The Effectiveness of Medical Therapy for Severe Carotid Stenosis in Reducing Large-Vessel Embolic Stroke: Open Question or Question Answered?

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Conflicts of Interest

• Consultant
  – Abbott Vascular
  – Arsenal Medical
  – Atheromed
  – Baxter, Incorporated
  – Becker Venture Services Group
  – Harvard Clinical Research Institute
  – I.C.Sciences, Incorporated
  – Micell, Incorporated
  – Nexeon Medical Systems
  – Takeda Pharmaceuticals

• Equity
  – Access Closure, Inc
  – Hotspur, Inc
  – Icon Interventional, Inc
  – Sadra Medical
  – Square One, Inc
  – Vascular Therapies, Inc

• Board Member
  – VIVA Physicians (Not For Profit 501(c) 3 Organization)
    • www.vivapvd.com

September, 2009
Can Medical Therapy Prevent This???
The Differences in Opinion Regarding the Same Literature Has Boxed Us Into a Corner…
There Has Been a Great Deal of Excitement Around Carotid Revascularization Lately…

- Carotid Endarterectomy
- Carotid Stent with Embolic Protection
  - Proximal
  - Distal
## Annual Percentage Rate of Vascular Events

696 patients with asymptomatic carotid artery disease followed for a mean of 43 months

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>TIA</th>
<th>Stroke</th>
<th>Cardiac Event</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>1.0</td>
<td>1.3</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>50-75%</td>
<td>3.0</td>
<td>1.3</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>7.2</td>
<td>3.3</td>
<td>8.3</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Norris et al., Stroke, 1991
Asymptomatic Carotid Artery Study

- Multicenter trial of carotid endarterectomy in patients with asymptomatic carotid artery stenosis >60% in diameter
- 1662 patients randomized to CEA or no CEA
- Primary outcome: Ipsilateral stroke or perioperative death or stroke
- Median follow-up = 2.7 years

Executive Committee for ACAS. J.A.M.A., 1995
ACAS: Stroke and Death At 5 Years

Percent

0 2 4 6 8 10 12 14

Med  CE  Med  CE
Men  Women

A Teaching Affiliate of Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL VASCULAR CENTER
MRC Asymptomatic Carotid Surgery Trial (ACST)

- 3120 asymptomatic patients with 60-99% carotid stenosis
- 126 hospitals, 30 nations
- Excluded for poor surgical risk, a cardioembolic possibility
- Follow up was 5 years
- Enrolled from 4/93 to 7/2003
- Report is for first five years of trial

ACST Collaborative Group. Lancet 2004; 363: 1491
MRC Asymptomatic Carotid Surgery Trial (ACST): Results

Mean Follow Up 3.4 Years

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carotid Strokes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>13 (1)</td>
<td>62 (4)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>11 (1)</td>
<td>35 (2.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (&lt;1)</td>
<td>8 (&lt;1)</td>
</tr>
<tr>
<td><strong>Other Strokes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebrobasilar</td>
<td>8 (&lt;1)</td>
<td>8 (&lt;1)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>4 (&lt;1)</td>
<td>7 (&lt;1)</td>
</tr>
</tbody>
</table>

ACS T Collaborative Group. Lancet 2004; 363: 1491
The Real ACST Results

![Bar chart showing the comparison between CEA and Medical RX in terms of Deaths, Major CVA & Death, and Any CVA & Death.](chart)

**Primary Prevention of Ischemic Stroke: AHA/ASA 2006 Guidelines**
The Real ACST Results

Primary Prevention of Ischemic Stroke: AHA/ASA 2006 Guidelines
CEA vs. Med Rx for Stroke Prevention

Recommendation based on Asx RCT’s (Level I)

- CEA, on top of contemporary medical therapy, is beneficial in selected ("e.g. conventional risk") patients, ages 40-75 years, who are expected to live for ≥5 years, if:
  - Stenosis 60-99% and physician/hospital stroke/death rate ≤ 3%

-AHA/ASA Guideline; Stroke, Feb 06
# Mortality Rate ACST vs ArCHER

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACST (3.4 yr)</td>
<td>16.9 (Standard Risk)</td>
</tr>
<tr>
<td>ArCHER (3.0 yr)</td>
<td>19.1 (High Risk)</td>
</tr>
</tbody>
</table>
30-Day Outcomes from XACT and Capture 2 (N=6320)—All High Risk Patients

