Carotid Artery Revascularization: Best Options for Specific Patients

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Conflicts of Interest

- **Consultant**
  - Abbott Vascular
  - Arsenal Medical
  - Atheromed
  - Bacchus Vascular
  - Baxter, Incorporated
  - Becker Venture Services Group
  - Harvard Clinical Research Institute
  - Hypermed, Incorporated
  - I.C. Sciences, Incorporated
  - Micelle, Incorporated
  - Nexeon Medical Systems
  - Takeda Pharmaceuticals

- **Equity**
  - Access Closure, Inc
  - Icon Interventional, Inc
  - Sadra Medical
  - Square One, Inc
  - Vascular Therapies, Inc

- **Research Support**
  - Abbott Vascular
  - Genzyme
  - Philips Medical Systems

- **Board Member**
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
    - [www.vivapvd.com](http://www.vivapvd.com)

April, 2009
The World Has NO Idea How to Treat Asymptomatic Carotid Artery Stenosis
The ACCULINK™ Carotid Stent System and the RX ACCULINK™ Carotid Stent System, used in conjunction with Guidant carotid embolic protection systems, is indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below.

1. Patients with neurological symptoms and ≥50% stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and ≥80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND

2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.
ACE Inhibition Prevents Recurrent Stroke
The Progress Trial

6105 subjects with previous stroke randomly assigned to perindopril (n=3051) or placebo (n=3054)

PROGRESS Collaborative Group. Lancet 2001:358; 1033
SPARCL: High Dose Atorvastatin vs Placebo In Patients with Prior CVA/TIA

![Graph showing the comparison of Stroke or TIA events between Atorvastatin and Placebo over time. The graph indicates a lower risk of stroke or TIA with Atorvastatin compared to Placebo, with a hazard ratio (HR) of 0.77 (95% CI, 0.67–0.88) and p < 0.001.]

No. at Risk
Atorvastatin: 2365, 2148, 2023, 1933, 1837, 871, 119
Placebo: 2366, 2132, 1998, 1871, 1780, 803, 126

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%!
Effect of Antiplatelet Therapy in Patients with TIA or Stroke

287 Studies: 135,000 Patients in Comparisons of Antiplatelet Rx vs Control
Aspirin & Dipyridamole Decreases Stroke after TIA

European Stroke Prevention Study

6602 pts with recent TIA or CVA followed for 2 years

-- Stroke (%) --

ASA  DYP  ASA-DYP  Placebo

J Neurol Sci 1996; 143(1-2):1
PROFESS: ASA/Dipyridamole vs Clopidogrel to Prevent Recurrent Stroke

A Primary Outcome

Recurrent Stroke

B Secondary Outcome

Composite of CVA/MI/Death

N Engl J Med 2008;359:1
Asymptomatic carotid stenosis: what to do
Jessica N. Redgrave and Peter M. Rothwell

Purpose of review
Patients with asymptomatic carotid stenosis are at increased vascular risk but optimal treatment is

Optimal medical treatment is the most important aspect of management of patients with asymptomatic carotid stenosis. On the basis of previous trials, endarterectomy is only of overall benefit in men, and this benefit may now be obviated by improved medical treatment. There is insufficient evidence to advocate the routine use of carotid angioplasty or stenting in patients with asymptomatic stenosis. Inaccuracy in the measurement of carotid stenosis are lacking.

Summary
Absolute benefit from endarterectomy for asymptomatic carotid stenosis is small, but can sometimes be justified in men. Further research is required to determine long-term benefit in women and to risk stratify patients, particularly in the light of advances in medical treatment.
Early vs Deferred Carotid Endarterectomy in Asymptomatic Patients with >70% ICA Stenosis

Any Stroke or Perioperative Death

Long-term results of 442 consecutive, standardized carotid endarterectomy procedures in standard-risk and high-risk patients

D. Preston Flanigan, MD, Meghan E. Flanigan, Andrew L. Dorne, Timothy R.S. Harvard, MD, Mahmood K. Razavi, MD, and Jeffrey L. Ballard, MD, Orange, Calif
Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004

James T. McPhee, MD, a Joshua S. Hill, MD, MS, b Rocco G. Ciocca, MD, b Louis M. Messina, MD, b and Mohammad H. Eslami, MD, b Worcester, Mass

Objective: Although carotid endarterectomy (CEA) is the gold standard for the treatment of carotid artery stenosis, the recent United States Food and Drug Administration approval of carotid artery stenting (CAS) may have led to its widespread use outside of clinical trials and registries. This study compared in-hospital postoperative stroke and mortality rates after CAS and CEA at the national level.

