What Is The Risk?

- 73 year old NS right-handed male applicant for $1 Million Life Insurance
- Five months prior suffered an episode of garbled speech and right-sided arm greater than leg weakness lasting about 45 minutes. He was subsequently placed on aspirin. No further symptoms.
- Current neurological examination is normal
- Left carotid artery bruit is present
- Mildly hypertensive, controlled on medications
- Started on lipitor for elevated cholesterol 2 years prior
- No history for heart disease, FH Negative
- APS reports doppler study of applicant’s carotid artery
Applicant Demonstrates Findings of “Critical” (70 – 99%) Carotid Artery Stenosis

Doppler Criteria for Critical (70 – 99%) Stenosis

- End Diast. > 115 cm / sec
- Peak Syst. > 230 cm / sec
- Flow character: spectral broadening

Normal
ED < 100 cm / sec
PS < 125 cm / sec

Applicant
ED 131 cm / sec
PS 427 cm / sec

SYMPTOMATIC CAROTID ARTERY DISEASE

NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTERECTOMY TRIAL (NASCET)
NASCET Entry Criteria

- Within last 6 months
  - Focal neurological symptoms referable to diseased / stenotic (ipsilateral) carotid circulation
    - Transient Ischemic Attack (TIA) – sx’s resolve within 24 H (Hemispheric or retinal)
    - “Non-disabling” cerebral vascular accident(s) (CVA)
      - Criteria for “Non-disabling” CVA: mRS scores 0 - 2


Modified Rankin Scale (mRS)
“Non-disabling Stroke:” Rankin Scores 0 - 2

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

NASCET Structure for Each Gender

Medical Treatment: Risk Factor Control and ASA

- 70 – 99% (critical stenosis)
- 50 – 69 % (severe stenosis)
- < 50% (minimal – mild stenosis)

Surgical Treatment: Carotid Endarterectomy (CEA) + Medical Rx

- 70 - 99% (critical stenosis)
- 50 – 69 % (severe stenosis)
- < 50% (minimal – mild stenosis)

NASCET Results for 70 – 99 % Carotid Stenosis (critical stenosis)

“Critical Stenosis” is beyond these values: PS > 230 cm / sec and ED > 115 cm / sec
After 2 Years Those Having 70 - 99% Carotid Artery Stenosis Were Found to Benefit from Endarterectomy

**NASCET: Failure Rates at Two Years of Follow-up According to Event Defining Treatment Failure**

<table>
<thead>
<tr>
<th>Event</th>
<th>Medical RX (%)</th>
<th>Surgical Rx (%)</th>
<th>Delta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ipsilateral stroke</td>
<td>26.0</td>
<td>9.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Any disabling or fatal ipsilateral stroke</td>
<td>13.1</td>
<td>2.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Any disabling stroke or death from any cause</td>
<td>19.1</td>
<td>8.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>


**Functional Outcome 3 Months After Stroke (~85% Ischemic) Predicts Long-Term Survival**

**Follow up begins at 3 months post CVA per modified Rankin Scale score**

<table>
<thead>
<tr>
<th>mRS Score</th>
<th>Mortality Ratio (%)</th>
<th>Average ED / K / Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 2</td>
<td>122</td>
<td>8.5</td>
</tr>
<tr>
<td>3</td>
<td>188</td>
<td>47.9</td>
</tr>
<tr>
<td>4</td>
<td>277</td>
<td>82.4</td>
</tr>
<tr>
<td>5</td>
<td>372</td>
<td>147.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>341</td>
<td>84.2</td>
</tr>
</tbody>
</table>
**NASCET Results for 50 – 69 % Carotid Stenosis**

(severe stenosis)

“Severe stenosis” is beyond these values: PS = 125 cm / sec and ED = 100 cm / sec