Symptomatic Patients <80

N=589

- Death/Stroke: 5.3%
- Death/Major Stroke: 2.2%
- Death: 1.0%
- Stroke Minor (3.1%)
- Stroke Major (1.4%)

6% AHA guideline
So, Despite the Confusing Data, It Looks Like CAS Is Effective in Stroke Prevention Compared to CEA
Medical Treatments That Did Not Exist During Revascularization Trials

• Modulators of Renin Angiotensin System
  – ACE inhibitors
    • Hope
  – Angiotensin Receptor Blockers
    • Life
• Statins
  • HPS
  • CARDS
ACE Inhibition Decreases Stroke in a High Risk Population

9297 patients with vascular disease or diabetes plus an additional risk factor randomized to ramipril or placebo f/u 4.5 yrs

1.5% Absolute Reduction
34% Relative Reduction

Bosch J. BMJ 2002; 324:699
Effect of ACE-Inhibitor Therapy vs. Placebo on Cardiovascular Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Events/Total Patients</th>
<th>ACE-I</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>166/6060 240/6064</td>
<td>0.70 (0.57-0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>539/6060 672/6064</td>
<td>0.80 (0.72-0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>154/6060 183/6064</td>
<td>0.84 (0.68-1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>307/6060 416/6064</td>
<td>0.74 (0.64-0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total death</td>
<td>533/6060 632/6064</td>
<td>0.84 (0.76-0.94)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blood Pressure Lowering Treatment Trialists’ Collaboration
*Lancet*, 2000; *355*: 1955-64; HOPE, PART2; QUIET, SCAT
ARBs Decrease Risk of Stroke in High Risk Patients

*LIFE: Fatal/Nonfatal Stroke*

**Adjusted Risk Reduction 24.9%, p=0.001**

Statins Decrease the Risk of Stroke in High Risk Patients: 

*Heart Protection Study*

ARR 1.4% p = .0001

A 50% reduction in CEA or angioplasty (ARR .4% P=0.0003).
SPARCL: High Dose Atorvastatin vs Placebo In Patients with Prior CVA/TIA

Stroke or TIA

• 1007 patients with carotid stenosis (not requiring revascularization) at baseline
  – 3271 patients had no carotid stenosis at baseline
• All patients had stroke/TIA within 6 months of randomization
  – Randomized to Atorvastatin 80 mg/d vs Placebo
    • No known CHD
    • LDL Cholesterol between 100-190 mg/dL
• Of those patients with carotid artery stenosis at baseline…
  – Atorvastatin lowered any stroke risk by 33%
  – Atorvastatin lowered any CHD event by 43%
  – Later carotid revascularization was reduced by 56%!
Stroke Prevention with Statin Therapy

Lancet Neurol 2009;8:453-63
Stroke Prevention with Statin Therapy

Estimates of relative risk reduction
- 10% LDL reduction: relative risk reduction 7.5% (2.3-12.5) overall
- 1 mmol/L (39 mg/dL) LDL reduction: relative risk reduction 13.5% (7.7-18.8) for primary prevention of stroke
- relative risk reduction 21.1% (6.3-33.5) overall
- relative risk reduction 35.9% (21.7-47.6) for primary prevention of stroke
Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis

Results of a Systematic Review and Analysis

Anne L. Abbott, PhD, MBBS, FRACP

Abstract—Significant advances in vascular disease medical intervention since large randomized trials for asymptomatic severe carotid stenosis were conducted (1983–2003) have prompted doubt over current expectations of a surgical benefit. In this systematic review and analysis of published data it was found that rates of ipsilateral and any-territory stroke (+/−TIA), with medical intervention alone, have fallen significantly since the mid-1980s, with recent estimates overlapping those of operated patients in randomized trials. However, current medical intervention alone was estimated at least 3 to 8 times more cost-effective. In conclusion, current vascular disease medical intervention alone is now best for stroke prevention associated with asymptomatic severe carotid stenosis given this new evidence, other cardiovascular benefits, and because high-risk patients who benefit from additional carotid surgery or angioplasty/stenting cannot be identified. (Stroke. 2009;40:00-00.)

