ALL THAT JAZZ

Controversies in Carotid Disease

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DISCLOSURE

Relevant to Carotid Artery Stenting

- Relationships with industry:
  - Research: CREST 2
  - Stock Ownership: None
  - Speakers Bureau: None
  - Consultant: None

“So, I’m the only one who sees a conflict of interest here?”
Controversies in Carotid Disease

1st.
Who gets carotid revasc to prevent stroke.

2nd.
Revascularization choices: CEA vs CAS.
Carotid Disease Natural History

Symptomatic
25%

Asymptomatic
75%
Stroke Prevention

- Carotid plaque most often causes symptoms due to **EMBOLIZATION**, rather than thrombosis.

- Extracranial carotid **OCCLUSION** is the source of ischemic stroke in fewer than 20%.

- Symptomatic patients have a much higher stroke rate than asymptomatic patients.

- Asymptomatic patients outnumber symptomatic patients by 4:1.
Figure 2. Average annual risk rates of stroke in patients with at least 50% asymptomatic carotid stenosis in OXVASC and in other published studies that reported data. The size of each bubble reflects the relative number of patients in the study. a, Risk of any and/or ipsilateral stroke, displayed by year of publication. b, Risk of any and/or ipsilateral stroke, displayed by recruitment period (horizontal bar; dashed line indicates estimated recruitment period). c, Risk of ipsilateral (to asymptomatic carotid stenosis) stroke displayed by recruitment period (horizontal bar; dashed line indicates estimated recruitment period).
All patients were given advice on lifestyle, particularly the need to stop smoking if relevant. Blood glucose was measured in all patients. Antihypertensive medication was initiated or increased in all patients whose blood pressure was 130/80 mm Hg. All patients were treated with a statin, most commonly simvastatin 40 mg daily, unless contraindicated. Antiplatelet agent(s), usually aspirin and/or clopidogrel, for the first 30 days and then usually aspirin and dipyridamole. Nonvascular death.

Vascular death.

Unstable angina.

Myocardial infarction.

Other territory TIA.

Other territory stroke.

Ipsilateral TIA.

Ipsilateral stroke.

Events | Average Annual Risk, % (95% CI)
--- | ---
Ipsilateral stroke | 0.34 (0.01–1.87)
Ipsilateral TIA | 1.78 (0.58–4.16)
Other territory stroke | 8.32 (5.08–12.85)
Other territory TIA | 5.15 (2.74–8.81)
Myocardial infarction | 4.70 (2.50–8.04)
Unstable angina | 1.03 (0.21–3.01)
Vascular death | 7.70 (5.79–12.98)
Nonvascular death | 2.01 (0.82–4.76)

★ Antiplatelet agent(s), usually aspirin and/or clopidogrel, for the first 30 days and then usually aspirin and dipyridamole.
★ All patients were treated with a statin, most commonly simvastatin 40 mg daily, unless contraindicated.
★ Antihypertensive medication was initiated or increased in all patients whose blood pressure was 130/80 mm Hg.
★ Blood glucose was measured in all patients.
★ All patients were given advice on lifestyle, particularly the need to stop smoking if relevant.
Asymptomatic Carotid Stenosis

- Risk of progression to occlusion is low.
  - **ACST**\(^1\): 1,469 MED Group:
    - 94 progressed to occlusion.
    - 12 with symptoms.
    - 1 with stroke.
  - **Yang et al**\(^2\): 3,681 MED for 20 yrs.
    - 80% occlusions before 2002.
    - Only 1 stroke with occlusion.

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Stroke Risk: Symptomatic

- NASCET (70% - 99%):
  - ★ (+) ulcer = 30% stroke.
  - ★ (–) ulcer = 17% stroke.

<table>
<thead>
<tr>
<th></th>
<th>1 yr risk of stroke</th>
<th>5 yr risk of stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>12%</td>
<td>30-35%</td>
</tr>
<tr>
<td>Stroke</td>
<td>5-9%</td>
<td>25-45%</td>
</tr>
</tbody>
</table>
Stroke Prevention

- Stabilize plaque (Statin therapy).
- BP control (ACE-Inhibitor).
- Antiplatelet therapy.
- No smoking.
- Exercise program.
High Risk of CEA ≠ CAS

