING

Although the world-wide prevalence of tobacco use has decreased, the total number of smokers has increased due to population growth. Certain countries have rates of tobacco use >50% in men (Le Furuc).
WHAT ABOUT COST?

INDEX HOSPITALIZATION COSTS CAS VS CEA (CREST TRIAL)

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>Difference</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>$6782 ± 1412</td>
<td>$5743 ± 1370</td>
<td>$1039</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Post procedure</td>
<td>$6759 ± 4810</td>
<td>$7122 ± 6895</td>
<td>- $363</td>
<td>0.927</td>
</tr>
<tr>
<td>Physician fees</td>
<td>$1514 ± 646</td>
<td>$1951 ± 693</td>
<td>- $437</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total index hospitalization</td>
<td>$15,055 ± 5539</td>
<td>$14,816 ± 7709</td>
<td>$239</td>
<td>0.185</td>
</tr>
</tbody>
</table>

NUMBER NEEDED TO TREAT

- 9 strokes prevented per 1000 patients treated with statins for 5 years
  - NNT = 111
- ACST-1 data reported needed to treat 13-20 patients to prevent one stroke
  - NNT = 39
COST COMPARISON

Statins
Lipitor
$4000 / year x 5 years = 20,000 x 111 patients = $ 2,220,000 to prevent 1 stroke

CEA / CAS
$15,000 per procedure x 20 procedures = $ 300,000 prevent 1 stroke

CLOSING THOUGHTS

SPACE-2

Designed as three armed randomized trial to compare best medical therapy alone, best medical therapy plus CAS and best medical therapy plus CEA
Low recruitment has halted the study (Jan 2015)
Plans to analyse and report out available data later this year.
CREST-2
Randomized trial of patients with asymptomatic carotid stenosis ≥ 70%
Medical treatment alone versus medical treatment and endarterectomy
Medical treatment alone versus medical treatment and stenting
Recruiting 2480 patients in US and Canada

COGNITIVE EFFECTS OF CEA
Patients with asymptomatic severe carotid stenosis perform poorer on tests of cognitive function than controls.


REFERENCES
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