Key Words: asymptomatic carotid stenosis ■ carotid endarterectomy ■ endovascular treatment ■ health policy ■ stroke prevention
associated with asymptomatic severe carotid stenosis. It is no longer appropriate to refer to vascular disease medical intervention as “conservative,” “control,” or “natural history” therapy, as has been done in the past.\textsuperscript{12,71,72,96,97} It is also inappropriate to reserve more effective sounding terminology, like “intervention,” “revascularization,” and “repair,” to surgery, angioplasty, or stenting.\textsuperscript{39,98–100} The appropriate referral path for patients identified with asymptomatic severe carotid stenosis is to an enthusiastic clinician expert in current best practice vascular disease medical intervention.
319 ACS patients between 2000 and 2004

10% had microemboli

<table>
<thead>
<tr>
<th>1-year Stroke Risk</th>
<th>No Emboli</th>
<th>Emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>15.6%</td>
<td></td>
</tr>
</tbody>
</table>

95% CI (1.01-1.36) (4.1-79)

p < 0.0001

Stroke risk over 2 years by Baseline Microemboli Status

Spence JD et al. Stroke 2005;36:2373-2378
Decline in Events in Asymptomatic Patients with More Intensive Medical Therapy

<table>
<thead>
<tr>
<th></th>
<th>No emboli</th>
<th>Micro-emboli</th>
<th>p</th>
<th>Before 2003</th>
<th>Since 2003</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke in year 1</td>
<td>1.2%</td>
<td>14.3%</td>
<td>&lt;0.0001</td>
<td>4%</td>
<td>0.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke in year 2</td>
<td>0.5%</td>
<td>0%</td>
<td>0.85</td>
<td>1</td>
<td>0%</td>
<td>0.19</td>
</tr>
<tr>
<td>MI in year 1</td>
<td>2.4%</td>
<td>8.6%</td>
<td>0.07</td>
<td>6.5%</td>
<td>0%</td>
<td>0.0001</td>
</tr>
<tr>
<td>MI in year 2</td>
<td>1.2%</td>
<td>5.7%</td>
<td>0.096</td>
<td>3.5%</td>
<td>0%</td>
<td>0.003</td>
</tr>
<tr>
<td>Death in year 1</td>
<td>2.9%</td>
<td>12.1%</td>
<td>0.027</td>
<td>5.1%</td>
<td>2%</td>
<td>0.12</td>
</tr>
<tr>
<td>Death in year 2</td>
<td>1.9%</td>
<td>6.1%</td>
<td>0.17</td>
<td>4%</td>
<td>0%</td>
<td>0.011</td>
</tr>
<tr>
<td>CEA year 1</td>
<td>1.4%</td>
<td>5.7%</td>
<td>0.12</td>
<td>2.5%</td>
<td>1.2%</td>
<td>0.23</td>
</tr>
<tr>
<td>CEA year 2</td>
<td>0.5%</td>
<td>8.6%</td>
<td>0.004</td>
<td>2.5%</td>
<td>0%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

CEA = carotid endarterectomy

Data from J. D. Spence, MD
“At least 95% of Asymptomatic Patients with Carotid Stenosis Should be Treated Medically Only”

• The treatment of choice for ACS should be intensive medical therapy

• Less than 5% of ACS patients can benefit from revascularization

• Only those with microemboli should be considered for endarterectomy or stenting

J. D. Spence, MD
So, Do We Know that Medical Therapy Is the Best Therapy to Prevent Stroke in Patients with Extracranial Carotid Stenosis?

• Despite what I have shown you….

• **We DO NOT KNOW!**
  
  – No one takes into account compliance
  
  – Treatment rates are always better in trial patients compared to non-trial patients
  
  – No large scale trial has been performed comparing best medical therapy alone vs best medical therapy and revascularization
<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>High-risk</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Standard-risk</td>
<td>Standard-risk</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Like It Or Not.....WE Need to Do This Trial.....
Or Someone Else Will Tell Us What To Do…

Expands research comparing the effectiveness of medical treatments to give patients and physicians better information on what works best.
Proposed Decision Memo for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting (CAG-00085R7)

Proposed Decision Memo

TO: Administrative File CAG-00085R7

FROM: Tamara Syrek Jensen, JD
Acting Director, Coverage and Analysis Group

We propose to make no changes in coverage of patient groups for percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with stenting (Medicare National Coverage Determination (NCD) Manual 20.7B4). We
Director, Division of Medical and Surgical Services

Sarah McClain, MHS
Lead Analyst, Division of Medical and Surgical Services

Joseph Chin, MD, MS
Medical Officer, Division of Medical and Surgical Services

SUBJECT: Proposed Coverage Decision Memorandum for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting (CAG-00085R7)

DATE: September 10, 2009
CDC Warning: ***DO NOT DO THIS!!!***