Anatomic Criteria | Medical Comorbidity
--- | ---
High cervical or intrathoracic lesion | Age ≥80 yrs
Prior radical neck surgery or radiation | Class III/IV congestive heart failure
Contralateral carotid artery occlusion | Class III/IV angina pectoris
Prior ipsilateral CEA | Left main coronary disease
Contralateral laryngeal nerve palsy | Multivessel coronary artery disease
Tracheostoma | Urgent (<30-day) heart surgery
LV ejection fraction ≤30% | Recent (≤30-day) myocardial infarction
Severe lung disease | Severe renal disease

Comorbidities | Anatomic Features | Procedural Factors
--- | --- | ---
Age ≥80 yrs | Complex aortic arch | Operator inexperience
Symptomatic | Tortuosity | No emboli protection device
Decreased cerebral reserve | Calcification | Time delay from symptom onset
Hypercoagulable state | Intraluminal thrombus | Open cell stents
Severe renal disease | Echolucent plaque | Vascular access difficulty
Increased bleeding risk

White; J. Am. Coll. Cardiol. Intv. 2010;3;467-474
Rosuvastatin in the Prevention of Stroke Among Men and Women With Elevated Levels of C-Reactive Protein

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)

Brendan M. Everett, MD, MPH; Robert J. Glynn, ScD; Jean G. MacFadyen, BA; Paul M Ridker, MD, MPH

Background—Prior primary prevention trials of statin therapy that used cholesterol criteria for enrollment have not reported significant decreases in hard events among individuals with low levels of low-density lipoprotein cholesterol (<130 mg/dL) and high-sensitivity C-reactive protein.

Methods and Results—In Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), 17,802 apparently healthy adults were randomly assigned to rosuvastatin 20 mg daily or placebo and then followed up for the primary endpoint of nonfatal myocardial infarction, myocardial infarction death, stroke, or peripheral arterial revascularization. Compared with placebo (incidence rate, 0.34 per 100 person-years; 95% confidence interval, 0.28 to 0.40), rosuvastatin (incidence rate, 0.20 per 100 person-years; 95% confidence interval, 0.16 to 0.24; P=0.002) significantly reduced the composite endpoint at a median follow-up of 5.9 years (maximum, 7.4 years). The incidence of stroke was significantly lower with rosuvastatin treatment than with placebo (0.04 per 100 person-years; P=0.004). These reductions were observed for both men and women and were not modified by age, hypertension, or diabetes.

Conclusion—Rosuvastatin reduced the risk of hard cardiovascular events among adults with low levels of low-density lipoprotein cholesterol and high-sensitivity C-reactive protein.

Clinical Trial Registration—clinicaltrial.gov. Unique identifier: NCT00239681. (Circulation. 2010;121:143-150.)
## Risk of Stroke in Four Statin Primary Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>0.89 (0.53-1.51)</td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>0.82 (0.33-2.08)</td>
<td></td>
</tr>
<tr>
<td>MEGA</td>
<td>0.83 (0.57-1.21)</td>
<td></td>
</tr>
<tr>
<td>JUPITER</td>
<td>0.52 (0.34-0.79)</td>
<td></td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td><strong>0.75 (0.57-0.97)</strong></td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>
Asymptomatic Carotid Stenosis

- ACAS¹ and ACST² in the 1990’s:
  - **CEA vs. MED**
    - 5 yr relative risk reduction for ipsilateral stroke 50%.
    - 1 yr absolute risk reduction of 0.5% to 1.0%.
    - NNT 100-200 to prevent one stroke per year.
    - CEA did not reduce combined stroke and death.
    - CEA did not benefit women.
    - CEA did not benefit men ≥ 75 years.

- **CMS 2004-2006**
  - Asx CEA = 88%, Asx CAS = 87%.

ACT-1: ASX CAS vs. CEA

Freedom from death, stroke, and myocardial infarction within 30 days and from ipsilateral stroke within 365 days after the procedure in the intention-to-treat population.

Stenting N=1089
Endarterectomy N=364

P=0.69 (by Wilcoxon rank-sum test)
0 Censored

Event-free Survival (%)

0 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375

DOI: 10.1056/NEJMoa1515706
Composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 10 years after randomization.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>205/2502</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>39–64 yr</td>
<td>50/791</td>
<td></td>
<td></td>
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<td>65–74 yr</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≥75 yr</td>
<td>72/686</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Male</td>
<td>130/1630</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75/872</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>122/1321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>83/1181</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Severe</td>
<td>171/2152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>34/350</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAS vs CEA: Asymptomatic