Methods: The Nationwide Inpatient Sample (NIS) was queried to identify all patient-discharges that occurred during the period of the study. The International Classification of Diseases, 9th Revision, Clinical Modification procedure codes for CEA (38.12), CAS (00.63), and insertion of noncoronary stents (39.50, 39.90) were used in conjunction with the diagnostic codes for carotid artery stenosis, with 433.11 and without 433.10 stroke. Primary outcome measures included in-hospital postoperative stroke and death rates. Multivariate logistic regressions were performed to evaluate independent predictors of postoperative stroke and mortality. Adjustment was made for age, sex, medical comorbidities, admission diagnosis, procedure type, year, and hospital type.

Results: During the calendar years 2003 and 2004, an estimated 259,800 carotid revascularization procedures were performed in the United States. CAS had a higher rate of in-hospital postoperative stroke (2.1% vs 0.88%, P < .0001) and higher postoperative mortality (1.3% vs 0.39%) than CEA. For asymptomatic patients (92%), the postoperative stroke rate was significantly higher for CAS than CEA (1.8% vs 0.86%, P < .0001), but the mortality rate was similar (0.44% vs 0.36%, P = .36). For symptomatic patients (8%), the rates for postoperative stroke (4.2% vs 1.1%, P < .0001) and mortality (7.5% vs 1.0%, P < .0001) were significantly higher after CAS. By multivariate regression, CAS was independently predictive of postoperative stroke (odds ratio [OR], 2.49; 95% confidence interval [CI], 1.91 to 3.25). CAS was also associated with in-hospital postoperative mortality for asymptomatic (OR, 2.37; 95% CI, 1.46 to 3.84) and symptomatic (OR, 2.64; 95% CI, 1.89 to 3.69) patients.

Conclusions: As determined from a large representative national sample including the years 2003 and 2004, the in-hospital stroke rate after CAS for asymptomatic patients was twofold higher than after CEA. For symptomatic patients, the respective in-hospital stroke and mortality rates were fourfold and sevenfold higher. These unexpected results indicate that further randomized controlled trials with homogenous symptomatic and asymptomatic patient groups should be performed. (J Vasc Surg 2007;46:1112-8.)
### National Inpatient Sample Data (N=259,080)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAS</th>
<th>CEA</th>
<th>p Value</th>
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<tbody>
<tr>
<td>In Hospital CVA</td>
<td>2.1%</td>
<td>0.88%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.3%</td>
<td>0.39%</td>
<td>NS</td>
</tr>
<tr>
<td>Asymp CVA</td>
<td>1.8%</td>
<td>0.86%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symp CVA</td>
<td>4.2%</td>
<td>1.1%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Endarterectomy vs stenting for carotid artery stenosis: A systematic review and meta-analysis

M. Hassan Murad, MD, MPH, a,b David N. Flynn, BS, b Mohamed B. Elamin, MBBS, b
Gordon H. Guyatt, MD, c Robert W. Hobson II, MD, d,† Patricia J. Erwin, MLS, b and
Victor M. Montori, MD, MSc, b,c Rochester, Minn; Hamilton, Ontario, Canada; and Newark, NJ
## Studies Included

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Trial name</th>
<th>Patients, No.</th>
<th>Use of stents (%)</th>
<th>Use of cerebral protective devices, %</th>
<th>Mean age of subjects, year</th>
<th>Symptoms</th>
<th>Operative risk</th>
<th>Follow-up, months</th>
<th>Degree of stenosis, %</th>
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<td>Kentucky</td>
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<td>68.2</td>
<td>No</td>
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<td>&gt;80</td>
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<td>Yadav (2004)15</td>
<td>SAPPHIRE</td>
<td>334</td>
<td>100</td>
<td>95.6</td>
<td>72.6</td>
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<td>High</td>
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<td>Mas (2006)15</td>
<td>EVA-3S</td>
<td>527</td>
<td>100</td>
<td>91.90</td>
<td>69.7</td>
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<td>Average</td>
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<td>SPACE</td>
<td>1200</td>
<td>100</td>
<td>NR (mixed)</td>
<td>67.9</td>
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<tr>
<td>Ling (2006)20</td>
<td>TESCAS-C</td>
<td>166</td>
<td>100</td>
<td>100</td>
<td>63</td>
<td>Mixed</td>
<td>NR</td>
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<td>100</td>
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# Death

