
MORTALITY AND MORBIDITY RISK FROM CAROTID ARTERY ATHEROSCLEROSIS

October 17, 2012
AAIM Triennial Conference, San Diego

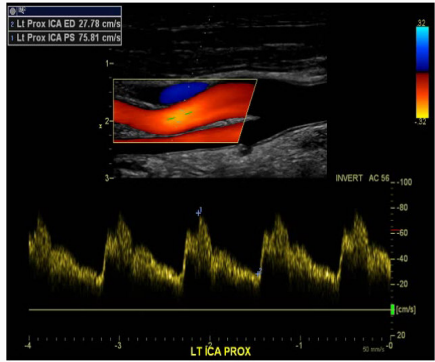
Robert Lund, MD

What Is The Risk?

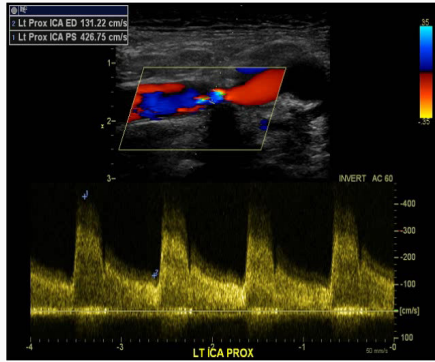
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- 73 year old NS right-handed male applicant for \$1 Million life insurance
 - Five months prior suffered an episode of garbled speech and right-sided arm greater than leg weakness lasting about 45 minutes. He was subsequently placed on aspirin. No 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

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



Applicant ED 131 cm / sec
PS 427 cm / sec



Doppler Criteria for Critical (70 – 99%) Stenosis

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

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

Barnett HJ, et al, *NEJM* 1998;339(20):1415 – 25

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

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

NASCET
Entry
Criteria for
Non-disabling
Stroke



Chiu HT, et al, *Arch Phys Med Rehabil* 2012;93:527 – 31.

NASCET Structure for Each Gender

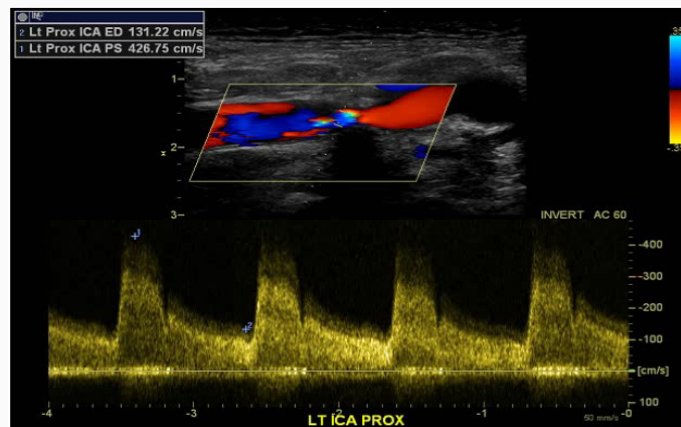
Medical Treatment: Risk Factor Control and ASA

- 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)



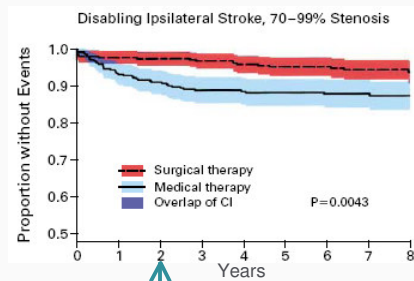
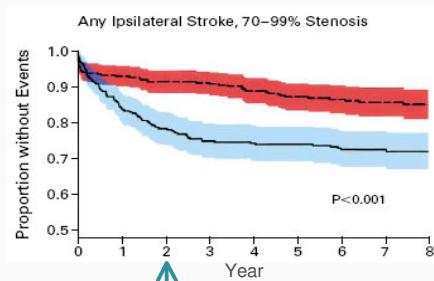
“Critical Stenosis” is beyond these values: PS > 230 cm / sec and ED > 115 cm / sec