Death, Stroke, or MI during peri-procedural period and Ipsilateral Stroke during 4 year follow up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>CAS Events</th>
<th>Total</th>
<th>Weight</th>
<th>CAS M-H, Random, 95% CI</th>
<th>CEA M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT I 2016</td>
<td>41</td>
<td>1089</td>
<td>12</td>
<td>364</td>
<td>22.9%</td>
<td>1.15 [0.60, 2.21]</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Brooks et al</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREST 2016</td>
<td>42</td>
<td>594</td>
<td>41</td>
<td>587</td>
<td>49.2%</td>
<td>1.01 [0.65, 1.58]</td>
<td></td>
</tr>
<tr>
<td>SAPPHIRE 2008</td>
<td>25</td>
<td>117</td>
<td>35</td>
<td>120</td>
<td>28.0%</td>
<td>0.66 [0.37, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1843</td>
<td>1113</td>
<td>108</td>
<td>88</td>
<td></td>
<td>0.92 [0.68, 1.26]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%

Test for overall effect: Z = 0.49 (P = 0.62)

ACT-1

Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis


CREST

Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis


SAPPHIRE

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

Jay J. Yeager, M.D., Mark H. Nielsen, M.D., Richard E. Kozic, M.D., Paul J. Fowles, M.D., Barry T. Zarets, M.D., Gregory J. Michalek, M.D., Donald R. Breya, M.D., Thomas W. M. Ascher, M.D., Mark E. S. Brown, M.D., Michael J. P. J. W. J. N. A. Brown, M.D., Brian R. Innes, M.D., Ph.D., and Kenneth Curti, M.D., for the Stent and Angioplasty with Protection in Patients at High Risk for Carotid-Artery Investi

John Ochsner Heart & Vascular Institute
• 67-year-old man with a carotid bruit and 80% RICA.
  - nonsmoker
  - hypertension
  - hyperlipidemia

NIH Funded CREST – 2

**Endpoint = all 30 day stroke & death plus 4 yr ipsilateral stroke.**

Inclusion Criteria

- Asymptomatic for ≥ 6 mos
- Stenosis ≥ 70%
- Eligible for CEA/CAS
SURGERY: Stroke Prevention

- Symptomatic ≥ 70% stenosis.
  - ★ Marked benefit. NNT = 6 at 2 yrs

- Symptomatic 50 - 69%.
  - ★ Heterogenous benefit. NNT = 22
    - ✦ Males NNT = 12
    - ✦ Females NNT = 67

- Symptomatic < 50%.
  - ★ No revascularization benefit.
International Carotid Stenting Study (ICSS):

Symptomatic Pts: 1° Endpoint: Fatal or Disabling Stroke

Cumulative incidence (%)

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.9%</td>
<td>3.2%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
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HR 1.06 (95% CI 0.72–1.57), p=0.77

at risk

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<th>Time (years)</th>
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<th>CEA</th>
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<tbody>
<tr>
<td>0</td>
<td>853</td>
<td>857</td>
</tr>
<tr>
<td>1</td>
<td>777</td>
<td>789</td>
</tr>
<tr>
<td>2</td>
<td>733</td>
<td>750</td>
</tr>
<tr>
<td>3</td>
<td>651</td>
<td>661</td>
</tr>
<tr>
<td>4</td>
<td>498</td>
<td>482</td>
</tr>
<tr>
<td>5</td>
<td>328</td>
<td>310</td>
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<tr>
<td>6</td>
<td>163</td>
<td>140</td>
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<td>7</td>
<td>85</td>
<td>79</td>
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CREST: CAS = CEA

30 Day Stroke, Death, MI and 4 Yrs Ipsilateral Stroke

2500 PATIENTS RANDOMIZED
Level I Evidence for Equipoise
CAS = CEA for Average Surgical Risk

Composite of stroke, myocardial infarction, or death from any cause during the peri-procedural period or ipsilateral stroke within 10 years after randomization.

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</table>
For patients who are reasonable candidates for either procedure, with an equally skilled treatment team, the outcomes are not different.
Stroke Prevention

SYMPTOMATIC > 50%

- Revascularize symptomatic > 50% carotid.
- Best medical therapy.
- Equipoise for CAS vs. CEA.
  - Expertise for CAS and CEA important.
  - Patient suitable for either procedure.
**Stroke Prevention**

**ASYMPTOMATIC > 70%**

- Randomize to CREST - 2.
- Best medical therapy.
- Equipoise for CAS vs. CEA.
  - Expertise for CAS and CEA important.
  - Patient suitable for either procedure.

### RISK FACTOR
- Blood Pressure
- Atrial Fibrillation
- Smoking
- Cholesterol
- Diabetes
- Exercise
- Diet
- Stroke in Family
Thank You