How Do You Choose Between Medicine, CEA, and CAS for Carotid Artery Stenosis?

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For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

- **Honoraria received from:** Bard Peripheral Vascular, Bayer, Bayer-Schering, Bristol-Meyers Squibb, CardioMEMS, Contego Medical, Cook Medical, Cordis Corp., Gore & Associates, ICON Interventional Systems, sanofi-aventis, WL Gore

- **Consulted for:** Contego Medical

- **Held common stock in:** CardioMEMS, Contego Medical, ICON Interventional Systems, HealthSpot


I will be discussing products that are investigational or not labeled for use under discussion.
Background

- Carotid atherosclerosis accounts for 7 - 10% of ischemic stroke cases.
- Multifaceted medical therapy reduces the risk of stroke in patients with carotid stenosis.
- Revascularization with CEA or CAS can benefit select patients.
How do you Choose?

The Answer to the Question.....

• The answer to the question is in flux.....
• BUT, we know you have to consider:
  – The Patient (Symptoms?/The whole body/Functional status)
  – The Anatomy (The artery/The aorta)
  – Their Current Medical Regimen (Room to improve?)
  – The Local Expertise (Be honest)
  – The Patient’s Preference (After a fair and balanced discussion)

• The declining rate of stroke with improved medical therapy has led to the launch of new clinical trials to determine the contemporary risk/benefit ratio of revascularization relative to aggressive medical therapy.
Historical Perspective
1990’s
Predictors of > 70% Carotid Stenosis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yrs)</td>
<td>2.2 (1.7-2.8)</td>
</tr>
<tr>
<td>Male</td>
<td>2.5 (1.7-3.6)</td>
</tr>
<tr>
<td>History of vascular disease</td>
<td>2.5 (1.7-3.5)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mm Hg)</td>
<td>1.3 (1.2-1.5)</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio (per point)</td>
<td>1.2 (1.1-1.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.6 (1.0-2.5)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3.0 (2.1-4.4)</td>
</tr>
</tbody>
</table>

*Data are from de Weerd et al. (5). HDL = high-density lipoprotein
Prevalence and Predictors of Carotid Stenosis and Stroke

- In the Framingham Heart Study, the degree of carotid stenosis was predicted by common baseline vascular risk factors such as older age, tobacco use, SBP, and T Cholesterol.

- Patients with ASYMPTOMATIC ICA stenosis of 60-99% stenosis have an annual risk of stroke, based on 1990s med therapy of 2 – 2.5% per year.

- Patients with SYMPTOMATIC ICA stenosis over 70% carries an annual stroke risk of 10 – 15% based on 1990s med therapy.

Neurology 1994;44:1046-50
JAMA 1995;273:1421-8
Lancet 2010;376:1074-84
NEJM 1998;339:1415-25
ASYMPTOMATIC PATIENTS: Event rate average 2.3%/year with medical treatment *when risk factor control was far less aggressive than today’s practice.*
Improved Medical Therapy may Change Everything.....

• PERSPECTIVE

• The landmark carotid stenosis trials that established the value of CEA were initiated over 25 years ago before the widespread use of statins.

• Blood pressure control, management of lifestyle, and other vascular risk factors was suboptimal in older studies.

• In NASCET, the mean SBP 2 years into the study was 147 mmHg!!!

JAMA 1995;273:1421-8
NEJM 1998;339:1415-25
Stroke 2013;44:2957-8
Stroke Rates Are Reducing Over Time

Marquardt, L. Stroke. 2010;41:e11-e17.
Current Evidence for the Treatment of Carotid Stenosis

Medical Therapy
Current Evidence for the Treatment of Carotid Stenosis

• Contemporary recommendations for patients with symptomatic or asymptomatic ICA stenosis include medical therapy for all patients and revascularization (CEA or CAS) for select patients.
Current Evidence for the Treatment of Carotid Stenosis

• The core elements of medical therapy
  – Antiplatelet therapy
  – Aggressive treatment of dyslipidemia
  – Treatment of HTN to national guideline targets
  – Treatment of diabetes to national guideline targets
  – Smoking cessation
  – Lifestyle modification (diet and exercise)
Current Evidence for the Treatment of Carotid Stenosis

• For antiplatelet therapy, ASA is typically used (81 – 325 mg/day) for asymptomatic patients, although there is no level A evidence that ASA reduces stroke in the setting of asymptomatic carotid stenosis.

