Asymptomatic Carotid Stenosis – Treatment Options

Scott R. Geraghty, M.D.
Interventional Neuroradiology/ Endovascular Neurosurgery
Advocate Neurovascular Center
DISCLOSURES

- I have no commercial biases
- However, I am biased…
- I LOVE MY JOB
- I think I have the coolest job on the planet!
15 Coolest Jobs on the Planet
www.krantcents.com/15-coolest-jobs-on-the-planet
What are the 15 coolest jobs on the planet? Recently, I read an article called 'Jon Favreau has the world's best job'. Jon Favreau is President Obama's guy, ...

Another 15 Coolest Jobs on the Planet
Here are another 15 coolest jobs on the planet? Since it is Labor Day, I am continuing my series on the coolest jobs on the planet. As a reminder, I wrote a very ...

Cool Jobs is about the coolest jobs on the planet
www.cool-jobs.org/
Coolest Jobs in the USA, UK, Canada and all over the world.

The Coolest Job on the Planet | MarketingProfs Daily Fix Blog
www.mpdailyfix.com/the-coolest-job-on-the-planet/
Jul 16, 2007 – I started a new job last week at HP as Vice President, Marketing for its Digital Photography and Entertainment businesses. Think digital ...

Coolest working holiday jobs - travel tips and articles - Lonely Planet
www.lonelyplanet.com/usa/travel-tips-and-articles/76044
Oct 1, 2010 – Read Coolest working holiday jobs for travel tips, advice, news and articles from all around the world by Lonely Planet.

Ben Bailey has the coolest job on the planet!!! | Facebook
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cooljobs.com: the coolest jobs in entertainment, travel, sports, and...
www.cooljobs.com/
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The coolest job on the planet?
planetearth.merc.ac.uk/features/story.aspx?id=1003
The coolest job on the planet? 5 August 2011. When people ask Jonathan James what he does, he says 'I'm the researcher'. &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;
15 Coolest Jobs on the Planet
by KRANTCENTS - 34 COMMENTS

What are the 15 coolest jobs on the planet?
Recently, I read an article called "Jon Favreau has the world's best job". Jon Favreau is President Obama's guy, a low profile speech writer, unofficial mascot of the Obama phenomenon and mind reader. Politics aside, presidential speech writers are considered one of the coolest jobs! Scouring the planet or at least the internet, I tried to identify the 15 coolest jobs on the planet!

Before I started accumulating the coolest jobs, I thought a Playboy photographer, boat salesman or writer were some of the coolest jobs. Playboy photographer seemed cool for the obvious reasons. Taking pictures to make beautiful women even more beautiful just doesn't seem like work. Boat salesman was cool because you are selling a leisure activity and typically you take the customer out on the boat for a cool spin just seems like too much fun! Writer is cool because you are paid to do something you love anywhere in the world. Recently, I wrote called "I Want a Job" which describes a new way of networking. You will have to extend your network to find these jobs. Forget Facebook or Twitter, here are the coolest jobs on the planet!

Whiskey Maker – Yes, there is such a job! People following their passion only need apply. The title is Master Distiller who is responsible for the final product and how much to produce. He is responsible to determine how much they will sell 10-20 years from now.

Brew Master – Whether you work for the large breweries or a micro pub, this can be a cool job. You get to brew your own beer for you and your friends, who do product research. How cool is that!
Meta-analysis: Krant et. al

Top 15 Jobs on Planet Earth

- Whiskey Maker
- Brewmaster
- Pyrotechnician
- Videogame Tester
- Fake Executive
- Director of Golf
- Waterslide Tester
- Chocolate Taster
- TV Corpse
- Luxury bed tester
- Travel Blogger
- Cyclist in Paris
- Caretaker of Paradise Island
- Racecar Engineer
- Astronaut
Objectives

- Brief overview of asymptomatic carotid stenosis
- Treatment options
  - Carotid Endarterectomy (CEA)
  - Carotid Stenting (CAS)
- Current guidelines for treatment vs. medical management
- Future areas of study and ongoing trials
Epidemiology

- The estimated risk of ipsilateral stroke in patients with asymptomatic carotid atherosclerosis (stenosis ≥50 percent) is approximately 0.5 to 1.0 percent annually.

- Asymptomatic carotid atherosclerosis is also a marker of increased risk for myocardial infarction and vascular death
In studies largely performed before the advent of modern intensive medical therapy the rate of unheralded stroke ipsilateral to an asymptomatic but hemodynamically significant extracranial carotid artery stenosis was about 1 to 2 percent annually, a rate that represented a large incidence on a population basis.
Treatment Options

- Carotid Endarterectomy (CEA)
- Carotid Stenting (CAS)
Carotid Endarterectomy
Selected CEA Exclusions
Generally needs a good history & physical

- Radical neck dissection
- Surgically inaccessible lesions
- Adverse neck anatomy that limits surgical exposure
- Presence of tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel
The efficacy of CEA for patients with asymptomatic high-grade carotid stenosis was evaluated in three high-quality randomized controlled trials.

