The Medical Management of Carotid Artery Stenosis

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None
Ms. BS is a 80 y/o non-smoker with a PMH of HLD & HTN who was found to have hollenhorst plaque on routine eye exam.

- Denies any vision changes or focal deficits.
- Had a normal eye exam 12 months prior.
- Meds: Lipitor 10mg, ASA 81mg, & Fosamax
- VSS, PE unremarkable
- Carotid duplex with 50% stenosis of left ICA
Outline

- Background
- Diagnosis
- Management
  - Carotid Endarterectomy (CEA)
  - Carotid Angioplasty and Stenting (CAAS)
- Medical management
- 22 million people worldwide will experience a CVA annually
- 2nd leading cause of death worldwide
- 5th leading cause of death in the US
- >4.4 million in US suffering from CVA

Rosamand et al Circulation 2012
20 % mortality from the acute event

50 to 60 % mortality at five years.

Among survivors, data from the Framingham study reveal that:

- 18% are unable to return to work
- 4% require total custodial care
- 25% of those > 65 years require long-term institutional care after a first stroke

Roger et al Circulation 2012
Anatomy

- 85% of strokes are ischemic
- 20-30% of those are related to CAS
- >3000 strokes per year

Roger et al Circulation 2012
Thrombolytic therapy can salvage brain tissue in some patients.

There is little that can be done to reverse the devastating effects of brain injury.

For this reason, the greatest impact on this disease comes from prevention.
# Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Journal</th>
<th>Time</th>
<th>Primary Benefit</th>
<th>Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAST - Italy (n=622)</td>
<td>Lancet 1995</td>
<td>&lt;6hr</td>
<td>None</td>
<td>Increased early death</td>
</tr>
<tr>
<td>ECASS-I (n=620)</td>
<td>JAMA 1995</td>
<td>&lt;6hr</td>
<td>None</td>
<td>Benefit not outweigh the risk</td>
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<tr>
<td>NINDS-I (n=291)</td>
<td>NEJM 1995</td>
<td>&lt;3hr</td>
<td>None</td>
<td>No difference</td>
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<tr>
<td>NINDS -II (n=333)</td>
<td>NEJM 1995</td>
<td>&lt;3hr</td>
<td>~13% absolute benefit mRS at 90d</td>
<td>Increase ICH</td>
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<tr>
<td>MAST - Eu (n=310)</td>
<td>NEJM 1996</td>
<td>&lt;6hr</td>
<td>None</td>
<td>Stopped early due to harm</td>
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<tr>
<td>ASK (n=340)</td>
<td>JAMA 1996</td>
<td>&lt;4hr</td>
<td>None</td>
<td>Stopped early due to harm</td>
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<td>ECASS-II (n=800)</td>
<td>Lancet 1998</td>
<td>&lt;6hr</td>
<td>None</td>
<td>No difference</td>
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<tr>
<td>ATLANTIS-B (n=613)</td>
<td>JAMA 1999</td>
<td>3-4hr</td>
<td>None</td>
<td>Stopped early &quot;unlikely to prove beneficial&quot;</td>
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<tr>
<td>ATLANTIS-A (n=142)</td>
<td>Stroke 2000</td>
<td>&lt;6hr</td>
<td>None</td>
<td>Stopped early due to harm</td>
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<td>ECASS-III (n=821)</td>
<td>NEJM 2008</td>
<td>3-4.5hr</td>
<td>7% absolute benefit</td>
<td>Increase ICH</td>
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<td>DIAS-2 (n=193)</td>
<td>Lancet 2009</td>
<td>3-9hr</td>
<td>None</td>
<td>No difference</td>
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<td>IST-3 (n=3035)</td>
<td>Lancet 2012</td>
<td>&lt;6hr</td>
<td>None</td>
<td>No difference</td>
</tr>
</tbody>
</table>
Outline

- Background
- **Diagnosis**
- Management
  - Symptomatic
  - Asymptomatic
- Case for medical management
Carotid auscultation should be part of the routine PE of patients with risk factors for vascular disease.

- Bruits are a better indicator of general atherosclerotic disease than of stroke risk.
- The rate of CVD death in patients with carotid bruits is 2x that of patients without carotid bruits.
- Patients with CAS are more likely to die from MI than cerebrovascular disease.