• There are no data comparing alternative antiplatelet regimens (clopidogrel or aggrenox) to aspirin for patients with asymptomatic carotid stenosis.

• For symptomatic patients, either ASA, clopidogrel, or aggrenox are recommended.

Stroke 2014;45:2160-236
Current Evidence for the Treatment of Carotid Stenosis

- Ongoing trials are evaluating the 90 day use of clopidogrel plus ASA compared with ASA alone for patients with TIA and minor stroke (POINT)
- As well as ticagrelor compared with ASA (SOCRATES)
- Currently, long term treatment with ASA and clopidogrel is not recommended in stroke prevention guidelines.

Stroke 2014;45:2160-236
Statins Decrease the Risk of Stroke in High Risk Patients: *Heart Protection Study*

**ARR 1.4% p = 0.0001**

A 50% reduction in CEA or angioplasty ARR 0.4% P=0·0003.
Current Evidence for the Treatment of Carotid Stenosis

• The role of lipid lowering with statins in patients with carotid stenosis has been well established.

• In the SPARCL trial, atorvastatin 80 mg/day was compared with placebo in patients with a prior stroke or TIA. (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)
  – Atorvastatin: LDL 132 to 70 mg/dl
  – Placebo: LDL 133 to 130 mg/dl
  – Atorvastatin: stroke reduction 33%, coronary event reduction 43%, carotid revascularization later down 56%

Circulation 2006;113:2021-30
Current Evidence for the Treatment of Carotid Stenosis

• ACST Trial (Asymptomatic Carotid Surgery Trial)
  – No lipid therapy 10 year stroke risk 24.9%
  – Lipid Therapy 10 year stroke risk risk 14.5%

• Treatment with high potency statins is an important element of the management of patients with carotid stenosis.

Lancet 2010;376:1074-84
Current Evidence for the Treatment of Carotid Stenosis

Revascularization
Current Evidence for the Treatment of Carotid Stenosis

• As pertains to carotid revascularization, current recommendations were revised on the basis of data from CREST

• 2,502 patients with either symptomatic or asymptomatic carotid stenosis assigned to either CEA or CAS.

• Inclusion
  – >70% duplex or >50% angiogram for symptomatic
  – >60% for asymptomatic

NEJM 2010;363:11-23
Current Evidence for the Treatment of Carotid Stenosis

• CREST
  – Primary endpoint: stroke/death/MI within 30 days plus ipsilateral stroke beyond 30 days
  – No difference between CEA and CAS (6.8 vs 7.2 % at 4 years)
  – CEA had sig lower risk of periprocedural stroke (2.3 vs 4.1%)
  – CAS had sig lower risk of periprocedural MI (1.1 vs 2.3%)

NEJM 2010;363:11-23
Current Evidence for the Treatment of Carotid Stenosis

• CREST
  – There was no significant variation in treatment results for men compared with women.
  – There was no significant variation in treatment results for symptomatic compared with asymptomatic status.
  – There was no difference in the risk of major stroke during the 4 year study period (8% CEA vs 11% CAS).