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

	Medical RX (%)	Surgical Rx (%)	Delta (%)
Any ipsilateral stroke	26.0	9.0	17.0
Any disabling or fatal ipsilateral stroke	13.1	2.5	10.6
Any disabling stroke or death from any cause	19.1	8.0	11.1

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

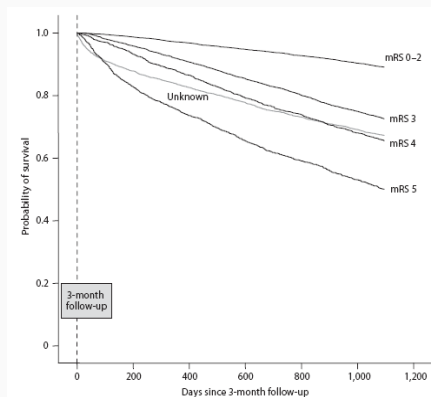


Barnett HJ, et al, *NEJM* 1998;339(20):1415 - 25.

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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



Major Stroke (mRS scores 3, 4, 5)

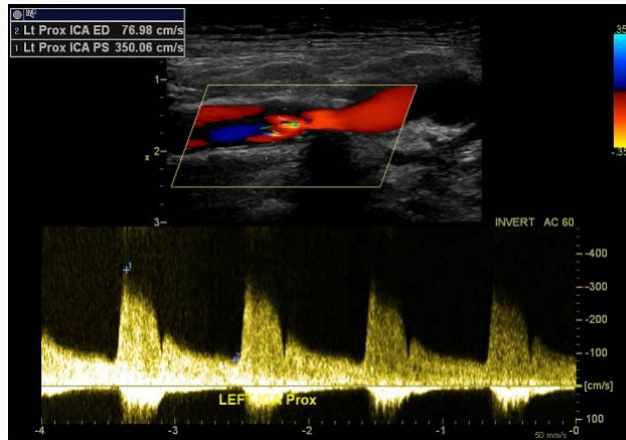
mRS Score	Mortality Ratio (%)	Average ED / K / Y
0 - 2	122	8.5
3	188	47.9
4	277	82.4
5	372	147.5
Unknown	341	84.2

Disabling

Eriksson M, et al, *Cerebrovasc Dis* 2008;25:423 - 429.

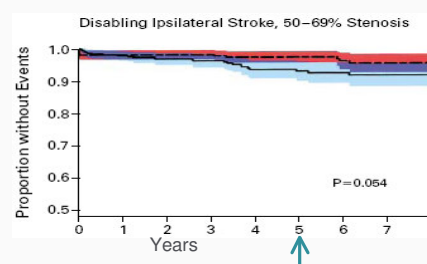
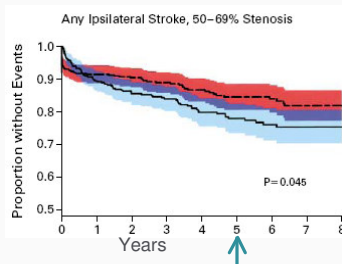
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NASCET Results for 50 – 69 % Carotid Stenosis (severe stenosis)



“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



Failure Rates at Five Years of Follow-up According to Event Defining Treatment Failure

	Medical Rx (%)	Surgical Rx (%)	Delta (%)
Any ipsilateral stroke	22.2	15.7	6.5
Disabling ipsilateral stroke	7.2	2.8	4.4
Any disabling stroke or death, any cause	25.2	18.3	6.9

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

Beginning 30 days after carotid endarterectomy



- 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

Cunningham EJ, et al, *Stroke* 2002;33:2658 – 2663.

