How the 2013-2014 Data Will Influence Treatment of Carotid Disease

The Symptomatic vs. the Asymptomatic Patient Challenges

Ralph L. Sacco, MS MD FAHA FAAN FANA
Olemberg Professor and Chair of Neurology
University of Miami, Miller School of Medicine
Treatment of Carotid Disease

• Case Example and Prevalence
• Current Recommendations and the Evidence for symptomatic and asymptomatic disease
• Ongoing Trials Update
  – CEA vs CAS vs Optimal Medical Management
• Stroke Risk Stratification
  – Vulnerable Carotid Plaque
  – Brain MRI White Matter Hyperintensities
Case
TIA, Symptomatic Carotid Stenosis

A 64-year-old woman has sudden, transient loss of vision in her L eye. She reports a prior episode of difficulty speaking and mild weakness of the R hand.

PMH: smoking and hypercholesterolemia
EXAM: Normal except for a L neck bruit
WORK-UP: CT negative; L carotid artery stenosis of 80-99% on carotid Doppler confirmed by MRA.
NORTHERN MANHATTAN STROKE STUDY

Ischemic Stroke Subtypes

CRYPTOGENIC: 36%
LACUNAR: 26%
CARDIOEMBOLIC: 19%
INTRACRANIAL: 8%
EXTRACRANIAL: 8%
OTHER: 3%
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association


*Stroke*. published online May 1, 2014:

Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association


*Stroke*. published online October 28, 2014;
Recommendations for the Management of Extracranial Carotid Stenosis

Extracranial Carotid Stenosis
Symptomatic

Mild Stenosis
< 50%

Moderate Stenosis
50-69%

Severe Stenosis
≥ 70%

Age < 75 years
Female Sex
Stroke ≥3 mo Earlier
Significant comorbidities

Lower Risk of Carotid Stroke

Age ≥ 75 years
Male Sex
Stroke <3 mo Earlier
Good intervention candidate

Higher Risk of Carotid Stroke

INTERVENTION

Medical Therapy
Risk Factor Control, Antiplatelets, Statins, ACE inhibitors
Symptomatic Carotid Disease

ASA 2014 Secondary Stroke Recs

• Ipsilateral severe (70% to 99%) carotid stenosis, CEA is recommended (Class I, Evidence A).

• Stenosis < 50%, there is no indication for CEA and CAS (Class III, Evidence A).

• Ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended depending on age, sex, comorbidities (Class I, Evidence B).

• CEA perioperative morbidity and mortality risk should be <6% and should be done within 2 weeks of symptoms.
CAS is an alternative to CEA for symptomatic patients at average or low risk of complications with stenosis >70% by noninvasive imaging or >50% by angiography. (Class IIa, Evidence B)

It is reasonable to consider patient age in choosing between CAS and CEA.
- Patients older than 70, CEA may be associated with improved outcome compared with CAS.
- Younger patients, CAS is equivalent to CEA (Class IIa; Level of Evidence B).
NINDS Carotid Revascularization Endarterectomy vs Stenting Trial

Interaction with Age

Under age 70: CAS

Over age 70: CEA

Trials For Symptomatic Stenosis
CAS vs CEA Non-inferiority Trials

• EVA-3S
  – CEA significantly better than CAS

• SPACE
  – Did not show non-inferiority for CEA vs CAS

• SAPPHIRE
  – CAS better than CEA but mainly lower 30D MI risk

• ICSS
  – CEA lower 30d risk than CAS
CEA vs CAS for Symptomatic Carotid Stenosis – 120 day outcomes
ICSS, SPACE, EVA Combined analysis among 3433 patients
Symptomatic Carotid Disease
ASA 2014 Secondary Stroke Recs

• CAS is reasonable (Class Ila, Evidence B)
  – Stenosis (>70%) difficult to access surgically,
  – medical conditions greatly increase surgery risk,
  – other circumstances exist such as radiation-induced stenosis or restenosis after CEA.

• CAS morbidity and mortality rates should be less than 6% (Class I, Evidence B).
Discriminant Factors in Choosing Between CEA and CAS

• Favors CEA
  – Age >70 years
  – Recently symptomatic patient (<2 weeks)
  – Tortuous or heavily calcified aorta
  – Long lesion, heavily calcified lesion

• Favors CAS
  – Contralateral carotid occlusion
  – Recurrent carotid stenosis
  – Presence of significant cardiac disease
  – Presence of significant lung disease
Symptomatic Carotid Disease
ASA 2014 Secondary Stroke Recs

• Optimal Medical Therapy should include antiplatelet, statin, and risk factor modification recommended for all patients with carotid artery stenosis and a TIA or stroke (Class I, Evidence A)

• ICAE – Aspirin 81-325mg
• CAS – Clopidogrel + ASA x 3 months, ASA
Asymptomatic Carotid Stenosis

- 79 yo man HTN DM CHOL presents with non-localizing Sxs – LOC, confusion, dysarthria, improved
- MRI – DWI negative; old WM changes
- R ICA high-grade >70% stenosis