<table>
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<tr>
<th>Study</th>
<th>RR</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>CAS</th>
<th>CEA</th>
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<td>Brooks, 2001</td>
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<td>0.01</td>
<td>7.70</td>
<td>0/53</td>
<td>1/51</td>
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<td>Yadav, 2004</td>
<td>0.50</td>
<td>0.09</td>
<td>2.69</td>
<td>2/167</td>
<td>4/167</td>
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<td>Ling, 2006</td>
<td>0.51</td>
<td>0.05</td>
<td>5.54</td>
<td>1/82</td>
<td>2/84</td>
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<td>The Space group, 2006</td>
<td>0.78</td>
<td>0.21</td>
<td>2.89</td>
<td>4/599</td>
<td>5/584</td>
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<td>Mas, 2006</td>
<td>0.66</td>
<td>0.11</td>
<td>3.91</td>
<td>2/265</td>
<td>3/262</td>
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<td>Fixed effect</td>
<td>0.61</td>
<td>0.27</td>
<td>1.37</td>
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<tr>
<td>Random effects</td>
<td>0.61</td>
<td>0.27</td>
<td>1.37</td>
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</tbody>
</table>

![Graph showing comparison of CAS and CEA death rates](chart.png)
Non-Fatal Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>CAS</th>
<th>CEA</th>
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<tr>
<td>Yadav, 2004</td>
<td>0.40</td>
<td>0.13</td>
<td>1.25</td>
<td>4 / 167</td>
<td>10 / 167</td>
</tr>
<tr>
<td>Ling, 2006</td>
<td>0.51</td>
<td>0.05</td>
<td>5.54</td>
<td>1 / 82</td>
<td>2 / 84</td>
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<tr>
<td>Mas, 2006</td>
<td>0.49</td>
<td>0.05</td>
<td>5.42</td>
<td>1 / 265</td>
<td>2 / 262</td>
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<tr>
<td>Fixed effect</td>
<td>0.43</td>
<td>0.17</td>
<td>1.11</td>
<td></td>
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<tr>
<td>Random effects</td>
<td>0.43</td>
<td>0.17</td>
<td>1.11</td>
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</table>

Favors CAS  Favors CEA
# Stroke

![Graph showing RR and 95% CI for Stroke/Total with data from different sources and comparisons between CAS and CEA.]  

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Stroke/Total</th>
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<tbody>
<tr>
<td>Yadav, 2004</td>
<td>0.83</td>
<td>0.37</td>
<td>1.88</td>
<td>10 / 167</td>
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<td>Ling, 2006</td>
<td>0.68</td>
<td>0.12</td>
<td>3.98</td>
<td>2 / 82</td>
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<tr>
<td>The Space group, 2006</td>
<td>1.22</td>
<td>0.80</td>
<td>1.86</td>
<td>45 / 599</td>
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<tr>
<td>Mas, 2006</td>
<td>3.25</td>
<td>1.42</td>
<td>7.44</td>
<td>72 / 265</td>
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<td>Hoffman, 2006</td>
<td>0.33</td>
<td>0.02</td>
<td>7.32</td>
<td>0 / 10</td>
</tr>
<tr>
<td>Fixed effect</td>
<td>1.29</td>
<td>0.93</td>
<td>1.80</td>
<td>1 / 10</td>
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<tr>
<td>Random effects</td>
<td>1.29</td>
<td>0.73</td>
<td>2.26</td>
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</table>

Favors CAS Favors CEA

---

Cumulative Outcomes: CEA vs CAS

- **Death**: Risk difference (95% CI) -0.40 (-1.02, 0.40)
- **Nonfatal MI**: Risk difference (95% CI) -0.70 (-1.90, 0.50)
- **Stroke**: Risk difference (95% CI) 1.00 (-1.00, 3.10)

Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients

Jay S. Yadav, M.D., Mark H. Wholey, M.D., Richard E. Kuntz, M.D., M.Sc., Pierre Fayad, M.D., Barry T. Katzen, M.D., Gregory J. Mishkel, M.D., Tanvir K. Bajwa, M.D., Patrick Whitlow, M.D., Neil E. Strickman, M.D., Michael R. Jaff, D.O., Jeffrey J. Popma, M.D., David B. Snead, Ph.D., Donald E. Cutlip, M.D., Brian G. Firth, M.D., Ph.D., and Kenneth Ouriel, M.D., for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators*
# SAPPHERE Data