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

Our Applicant: 73 YO ♂ with TIA in LMCA and 70 – 99% **Munich RE**
 Carotid Artery Stenosis: **Underwent Endarterectomy**

Critical Stenosis (70 – 99 %) – Yearly Risk Over Two Year Period

	Medical Treatment % / Year	Endarterectomy + Med. Rx. % / Year
Any disabling or fatal ipsilateral stroke	6.55	1.25
Any disabling stroke or death from any cause	9.55	4.0

Severe Stenosis (50 – 69 %) – Yearly Risk Over Five Year Period

Any disabling ipsilateral stroke	1.44	.56
Any disabling stroke or death from any cause	5.04	3.66

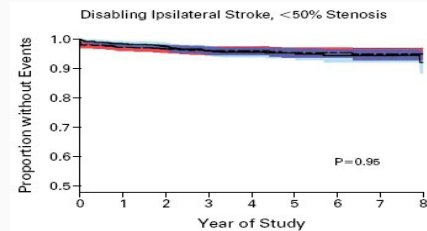
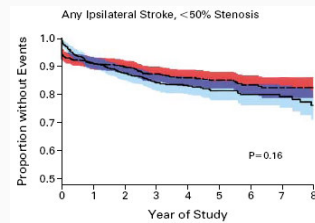
Yearly % risk for ipsilateral ischemic stroke over 10 years after carotid endarterectomy for symptomatic disease

**Any stroke: 0.97 / year
 Disabling stroke: 0.44 / year**

**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

Barnett HJ, et al, *NEJM* 1998;339(20):1415 – 25.

Questions Concerning NASCET Data

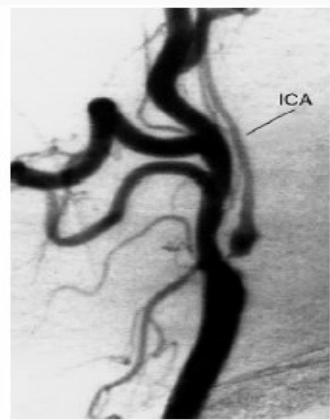
- NASCET
 - 70 - 99% stenosis major endpoint: **death or disabling** stroke at 2 years
 - Actual risk due to either is uncertain
 - 18.3 % of NASCET qualifying events were due to transient monocular visual loss (TMVL) which has lower associated risk
 - Unknown % NASCET qualifying events due to lacunar 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” (96% or greater stenosis) Showed No Benefit from CEA in NASCET/ECST

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



- 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

ASYMPTOMATIC CAROTID ARTERY STENOSIS

Carotid Artery Endarterectomy + Medical Treatment Vs. Medical Treatment Alone for Asymptomatic Disease

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

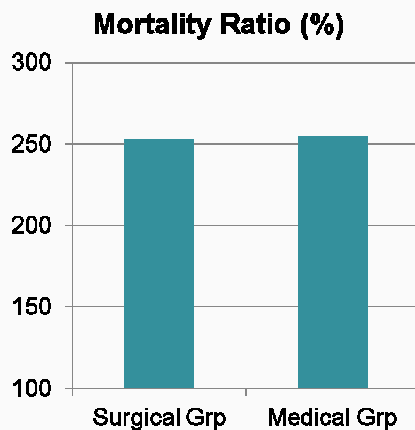
- Asymptomatic carotid stenosis $\geq 50\%$

CEA Somewhat Beneficial for Asymptomatic Carotid Artery Stenosis in Stroke Prevention, Mainly in Men

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

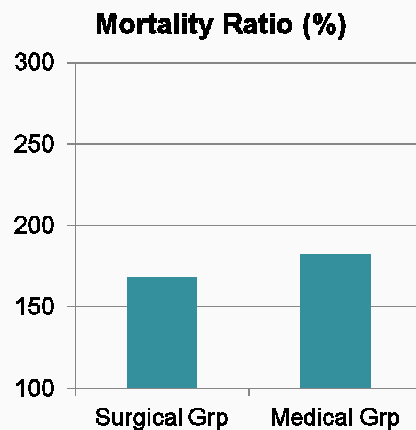
No Mortality Benefit from CEA for Asymptomatic Carotid Artery Stenosis – Most Deaths Due To Coronary Artery Disease

Veterans Affairs Cooperative Study Group



Hobson RW, et al. *NEJM* 1993;328(4):221 – 7.