**NASCET Showed That CEA Provided Moderate Benefit**

for 50 – 69% Symptomatic Ipsilateral Stenosis Vs. Medical Rx

<table>
<thead>
<tr>
<th>Event Defining Treatment Failure</th>
<th>Medical Rx (%)</th>
<th>Surgical Rx (%)</th>
<th>Delta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ipsilateral stroke</td>
<td>22.2</td>
<td>15.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Disabling ipsilateral stroke</td>
<td>7.2</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Any disabling stroke or death, any cause</td>
<td>25.2</td>
<td>18.3</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Risk for Subsequent Ipsilateral Stroke after CEA for Symptomatic Stenosis Remains Low for at Least 10 Years

Risk for any ipsilateral ischemic stroke post CEA is 9.7% at 10 years
- Risk for disabling ipsilateral ischemic stroke post CEA is 4.4% at 10 years

Beginning 30 days after carotid endarterectomy


Vive la Différence!
(If you are a man having CEA for symptomatic carotid artery stenosis)

- Benefit of CEA declines more rapidly in women
- Benefit of CEA in women generally confined to those having surgery within two weeks of onset of symptoms irrespective of degree of stenosis
- Most women having symptomatic carotid artery stenosis of 50 – 69% receive no benefit from CEA
- Peri-operative risk of death from CEA is significantly higher in women
- ON THE OTHER HAND
  Risk of stroke ipsilateral of symptomatic carotid artery stenosis is significantly lower in medically treated women

Mohler ER, et al, UpToDate March 2012: Management of symptomatic carotid atherosclerotic disease
Applicant: 73 yo ♂ with TIA in LMCA and 70 – 99% Carotid Artery Stenosis

<table>
<thead>
<tr>
<th>Risk over first 2 years:</th>
<th>Medical Treatment (ASA)</th>
<th>Risk over first 2 years:</th>
<th>Endarterectomy + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any disabling or fatal</td>
<td>13.1 %</td>
<td>Any disabling or fatal</td>
<td>2.5 %</td>
</tr>
<tr>
<td>ipsilateral stroke</td>
<td></td>
<td>ipsilateral stroke</td>
<td></td>
</tr>
<tr>
<td>Any disabling stroke or</td>
<td>19.1 %</td>
<td>Any disabling stroke or</td>
<td>8.0 %</td>
</tr>
<tr>
<td>death from any cause</td>
<td></td>
<td>death from any cause</td>
<td></td>
</tr>
</tbody>
</table>

What if applicant …

Had 50 – 69 % stenosis?
Were a woman?
Future risk for dementia increased?

After Endarterectomy

Risk over the next 10 years for…

Any ipsilateral ischemic stroke ~ 1 % / Y
Disabling ipsilateral ischemic stroke ~ 0.5 % / Y

NASCET Results for < 50 % Carotid Stenosis
(minimal – mild stenosis)
NASCET Results at Five Years Follow-up for Those Symptomatic with < 50% Stenosis

Those having stenosis < 50% did not benefit from CEA

Specifically:
- 30 – 49% stenosis: no benefit
- < 30 % stenosis: CEA was actually harmful


Questions Concerning NASCET Data

- NASCET
  - 70 - 99% stenosis major endpoint: death or major stroke at 2 years
    - Actual risk due to either is uncertain
  - 18.3 % of NASCET qualifying events were due to transient monocular visual loss (TMVL) which has lower associated risk
  - Unknown % NASCET qualifying events due to lacunar infarcts and cardioemboli
  - Use of STATIN therapy was not as extensive during NASCET or ECST as it is now for individuals with carotid artery disease
  - Currently, medical therapy appears to be providing improved results relative to the above noted studies
Remember, we have discussed results for only those having TIA’s and/or non-disabling strokes (Rankin scale 0 – 2) as presentations of their carotid artery stenosis.

Benefit of CEA for those having moderate to severe ischemic strokes not yet evaluated in randomized clinical trials.

“Near Occlusions” (95% or greater stenosis) showed no benefit from CEA in NASCET/ECST.

- Risk of stroke for medically-treated “near occlusions” was less than those having stenosis $\geq 70 – 95\%$.
- This diminished risk is probably due to development of good collateral circulation.
- No significant benefit from CEA has been demonstrated in this group.