<table>
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<tr>
<th>Event</th>
<th>Intention-to-Treat Analysis</th>
<th>Actual-Treatment Analysis</th>
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<tr>
<td></td>
<td>Stenting (N=167)</td>
<td>Endarterectomy (N=167)</td>
</tr>
<tr>
<td>Death</td>
<td>12 (7.4)</td>
<td>21 (13.5)</td>
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<tr>
<td>Stroke</td>
<td>10 (6.2)</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td>Major ipsilateral</td>
<td>1 (0.6)</td>
<td>5 (3.3)</td>
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<td>Major nonipsilateral</td>
<td>1 (0.6)</td>
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<td>Minor ipsilateral</td>
<td>6 (3.7)</td>
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<td>Minor nonipsilateral</td>
<td>3 (1.9)</td>
<td>4 (2.7)</td>
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<td>Myocardial infarction</td>
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<tr>
<td>Q-wave</td>
<td>0</td>
<td>2 (1.2)</td>
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<tr>
<td>Non-Q-wave</td>
<td>5 (3.0)</td>
<td>10 (6.2)</td>
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<td>Cranial-nerve palsy</td>
<td>0</td>
<td>8 (4.9)</td>
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<td>Target-vessel revascularization</td>
<td>1 (0.6)</td>
<td>6 (4.3)</td>
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<td>Conventional end point (stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 yr)</td>
<td>9 (5.5)</td>
<td>13 (8.4)</td>
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<tr>
<td>Primary end point (death, stroke, or myocardial infarction at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 yr)</td>
<td>20 (12.2)</td>
<td>32 (20.1)</td>
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SAPPHIRE 3-Year Outcomes

Freedom from MAE

No. at Risk

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<tr>
<th>Procedure</th>
<th>0</th>
<th>90</th>
<th>180</th>
<th>270</th>
<th>360</th>
<th>450</th>
<th>540</th>
<th>630</th>
<th>720</th>
<th>810</th>
<th>900</th>
<th>990</th>
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<tbody>
<tr>
<td>Stenting</td>
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<td>155</td>
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P = 0.27
SAPPHIRE 3-Year Outcomes

Freedom from Death

Freedom from Stroke

No. at Risk

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<th>180</th>
<th>270</th>
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<td>146</td>
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P = 0.80
SAPPHIRE 3-Year Outcomes

Freedom from TVR

Carotid Revascularization
Endarterectomy vs Stenting Trial

CREST
Carotid Revascularization
Endarterectomy vs. Stenting Trial

Grant Number: 2 R01 NS038384-07

Thomas G. Brott, MD, PI
Robert Hobson, II, MD, PI 1999-2007
Carotid stenting is not currently approved by the FDA for asymptomatic patients who are at standard risk for surgery.

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

Confidential: This information is confidential and is intended for distribution to ACT I Study Site participants ONLY. This document contains Abbott Laboratories and Abbott Vascular proprietary information and shall not be duplicated, disclosed to others, or used for purposes other than to carry out the intent for which this material is delivered.

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Asymptomatic Carotid stenosis, stenting versus endarterectomy Trial
30-Day Outcomes from XACT and Capture 2 (N=6320)—All High Risk Patients

Symptomatic Patients <80

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<thead>
<tr>
<th>(%) Subjects</th>
<th>Death/Stroke</th>
<th>Death/Major Stroke</th>
<th>Death</th>
<th>Stroke Minor (3.1%)</th>
<th>Stroke Major (1.4%)</th>
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<tbody>
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<td>5.3</td>
<td>2.2</td>
<td>1.0</td>
<td>3.1</td>
<td>1.4</td>
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</table>

6% AHA guideline

Circ Cardiovasc Intervent 2009;March 6
30-Day Outcomes from XACT and Capture 2 (N=6320)—All High Risk Patients

Asymptomatic Patients <80

- Death/Stroke: 2.9%
- Death/Major Stroke: 1.1%
- Death: 0.8%
- Stroke Minor (1.8%)
- Stroke Major (0.6%)

3% AHA guideline
So, Who Should Get What?

- Symptomatic patient with 70-99% stenosis who is at high risk for surgical events
  - CAS
So, Who Should Get What?

- Symptomatic patient with 70-99% stenosis who is at high risk for surgical events
- Asymptomatic patient with truly anatomic high risk scenario
  - CAS/CEA
So, Who Should Get What?

- Symptomatic patient with 70-99% stenosis who is at high risk for surgical events
- Asymptomatic patient with truly anatomic high risk scenario
- All others: Optimal Medical Therapy
So, Who Should Get What?

- Symptomatic patient with 70-99% stenosis who is at high risk for surgical events
- Asymptomatic patient with truly anatomic high risk scenario
- All others: Optimal Medical Therapy
- All others: Enroll in ACT I/FDA-IDE Approved Trial
We Still Don’t Know….

- The role of *modern* primary medical intervention in patients with carotid artery stenosis when compared head-to-head with
  - Carotid Endarterectomy
  - Carotid Artery Stent
But Remember, We Must Not Compare....