Picket et al Lancet 2008
Conventional Angiography

- Gold standard
- Visualize the entire cerebrovascular system
- Invasive
- Expensive
- Neurological morbidity/mortality
Noninvasive Testing

Indirect
- Supraorbital Doppler ultrasonography
- Oculoplethysmography

More Direct
- Carotid duplex ultrasonography (CDUS)
- Magnetic resonance angiography (MRA)
- Computed tomographic angiography (CTA)
Carotid Artery Duplex Sonography

- First line
- Accuracy
  - Sensitivity: 89%
  - Specificity: 84%
- Confirm finding with CTA or MRA

Wardlaw et al Lancet 2006
USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general population.

AHA & ASA acknowledge that "screening of general populations for asymptomatic carotid stenosis is unlikely to be cost-effective.”

Joint guidelines from multiple US societies advise that CDUS

- “is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis.”
- They also suggest that it is reasonable to screen asymptomatic individuals who have a carotid bruit.
- Screening “may be considered” for asymptomatic patients with known atherosclerotic disease.
- >2 risk factors for atherosclerotic disease.

Brott et al Stroke 2011
Outline

- Background
- Diagnosis
- Management
  - CEA
  - CAAS
- Medical management
Diagnosis of CAS

Symptomatic
- Embolic event
  - CVA
  - TIA
- Amaurosis fugax
- Ipsilateral
- Within 6 months

Asymptomatic
- Dizziness
- Syncope
- Altered mental status
The benefit of CEA for patients with symptomatic carotid disease was established by clinical trials designed in the 80s and early 90s.

The studies employed conventional contrast angiography to determine the degree of CAS.

Two major trials of CEA —
- North American Symptomatic Carotid Endarterectomy Trial (NASCET)
- European Carotid Surgery Trial (ECST)
Initiated in the mid-1980s to investigate the efficacy of CEA compared with medical treatment in patients with symptomatic carotid atherosclerotic disease

Randomized, prospective, multi-center trial

Enrolled 659 patients who had had:
- Hemispheric or retinal TIA
- Non-disabling stroke within the 120 days before entry
- Stenosis of 70 to 99% in the symptomatic (ipsilateral) carotid artery.

NEJM 2001
- The study was prematurely terminated because of evidence that surgery was beneficial in this selected group of patients.
- At the time of study termination, patients had been followed for a mean of 18 months.
- The risk of stroke and death was higher at 30 days in the patients treated with CEA (5.8 versus 3.3 percent with medical therapy)
2-years of follow-up:
- A lower risk of any stroke or death (15.8 versus 32.3 percent)
- A lower risk of any ipsilateral stroke (9 versus 26 percent)
- A lower risk of major or fatal ipsilateral stroke (2.5 versus 13.1 percent)
- A lower risk of any major stroke or death (8.0 versus 19.1 percent)
Randomized, prospective, multi-center trial

2518 patients with a non-disabling ischemic stroke, TIA, or retinal infarct due to a stenotic lesion in the ipsilateral carotid artery to medical therapy with aspirin or to surgery

The first report included 374 patients with a mild stenosis (0 to 29) and 778 patients with severe stenosis (70 to 99 percent).

Lancet 2001
Patients with mild stenosis had little risk of ipsilateral ischemic stroke; possible benefits of CEA were small and were outweighed by the early risks.

At 30 days, the incidence of stroke or death was 7.5 percent in the patients with a severe stenosis who underwent CEA.

At three years, patients treated with CEA had significant reductions in the incidence of ipsilateral ischemic stroke (2.8 versus 16.8 percent with aspirin alone).

Total risk of surgical death, surgical stroke, ipsilateral ischemic stroke, or any other stroke (12.3 versus 21.9 percent).
The risk varied with age and sex, with benefit being less likely in women and over a narrower range of carotid stenosis in younger patients.