NEJM 2010;363:11-23
Current Evidence for the Treatment of Carotid Stenosis

• Revascularization and age
  – CREST: age > 70 fared better with CEA, < 70 fared better with CAS
  – European Data meta analysis
    • CEA: age < 70: 5.7% event rate, > 70: 5.9% event rate
    • CAS: age < 70: 5.8% event rate, > 70: 12% event rate
  – EVA-3S
    • Age was the main modifier of treatment effect

NEJM 2010;363:11-23
Lancet 2010;376:1062-73
NEJM 2006;355:1660-71
Considerations for Selection of Revascularization Method

• CEA

• Symptomatic patients have a higher stroke risk than asymptomatic patients

• MI is the most serious systemic complication
  – CREST: periprocedural MI 2.3%
  – CREST: mortality was higher over 4 years for MI pts
  – CREST: Previous CABG was major predictor of MI

• Local complications of CEA include cranial nerve palsies, wound hematomas, and infection of operative site.
  – CREST: Cranial nerve palsy: 4.7% CEA, 0.3% CAS

References:
NEJM 2010;363:11-23
Stroke 2003;34:2290-301
Circulation 2011;123:2571-8
Considerations for Selection of Revascularization Method

- **CAS**
- In addition to the hazards of advanced age, the complication rate with CAS may be greater with:
  - Unfavorable aortic arch
  - Carotid bifurcation anatomic features
- 1/5 of CAS related strokes are not in the territory of the treated vessel supporting the theory of embolization from the aorta.

Circulation 2006;113:2021-30
Circ CV Intv 2009;2:159-66
Stroke 2014;45:146-51
Considerations for Selection of Revascularization Method

- CAS

- At the ICA bifurcation, angulation of the ICA, heavy calcification, and long lesion length have been associated with increased periprocedural stroke.

- Bradycardia or hypotension can be prolonged and lead to ICU admission and increased periprocedural morbidity.

Circ CV Intv 2009;2:159-66
Stroke 2014;45:146-51
Why Didn’t CREST End the Debate? 
Your perspective…. 

Surgeons:
• Carotid revascularization is performed for stroke prevention.
• CEA reduced stroke risk more than CAS
• Excess MI rate with CEA less of an issue

Interventionists:
• Interventionists feel that CAS performed as safely as CEA
• Excess stroke risk was minor stroke only
• MI risk of CEA is important

Neurologists
• Although outcomes were low, medical therapy is more effective than any revascularization
## Selection of Revascularization Method – Symptomatic Patient

<table>
<thead>
<tr>
<th>Factors in Choice of Carotid Revascularization Methods</th>
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</thead>
<tbody>
<tr>
<td>Recently symptomatic patient (&lt;2 weeks)</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Age (per 10 yrs)Age &gt;75 yrs</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Tortuous or heavily calcified aorta</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Long lesion, heavily calcified lesion</td>
<td>Favors CEA</td>
</tr>
<tr>
<td>Contralateral carotid occlusion</td>
<td>Favors CAS</td>
</tr>
<tr>
<td>Recurrent carotid stenosis</td>
<td>Favors CAS</td>
</tr>
<tr>
<td>Presence of significant cardiac disease</td>
<td>Favors CAS</td>
</tr>
<tr>
<td>Presence of significant lung disease</td>
<td>Favors CAS</td>
</tr>
</tbody>
</table>
Current Evidence for the Treatment of Carotid Stenosis

What about so called “Improved Medical Therapy or Optimal Medical Therapy”
Improved Medical Therapy and Relevance to Carotid Disease

Has optimal medical therapy (OMT) reduced the rate of stroke?

- **SYMPTOMATIC ICA STENOSIS**
- Merwick et al 2013
  - 2,770 TIA patients
  - 387 had > 50% ICA stenosis
  - 7 day risk of stroke: without statin 13.2%, with statin 3.8% (unrelated to revasc procedure)

*Stroke 2013;44:2814-20*
Improved Medical Therapy and Relevance to Carotid Disease

Has optimal medical therapy (OMT) reduced the rate of stroke?