- Veterans Affairs Cooperative Study Group (VA trial)
- Asymptomatic Carotid Atherosclerosis Study (ACAS)
- Asymptomatic Carotid Surgery Trial (ACST)
A meta-analysis of these trials found that CEA for asymptomatic carotid stenosis is associated with a small absolute risk reduction (ARR) for the outcome of any stroke

- In the VA trial, the ARR was 1.0 percent over a mean follow-up of 4 years
- In ACAS, the ARR was 3.0 percent over 2.7 years
- In ACST, the ARR was 3.1 percent over 3.4 years

NNT was approximately 33
The major asymptomatic CEA trials (ACAS and ACST) found no correlation between degree of stenosis and risk of stroke for patients with asymptomatic 60 to 99 percent stenosis.

The benefit of CEA may be greater for men than for women with asymptomatic carotid disease.

Unclear if women benefit at all.
- Delay to benefit
  - The ACAS and especially the ACST trials showed that the net benefit of CEA is delayed, as the asymptomatic population has an overall worse outcome after CEA for many months to nearly two years because of perioperative morbidity.
  - Significant benefit does not accrue until approximately two years or more after surgery.
Carotid Artery Stenting
Selected CAS Exclusions
Generally needs a good CTA or MRA

- Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries
- Type III, calcified aortic arch anatomy
- Angulation or tortuosity (≥90°) of the innominate, common or internal carotid artery
- No randomized trials comparing carotid stenting with medical therapy alone
  - SAPPHIRE
  - CREST
Carotid Stenting: SAPPHIRE Trial

- Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
- Randomized 307 patients to CEA or CAS using the Cordis Precise nitinol stent and the Angioguard XP distal protection device
Tested the hypothesis that CAS is not inferior to CEA in patients considered high risk for surgery
- Symptomatic patients with >50% stenosis
- Asymptomatic patients with >80% stenosis
- More than 70% of patients enrolled had asymptomatic stenosis
What was considered “high surgical risk” for the SAPPHIRE Trial

- Asymptomatic stenosis >80% or symptomatic stenosis >50%
- Age >80 years
- Congestive heart failure (Class III/IV) and/or EF <30%
- Open heart surgery needed within 6 weeks
- Recent myocardial infarction (>24 hours and <4 weeks)
- Unstable angina (CCS Class III/IV)
- Severe chronic obstructive pulmonary disease
- Contralateral carotid occlusion
- Contralateral laryngeal nerve palsy
- Severe tandem lesions
- Lesions distal or proximal to the usual location
- Previous endarterectomy with restenosis
- Previous radiation therapy or radical neck surgery
## SAPPHIRE Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>CAS</th>
<th>CEA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/death at 30d plus ipsilateral stroke or neurologic death to 1 yr</td>
<td>5.5%</td>
<td>8.4%</td>
<td>0.36</td>
</tr>
<tr>
<td>Stroke/death/MI at 30d plus ipsilateral stroke or neurologic death to 1 yr</td>
<td>12.2%</td>
<td>20.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>Asymptomatic Patients Stroke/death/MI at 30d</td>
<td>5.4%</td>
<td>10.2%</td>
<td>0.20</td>
</tr>
<tr>
<td>Symptomatic Patients Stroke/death/MI at 30d</td>
<td>2.1%</td>
<td>9.3%</td>
<td>0.18</td>
</tr>
<tr>
<td>All Patients Stroke/death/MI at 30d</td>
<td>4.4%</td>
<td>9.9%</td>
<td>0.06</td>
</tr>
</tbody>
</table>
• Conclusion that CAS is not inferior to CEA
• However, FDA only approved the devices for high-risk patients with symptomatic stenosis.
  • Likely due to the fact that outcomes for patients in both treatment groups was poor and periprocedural complication rates were higher than the 3% recommended rate.
CREST Trial

- Prospective, multicenter, randomized, controlled trial with blinded endpoint adjudication
- Comparing CEA and CAS in participants with symptomatic and asymptomatic stenosis
- 108 US and 9 Canadian sites
- Team included neurologist, interventionalist, surgeon, and research coordinator at each center
Primary Endpoint

- Peri-procedural
  A composite of
  - Any clinical stroke
  - Myocardial infarction
  - Death

- Post-procedural
  - Ipsilateral stroke up to 4 years
Secondary Aims

- Differential efficacy by symptomatic status, sex, and age
- Differential restenosis
- Quality of Life and cost effectiveness
Major Eligibility Criteria: Symptomatic

Conventional-risk (not low risk) patients with symptomatic carotid stenosis:

- $\geq 50\%$ by angiography
- $\geq 70\%$ by ultrasound, or
- $> 70\%$ by CTA/MRA if ultrasound is 50-69\%
Major Eligibility Criteria: Asymptomatic

Asymptomatic carotid stenosis

- ≥60% by angiography
- ≥70% by ultrasound, or
- >80% by CTA/MRA if ultrasound is 50-69%
CREST Cumulative Randomizations
2000 through July 2008
Primary Endpoint $\leq$ 4 years