A subsequent final report from ECST, based upon an ultimate total of 3024 patients followed for a mean of six years, noted two major findings:

- CEA was beneficial for symptomatic carotid stenosis of 80 to 99%.
- The risk of a major ischemic stroke ipsilateral to the unoperated carotid artery increased with the severity of the stenosis, particularly above 80 percent, but only for two to three years after randomization.
Overall, the ECST confirmed the results of the NASCET trial, demonstrating a benefit with CEA in symptomatic patients with severe ipsilateral carotid stenosis, although age and sex were important considerations in a decision about surgery. The reduced risk of recurrent stroke associated with CEA was durable during at least 10 years of follow-up.

Even in the areas where NASCET and ECST appeared to disagree (e.g., in patients with less than 80 percent stenosis), a reanalysis of the data suggests that if the same measurement criteria were used, these differences would disappear.
CEA was beneficial for patients with > 70% symptomatic stenosis.
   - The NNT to prevent one stroke over five years for this group was 6.3, ARR of 16%

No significant benefit of CEA with ICA occlusion was observed

CEA was beneficial for patients with 50 to 69% symptomatic stenosis. The NNT to prevent one stroke over five years in this group was 22, with an ARR of 4.6%.

CEA was not beneficial for symptomatic carotid stenosis of 30 to 49%.

CEA was harmful for symptomatic patients with < 30% stenosis.

CEA is not beneficial for most women with 50 to 69% symptomatic CAS.

Rothwell et al Lancet 2004
For patients with recent TIA or CVA within the past six months and ipsilateral severe (70 to 99 %) CAS, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6 %.

For patients with recent TIA or ischemic stroke and ipsilateral moderate (50 to 69 %) CAS, CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6 %.

When the degree of stenosis is <50 %, there is no indication for carotid revascularization by either CEA or CAS.

When CEA is indicated for patients with TIA or stroke, it is reasonable to perform the surgery within two weeks rather than delaying surgery if there are no contraindications to early revascularization.

Kernan et al Stroke 2014
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)
Patients with asymptomatic carotid artery stenosis should be screened for other treatable risk factors for stroke with institution of appropriate lifestyle changes and medical therapy.

Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences.

The use of aspirin in conjunction with CEA is recommended unless contraindicated.

Prophylactic CEA performed with <3 percent morbidity and mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60 percent by angiography, 70 percent by validated Doppler ultrasound).

It should be noted that the benefit of surgery may now be lower than anticipated based on randomized trial results, and the cited 3 percent threshold for complication rates may be high because of interim advances in medical therapy.
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- Background
- Diagnosis
- Management
  - CEA
  - CAAS
- Medical management
First case report of carotid angioplasty appeared in early 1980
Endovascular versus surgical treatment in patients with carotid stenosis: a randomised trial

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


Summary

Endovascular treatment of carotid stenosis has been established as standard management. We compared carotid artery stenting with carotid endarterectomy in patients at high risk for surgery.

Methods

A total of 179 patients with severe carotid stenosis were randomly assigned to endarterectomy or carotid artery stenting. The primary end point was a composite of death, stroke, or myocardial infarction at 30 days or 2 years.

Results

At 30 days, the rate of death, stroke, or myocardial infarction was similar between the two groups (10.0% vs 11.0%, p = 0.72). During the 2-year follow-up, the rate of the primary end point was 27.8% vs 30.2% (p = 0.48). Among patients with a prior stroke, the rate of death, stroke, or myocardial infarction was 14.8% vs 17.5% (p = 0.53). At 2 years, the rate of death was 2.0% in each group (p = 0.82). There were no differences in the rates of death, stroke, or myocardial infarction between the stent and endarterectomy arms.

Conclusions

Carotid artery stenting was noninferior to carotid endarterectomy in patients at high risk for surgery.

Endovascular versus surgical treatment in patients with carotid stenosis: a randomised trial

Results of the Stent-Protection Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic carotid stenoses at 2 years: a multinational, prospective, randomised trial

Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis

- CAAS is an alternative to CEA for the treatment of patients with carotid atherosclerotic disease
  - Particularly in patients considered to be poor candidates for surgery.