- SYMPTOMATIC ICA STENOSIS
- CHANCE study 2013
  - 5,170 patients
  - Minor stroke or TIA within 24 hour of symptom onset
  - ASA 75 mg vs ASA 75 mg/Clopidogrel 300mg > 75mg
  - 90 days: stroke 8.2% with DAPT vs 11.7% ASA monotherapy
  - No increased bleeding with DAPT

NEJM 2013;369:11-19
Improved Medical Therapy and Relevance to Carotid Disease

Has optimal medical therapy (OMT) reduced the rate of stroke?

- SYMPTOMATIC ICA STENOSIS
- Wong et al 2013
  - 14 studies: 9,012 patients
  - DAPT vs single anti platelet treated within 72 hours of index event
  - DAPT decreased the risk of stroke recurrence by 31% without a significant increase in bleeding complications.
Improved Medical Therapy and Relevance to Carotid Disease
Has optimal medical therapy (OMT) reduced the rate of stroke?

- **SYMPTOMATIC ICA STENOSIS**
- **CAUTION**
  - Studies of stroke patients with long term DAPT (> 18 months) (MATCH and PRoFESS) have reported increased rates of life threatening bleeding (2.6 and 1.3%)
- Confirms need for further study reproduction

Lancet 2004;364:331-7
NEJM 2008;359:1238-51
Improved Medical Therapy and Relevance to Carotid Disease
Has optimal medical therapy (OMT) reduced the rate of stroke?

- SYMPTOMATIC ICA STENOSIS
- SAMMPRIS Trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) 2012
- Inclusion:
  - TIA/Stroke within 30 days
  - 70 – 99% stenosis of major intracranial vessel
  - All patients received aggressive medical medical therapy

NEJM 2011;365;993-1003
Improved Medical Therapy and Relevance to Carotid Disease
Has optimal medical therapy (OMT) reduced the rate of stroke?

- SYMPTOMATIC ICA STENOSIS
- SAMMPRIS Trial
  - The primary endpoint occurred in 12% of patients at year one treated with OMT, or approximately 50% less than the projected event rate.
  - This result was superior to the more invasive approach with OMT plus intracranial stenting, which illustrates the potential of aggressive medical therapy.
Improved Medical Therapy and Relevance to Carotid Disease
Has optimal medical therapy (OMT) reduced the rate of stroke?

- ASYMPTOMATIC CAROTID DISEASE
- Spence et al 2010
  - 468 patients, > 60% ICA stenosis
  - 2003-2007 group had OMT
  - The combined rate of stroke, death, MI, or CEA performed because of symptoms declined from 17.6% to 5.6% (p<0.001)
Improved Medical Therapy and Relevance to Carotid Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients in Medical Arm</th>
<th>Stroke Risk Per Year (%)</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>834</td>
<td>2.2</td>
<td>(2)</td>
</tr>
<tr>
<td>ACST</td>
<td>1,560</td>
<td>2.4</td>
<td>(3)</td>
</tr>
<tr>
<td>London, Ontario (without ME)</td>
<td>431</td>
<td>1.2</td>
<td>(46)</td>
</tr>
<tr>
<td>Oxford</td>
<td>101</td>
<td>0.34</td>
<td>(54)</td>
</tr>
<tr>
<td>SMART</td>
<td>193</td>
<td>0.5</td>
<td>(55)</td>
</tr>
</tbody>
</table>

ACAS=Asymptomatic Carotid Atherosclerosis Study; ACST= Asymptomatic Carotid Surgery Trial; ME= microemboli; SMART= Second Manifestations of Arterial Disease
2684 consecutive patients with arterial disease or type 2 DM, but without a history of cerebral ischemia, with a mean follow-up of 3.6 years

No difference!  
$p = NS$

Goessens, BMB. Stroke. 2007;38:1470-1475.
Current Guidelines
**Guideline Recommendations**