Reduced flow distally in ICA, or evidence of collateral flow of contrast towards symptomatic cerebral hemisphere, or both.

ASYMPTOMATIC CAROTID ARTERY STENOSIS

1. **Asymptomatic Carotid Atherosclerosis Study (ACAS)**
   - Ages 40 to 79, ≥ 60 - 99% stenosis of carotid bulb / internal carotid artery
   - No history or symptoms for neurological event in study artery
   - Surgical wing
     - 325 mg ASA, risk factor modification, carotid endarterectomy (CEA)
   - Medical Wing
     - 325 mg ASA and risk factor modification

2. **Asymptomatic Carotid Surgery Trial (ACST)**
   - Ultrasound characterized carotid lesions as 60, 70, 80 or 90% stenotic

3. **Veterans Affairs Cooperative Study Group**
   - Asymptomatic carotid stenosis ≥ 50%
1. Risk of ipsilateral stroke in those undergoing CEA was 53% of those treated medically
   - 5 year risk for ipsilateral stroke or death: CEA = 5.1%, Med. Rx = 11.0%
   - (Benefit not as great as for those symptomatic receiving CEA)
2. Benefit not expressed until about 2 years after surgery
   - (Those symptomatic experience immediate benefit beginning 30 days post op)
3. Benefit is much less for women than for men
4. Severity of stenosis after 60% does not affect outcome
5. Medical wings of current studies do not well express effects of statin therapy

No Mortality Benefit from CEA for Asymptomatic Carotid Artery Stenosis – Most Deaths Due To Coronary Artery Disease

Veterans Affairs Cooperative Study Group

ACAS (N. American General Population)
Incidence of Cerebral (TIA and Stroke) and Cardiac Ischemic Events in Those with Asymptomatic Neck Bruits

Degree of carotid artery stenosis on initial doppler ultrasound

Cerebral Ischemic Events

Cardiac Ischemic Events


Comparing CEA for Symptomatic Versus Asymptomatic Carotid Artery Stenosis

Symptomatic

- 75 years & older benefit more from CEA than younger ages
- Benefits from CEA appear early
- Greater benefit from CEA for those having higher degrees of stenosis

Asymptomatic

- 75 years & older have uncertain benefit from CEA
- Benefits from CEA appear after 2 years
- Degree of stenosis did not affect the benefit from CEA

Mohler ER, et al, UpToDate March 2012; Management of asymptomatic carotid atherosclerotic disease
Asymptomatic Carotid Artery Bruits Followed for 5 Years; Compared With Gen. Population (No Symptoms or Bruit)

<table>
<thead>
<tr>
<th>Asymptomatic Carotid Bruit</th>
<th>Population Based Controls (No Symptoms, No Bruit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Probability of stroke: 1.5% / year</td>
<td>1. Probability of stroke: 0.5% / year</td>
</tr>
<tr>
<td>2. Probability of stroke or TIA: 2.4% / year</td>
<td>2. Probability of stroke or TIA: 0.7% / year</td>
</tr>
<tr>
<td>3. Probability of ipsilateral stroke: 1.0% / year</td>
<td></td>
</tr>
</tbody>
</table>

Mortality Ratio = 121%

Excess Deaths / K / Year = 6.233
mean q’ age = 68 years, 57% Women

TRANSIENT MONOCULAR VISUAL LOSS (TMVL) DUE TO IPSILATERAL CAROTID ARTERY DISEASE

HOLLENHORST PLATEAU, RETINAL ARTERY OCCLUSION

Three Year Risk of Ipsilateral Stroke Is Lower and Strokes Are Less Disabling for TMVL Relative to Hemispheric TIA’s