- CMS only reimburses the cost of CAS for patients with symptomatic carotid artery stenosis of a severity of at least 70% who are considered high-risk patients for surgery.
  - In all other patient categories, the procedure is reimbursed only in the setting of one of the numerous ongoing post-marketing registries or clinical trials.
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  - CAAS

- Medical management
Recent Trends

- During the past 2 to 3 decades, the prevalence of IHD has decreased by > 30%.
- Smoking has decreased by 14%.
- Atrial fibrillation has decreased by 6%.
- Peripheral artery disease may have decreased by 6%.
- ACST the rate of ipsilateral stroke in the last 5 years of the trial was ~0.7% per year compared with 1.1% during the first 5 years of the trial.
- ACAS 2.2% during the 5 years

Beckman JAMA 2013
Cardiac disease is the primary source of morbidity and mortality in patients with significant atherosclerosis, even when it presents in a non-cardiac bed.

Pickett et al reported that the presence of a carotid bruit increased the rate of MI by more than 3-fold to 5% per year.

The rate of stroke in asymptomatic ICA stenosis has been decreasing over the past 2 decades.

Picket et al Lancet 2008
Physicians' Health Study – NEJM 1989
- ASA 325 mg vs placebo no diff in CVA
- 44% RR in MI > 50 yr old

Asymptomatic Cervical Bruit Study – Ann Intern Med 1995
- No diff in the composite primary end point between ASA 325mg and placebo

CAPRIE Trial – Lancet 1996
- No diff in stroke rates between ASA 325mg and Plavix 75mg qd

Women's Health Study – NEJM 2005
- No diff in the composite primary end point ASA 81mg and Placebo
- 1.1% vs 1.3%

These trials are older and their applicability to contemporary practice of medicine in is unclear.
The benefit of blood pressure reduction in stroke prevention has been demonstrated for diuretics, calcium channel antagonists, β-blockers, and antagonists of the renin angiotensin system.

In the Heart Outcomes Prevention Evaluation (HOPE) trial, patients with cerebrovascular disease had a 30% RRR in the rate of stroke during 4.5 years of follow-up.

In the Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE) trial, losartan had a RRR of fatal and nonfatal stroke by approximately 25% compared with atenolol in patients with essential HTN and LVH.
Statin therapy may be largely responsible for the decrease in incidence of stroke in the past 10 years.

Heart Protection Study (HPS) – Lancet 2002
- 20,536 patients 40 to 80 years with history of CAD, other occlusive arterial disease, or diabetes
- 25% RRR of stroke between simvastatin 40mg and placebo
- Reduced the rate of carotid revascularization by 50%

Collaborative Atorvastatin Diabetes Study trial – Lancet 2004
- Patients with type 2 diabetes and an additional cardiovascular risk factor
- Atorvastatin 10 mg had a 48% RRR compared with placebo.
Multispecialty Guidelines Recommend:

- Statin therapy, blood pressure control, and tobacco cessation to reduce stroke
- Statin therapy, blood pressure reduction, tobacco cessation, and aspirin therapy to reduce MI and other cardiovascular events
Conclusions

- CAS is a problem commonly seen in clinical practice.
- Differentiation between symptomatic and asymptomatic patients with carotid artery stenosis is essential to tailor therapy properly.
- CEA should be strongly considered for symptomatic patients with 70% to 99% stenosis and should also be considered for selected symptomatic patients with 50% to 69% stenosis if no other etiologic basis for the ischemic symptoms can be found.
- Surgery should be recommended only in selected patients with asymptomatic carotid artery stenosis because of the marginal benefit from revascularization in this patient population.
- CAAS is a valid alternative to CEA for selected patients who have an indication for revascularization and are at high surgical risk.
- Aggressive correction of risk factors are the mainstays of medical therapy.
Ms. BS is a 80 y/o non-smoker with a PMH of HTN and HLD who was found to have hollenhorst plaque on routine eye exam.

- Denies any vision changes or focal deficits.
- Had a normal eye exam 12 months prior.
- Meds: Lipitor 10mg, ASA 81mg, Amlodipine 5mg & Fosamax
- VSS, PE unremarkable
- Carotid duplex with 50% stenosis of left ICA

MRI with no e/o prior CVA. MRA with no e/o stenosis.

She was switched to ramipril, started on plavix, and her lipitor was increased to 80mg.
THANK YOU!