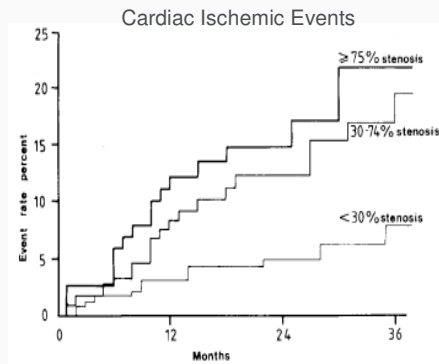
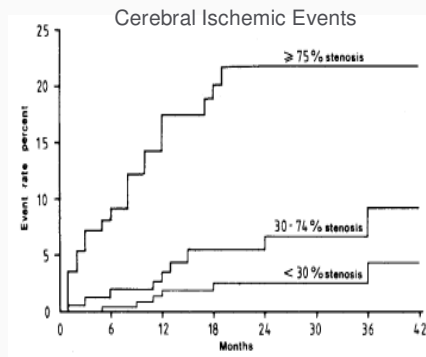
ACAS (N. American General Population)



ACAS Study, *JAMA* 1995;273(18):1421 – 1428. 24

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



Chambers BR and Norris JW, *NEJM* 1986;315(14):860 – 5.

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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](#)

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ASYMPTOMATIC CAROTID ARTERY BRUIT

Asymptomatic Carotid Artery Bruits Followed for 5 Years; Compared With Gen. Population (No Symptoms or Bruit)

Asymptomatic Carotid Bruit

1. Probability of stroke: 1.5% / year
2. Probability of stroke or TIA: 2.4% / year
3. Probability of ipsilateral stroke: 1.0% / year

Mortality Ratio = 121 %

Excess Deaths / K / Year = 6.233

mean age = 68 years, 57% Women

Population Based Controls (No Symptoms, No Bruit)

1. Probability of stroke: 0.5% / year
2. Probability of stroke or TIA: 0.7% / year

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

HOLLENHORST PLAQUE, 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

Munich RE 

Risk factors for stroke in TMVL

Age 75 years or more

Male gender

History of hemispheric stroke or TIA

History of intermittent claudication

Stenosis of 80 – 94 % luminal diameter

Absence of collateral circulation

Three year risk of stroke with medical treatment (ASA and targeted risk factors)

Number of risk factors	Risk (%)
0 - 1	1.8
2	12.3
3 or more	24.2

Three year absolute risk reduction of stroke with carotid endarterectomy

Number of risk factors	Risk Reduction (%)
0 – 1	Worse with CEA
2	4.9
3 or more	14.3

Benavente O, et al, NEJM 2001;345(15):1084 – 90.

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

Munich RE 

- 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

Wang JJ, et al, Stroke 2006;37:1833 – 1836.



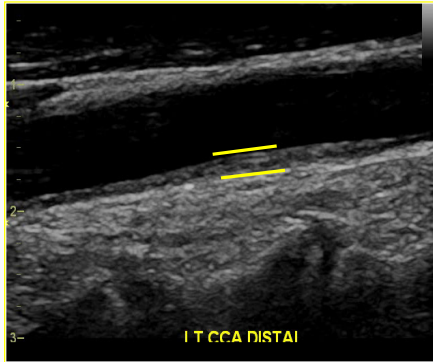
Fig. 1

- 39% were asymptomatic
- Only 8 percent had carotid stenosis greater than 60% and 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

Munich RE 



O'Leary DH, et al, NEJM 1999;340(1):14 – 22.

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

Maximum CCA IMT (mm)	Relative Risk
< 0.87	1.00
0.87 – 0.96	1.49
0.97 – 1.05	1.29
1.06 – 1.17	1.76
≥ 1.18	2.22

Role of Carotid Arterial IM Thickness in Predicting Coronary Events:

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

Hodis HN, et al, Ann Intern Med, 1998;128:262 – 269.

Carotid Artery Angioplasty And Stenting (CAS)

Munich RE 

- 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)