- TMVL relative to hemispheric TIA’s
  - More smokers
  - Twice as likely for stenosis \( \geq 70\% \)
  - More than three times as likely to have intracerebral collateral circulation
  - When both medically Rx’d, TMVL had \( \frac{1}{2} \) risk of stroke at 3 years
    - Post-TMVL strokes: 31% were retinal and 12.4% disabling hemispheric
    - Post-Hemispheric TIA strokes: 94% were hemispheric of which 28% were disabling
  - Those with TMVL had same 3 year stroke risk regardless of number and/or duration (95% < 60 minutes) of episodes of TMVL

Carotid Endarterectomy (CEA) Somewhat Beneficial in Preventing Stroke Over Next 3 Years in Those with TMVL

<table>
<thead>
<tr>
<th>Risk factors for stroke in TMVL</th>
<th>Three year risk of stroke with medical treatment (ASA and targeted risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 75 years or more</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td>History of hemispheric stroke or TIA</td>
<td></td>
</tr>
<tr>
<td>History of intermittent claudication</td>
<td></td>
</tr>
<tr>
<td>Stenosis of 80 – 94 % luminal diameter</td>
<td></td>
</tr>
<tr>
<td>Absence of collateral circulation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Risk ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>12.3</td>
</tr>
<tr>
<td>3 or more</td>
<td>24.2</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Risk Reduction ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1</td>
<td>Worse with CEA</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
</tr>
<tr>
<td>3 or more</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Retinal Arterial Emboli Associated with Modest Increases in All Cause and Stroke-Related Mortality

- Two combined population studies (Wisconsin and Australia)
- Retinal arterial emboli found in 1.3% of 8384 entrants
  (not recorded whether symptomatic or not)

  Mortality over next 12 years for those with retinal arterial emboli:

  All cause mortality \( HR = 1.3 \)
  Stroke related mortality \( HR = 2.0 \)
  Cardiovascular related mortality \( HR = 1.2 \)

Hollenhorst Plaque and Retinal Artery (or Retinal Artery Branch) Occlusions: Low Risk for Subsequent Hemispheric Neurological Events

- Only 39% were symptomatic
- Only 8 percent had carotid stenosis greater than 60% and \( \frac{2}{3} \) had stenosis less than 30
- None developed cerebral symptoms over three years
- Sequential fundoscopic examination demonstrated persistence of HP over time in greater than one half suggesting that the finding was old
- Mortality Ratio = 102%


ODDS AND ENDS
Intima-Media Atherosclerotic Carotid Artery Thickening Provides Some Indication of Risk Due to Coronary Artery Disease

Relative Risk for Stroke or Myocardial Infarction as Function of Common Carotid Intima-Media Thickness
Median Follow Up = 6.2 Years

<table>
<thead>
<tr>
<th>Maximum CCA IMT (mm)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.87</td>
<td>1.00</td>
</tr>
<tr>
<td>0.87 – 0.96</td>
<td>1.49</td>
</tr>
<tr>
<td>0.97 – 1.05</td>
<td>1.29</td>
</tr>
<tr>
<td>1.06 – 1.17</td>
<td>1.76</td>
</tr>
<tr>
<td>≥ 1.18</td>
<td>2.22</td>
</tr>
</tbody>
</table>


Role of Carotid Arterial IM Thickness in Predicting Coronary Events:

Carotid IM Thickness = 0.66 mm
Coronary artery percent diameter stenosis = 36.0 %


Carotid Artery Angioplasty And Stenting (CAS)

- CAS and CEA provide similar long-term results for individuals with symptomatic carotid occlusive disease
- CAS less invasive but with more periprocedural stroke and death relative to CEA
- Presently, CEA is recommended for most patients with symptomatic carotid occlusive disease
- CAS not recommended for those with asymptomatic disease
- CAS recommended for those recently symptomatic having 70 – 99 % stenosis and any of the following:
  - Carotid lesion not amenable to surgical access
  - Radiation-induced carotid stenosis
  - Restenosis after prior endarterectomy
  - Comorbidities increasing risk of general anesthesia (although elderly patients appear to do worse with CAS relative to CEA)

Mohler ER 111, et al, UpToDate March 2012, Management of symptomatic carotid atherosclerotic disease