- Any stroke, MI, or death within peri-procedural period plus ipsilateral stroke thereafter

CEA vs. CAS

<table>
<thead>
<tr>
<th>Hazard Ratio, 95% CI</th>
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<tbody>
<tr>
<td>6.8 vs. 7.28%</td>
</tr>
<tr>
<td>HR = 0.90; 95% CI: 0.66-1.23</td>
</tr>
</tbody>
</table>
Primary Endpoint

ITT analysis

% Event Free

Follow-up Time (years)

Assignment  
CAS  
CEA
Interaction with Primary Endpoint

- No effect detected for symptomatic status or sex
- Interaction suggested for age
Primary Outcome - 4 Years

$P_{interaction} = 0.020$

Hazard Ratio vs Age (Years)

CEA Superior

CAS Superior
Primary Endpoint: Peri-procedural Components

- Any death, stroke, or MI within peri-procedural period

CEA vs. CAS

<table>
<thead>
<tr>
<th>Hazard Ratio, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>HR = 0.85; 95% CI: 0.60-1.22</td>
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</tbody>
</table>

4.5 vs. 5.2%
<table>
<thead>
<tr>
<th></th>
<th>CAS vs. CEA</th>
<th>Hazard Ratio 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>4.1 vs. 2.3%</td>
<td>HR = 1.79; 95% CI: 1.14-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>1.1 vs. 2.3%</td>
<td>HR = 0.50; 95% CI: 0.26-0.94</td>
<td>0.03</td>
</tr>
<tr>
<td>CAS vs. CEA</td>
<td>Hazard Ratio, 95% CI</td>
<td>P-Value</td>
<td></td>
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<tr>
<td>0.3 vs. 4.7%</td>
<td>HR = 0.07; 95% CI: 0.02-0.18</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CAS vs. CEA</td>
<td>Hazard Ratio, 95% CI</td>
<td>P-Value</td>
<td></td>
</tr>
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<td>-------------</td>
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</tr>
<tr>
<td>2.0 vs. 2.4%</td>
<td>HR = 0.94; 95% CI: 0.50-1.76</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- CEA and CAS have similar net outcomes though the individual risks vary
  - lower periprocedural stroke with CEA
  - lower periprocedural MI with CAS

- Younger patients may have improved safety with CAS and older patients have improved safety with CEA
Conclusions

- At experienced centers both CEA and CAS appear to have low perioperative complications and excellent longer-term results.

- For the future, both CEA and CAS appear to be useful tools for preventing stroke.
Current recommendations

- It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%) (Class IIa; Level of Evidence A).

Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (Class IIb; Level of Evidence B).
It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention. (Class IIa; Level of Evidence B).

It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery (Class IIa; Level of Evidence B).
In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established (Class IIb; Level of Evidence B).
Future areas of study

- Progression in the severity of asymptomatic carotid stenosis
- Asymptomatic carotid embolism
- High-risk morphologic features of the carotid plaque
- Reduced cerebral blood flow reserve
- Ipsilateral silent embolic infarcts on neuroimaging
Carotid Revascularization for Primary Prevention of Stroke Trial (CREST-2)

- Two parallel multi-center randomized, observer blinded endpoint trials

- NINDS funded clinical trial (U01 NS080168)

- Notice of award received March 11\textsuperscript{th}, 2014

- Expected completion 2020
Primary Aims

- In patients with ≥70% asymptomatic stenosis, to assess:
  - The treatment differences between medical management and CEA
  - The treatment differences between medical management and CAS
Secondary Aims

- Differences in cognitive function, intensive medical management compared to CEA and to CAS at 4 years of follow-up.
- Differences in major stroke events at 4-years
- Are differences in primary outcomes affected by patient age, sex, severity of carotid stenosis, risk factor level, and duration of asymptomatic period.
Medical Management

- Patients in both trials will take aspirin 325 mg/day for the entire follow-up period (CAS patients will also take clopidogrel per protocol).
- Primary risk factors: systolic blood pressure and LDL
  - Managed by the study neurologist
  - Target systolic blood pressure <140 mmHg
  - Target LDL <70 mg/dl.
Secondary risk factor targets:
- Non-HDL cholesterol <100 mg/dl.
- Hemoglobin A1c <7.0%.
- Smoking cessation.
- Targeted weight management.
- >30 minutes of moderate exercise 3 times a week.
INTERxVent

- Lifestyle management and cardiovascular disease risk reduction program.
- Incorporates SAMMPRIS targets and national guidelines.
- Provides individualized risk factor counseling telephone sessions at regular intervals:
  - twice a month for 12 weeks.
  - monthly thereafter.
- Case Managers at INTERxVent call center, Savannah, GA.
Based on data from CREST:

- For ages 50-74, no favored procedure
- For ages <50 years, CAS is the favored procedure
- For ages >74 years, CEA is the favored procedure
- BUT, in CREST asymptomatic patients had few events, so there were wide confidence interval
- So choice of CEA or CAS cannot, and is not, mandated in CREST-2
- Individual patient characteristics and preferences may supersede guidelines based upon patient age