- **SYMPTOMATIC PATIENTS:**
  - For patients with a TIA or stroke within the past 6 months and ipsilateral severe stenosis (70 – 99%), CEA is recommended if the perioperative stroke/death rate is estimated to be < 6%. (Class I, Level of Evidence: A)
  - When the degree of stenosis is < 50%, CEA and CAS are not recommended (Class III, Level of Evidence: A)
Guideline Recommendations

• SYMPTOMATIC PATIENTS
  • When revascularization is indicated, it is reasonable to perform surgery within 2 weeks rather than delay surgery. (Class IIa, Level of Evidence: B).
  • CAS is indicated as an alternative to CEA if the anticipated perioperative stroke/death rate is < 6% (Class IIa, Level of Evidence: B).
  • It is reasonable to consider patient age in choosing between CEA and CAS (Class IIa, Level of Evidence: B).
Guideline Recommendations

• ASYMPTOMATIC PATIENTS
• Selection of asymptomatic patients for revascularization should be based on comorbid conditions and patient life expectancy (Class I, Level of Evidence: C).
• Highly selected patients may benefit from CEA if the perioperative stroke/death rate is < 3% (Class IIa, Level of Evidence: A)
Guideline Recommendations

- ASYMPTOMATIC PATIENTS
- CAS might be considered in highly selected patients if the perioperative stroke/death rate is < 3% (Class IIb, Level of Evidence: B). The advantage of CAS over medical therapy is not well established.
Current and Future Carotid Stenosis Trials

A new generation of clinical trials has been launched to determine whether advances in medical therapy have altered the decisions regarding the selection of revascularization procedures in important patient populations.....
# Current and Future Carotid Stenosis Trials

<table>
<thead>
<tr>
<th>Study Acronym</th>
<th>Design</th>
<th>Status (as of July 2014)</th>
</tr>
</thead>
</table>
| SPACE 2       | Two parallel trials  
Asymptomatic average surgical risk  
CEA + OMT vs OMT alone  
CAS + OMT vs OMT alone | Enrolling |
| ACST 2        | CEA vs CAS  
Average surgical risk patients | Enrolling |
| ECST 2        | OMT vs OMT + carotid revascularization  
Asymptomatic or symptomatic low risk | Enrolling |
| CREST 2       | Two parallel trials  
Asymptomatic average surgical risk  
CEA + OMT vs OMT alone  
CAS + OMT vs OMT alone | Enrolling |

**ACAS=Asymptomatic Carotid Atherosclerosis Study; ACST= Asymptomatic Carotid Surgery Trial; ME= microemboli; SMART= Second Manifestations of Arterial Disease; ECST= European Carotid Surgery Trial; OMT= optimal medical therapy; SPACE= Stent-Protected Angioplasty vs. Carotid Endarterectomy; CAS= carotid artery stenting; CEA= carotid endarterectomy; CREST= Carotid Revascularization Endarterectomy vs. Stenting Trial**
To Summarize…..

- Strokes can be catastrophic, but extra cranial carotid disease is not a common cause of stroke.
- Patients with carotid artery disease are at much greater risk of heart attack and nonvascular death than stroke.
- Revascularization works, but modality should be individualized based on anatomy, medical co-morbidity, and operator experience.
- Stroke rates are so low that even a 20% reduction maybe clinically, if not statistically, meaningless.
- Medical therapy works, should be multifactorial, and will lower overall cardiovascular morbidity and mortality.
The Answer to the Question.....

- The answer to the question is in flux.....
- BUT, we know you have to consider:
  - The Patient (Symptoms?/The whole body/Functional status)
  - The Anatomy (The artery/The aorta)
  - Their Current Medical Regimen (Room to improve?)
  - The Local Expertise (Be honest)
  - The Patient’s Preference (After a fair and balanced discussion)
  - Reimbursement. Asymptomatic CAS problematic.
  - FDA Approved. >70%, Symptomatic, Surgical high risk

- The declining rate of stroke with improved medical therapy has led to the launch of new clinical trials to determine the contemporary risk/benefit ratio of revascularization relative to aggressive medical therapy.