Case
Extracranial Carotid Stenosis
Asymptomatic

Stenosis < 70%

Age > 79 years
Unstable Cardiac Disease
Experienced Operator Unavailable

Procedure Risk > 2.3%

Medical Therapy
Risk Factor Control, Antiplatelets, Statins, ACE inhibitors

Stenosis ≥ 70%

Age ≤ 79 years
Stable Cardiac Disease
Experienced Operator Available

Procedure Risk ≤ 2.3%

Intervention?
Asymptomatic Carotid Disease
ASA 2014 Primary Stroke Recs

• Patients should be prescribed daily aspirin and a statin and screened for other risk factors and appropriate medical therapies and lifestyle changes should be instituted (Class I, Evidence C)

• CEA is reasonable with stenosis >70% if the perioperative risk is < 3%, however effectiveness vs best medical management alone is not well established (Class IIa, Evidence A)

• CAS might be considered in highly selected patients (Class IIb, Evidence B)
CREST Results

Asymptomatic vs Symptomatic Cases

Comparing CAS and CAE Results In Low Surgical Risk Patients

Risk of Peri-procedural Stroke or Post-procedural Stroke Within 4 Years of Procedure (%)

- Asymptomatic patients:
  - Artery Stenting: 4.5 ±0.9
  - Endarterectomy: 2.7 ±0.8
  - P=0.07

- Symptomatic patients:
  - Artery Stenting: 7.6 ±1.1
  - Endarterectomy: 6.4 ±1.1
  - P=0.25

White CJ, J Am Coll Cardiol 2014;64:722–31
Asymptomatic Carotid Disease
ASA 2014 Primary Stroke Recs

• In asymptomatic patients at high risk of complications for carotid revascularization (CEA or CAS), the effectiveness of revascularization vs medical therapy alone is not well established. (Class IIb, Evidence B)

• Screening low risk populations for asymptomatic carotid artery stenosis is not recommended. (Class III, Level of Evidence C).
Time to rethink management strategies in asymptomatic carotid artery disease

A. Ross Naylor


**Figure 1** | Annual rates of stroke in medically treated patients with asymptomatic carotid stenosis stratified for year of publication and baseline severity of stenosis. A sustained decrease in the annual rates of ipsilateral and any stroke has occurred over the past two decades. This decline is evident in both randomized and nonrandomized studies. Adapted from Naylor, A. R. What is the current status of invasive treatment of extracranial carotid artery disease? Stroke 42, 2080–2085 (2011) © Lippincott Williams & Wilkins.
Ongoing Trials for Carotid Stenosis

CREST-2

- CREST-2
  - In patients with $\geq 70\%$ ASX stenosis, to assess:
  - OMT vs CEA
  - OMT vs CAS

- Clinical Coordinating Center – Mayo Clinic Florida
- Statistical and Data Coordinating Center – University of Alabama at Birmingham
CREST-2
Parallel Study Design
(n = 1,240 in each trial)

Endpoint

CAS + Medical
n = 620
Medical
n = 620

CEA + Medical
n = 620
Medical
n = 620

Endpoint = all stroke & death in first 30 days and ipsilateral stroke thereafter up to 4 years.
CREST-2 Secondary Aims

To assess:

- Differences in cognitive function in patients randomized to intensive medical management compared to those randomized to CEA or CAS at 4 years of follow-up.

- Differences in major stroke events at 4-years.

- Differences in primary outcomes affected by age, sex, severity of carotid stenosis, risk factor level, and duration of asymptomatic period.
Ongoing Trials for Treatment of Carotid Stenosis

SPACE-2
- Severe Asx ICA stenosis ≥ 70%
- Optimal Med Rx vs CEA vs CAS
- Trial split into SPACE-2A and SPACE-2B like CREST-2

ECST-2
- Optimal Med Rx vs CAS or ICAE
- Sx or Asx ICA score with predicted 5-year risk < 15%

ACST-2
- CEA vs CAS in Asx Stenosis, 1600 patients recruited; 20% > 75yo; 1% complications
Treatment of Carotid Stenosis
Predictors of Increased Stroke Risk

• ECST Risk Model
  • age, sex, presentation type, time since last event and
  • 2 imaging characteristics (degree of stenosis and type of plaque—smooth/irregular)

• Carotid Plaque
  • Ulcerated “Unstable” Carotid Plaque
  • Carotid Plaque Echolucency

• Microemboli detected by Transcranial Doppler

• Brain MRI
  • Silent Brain Infarcts
  • White Matter Hyperintensities
Vulnerable Carotid Plaque Pathology Characteristics

• Predicted 5-year stroke risk was associated with
  – Plaque thrombus
  – Fibrous content
  – Macrophage infiltration
  – High microvessel density
  – Overall plaque instability

• Not associated with cap thickness, calcification, intraplaque hemorrhage, or lymphocyte infiltration

Howard et al. Symptomatic Carotid Atherosclerotic Disease Correlations Between Plaque Composition and Ipsilateral Stroke Risk; *Stroke* 2015;46; Published online Nov 2014
Ultrasound Plaque Echolucency Among Asx Carotid Stenosis > 50%

Risk of Ipsilateral Stroke
RR 2.61: 1.47–4.63; P=0.001

Gupta at al, Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis: A Systematic Review and Meta-Analysis; Stroke. 2015;46:Published online Nov 2014
Subclinical Vascular Brain Injury

White matter hyperintensities, subclinical infarction, and brain atrophy
CEA vs CAS – Effect of White Matter Disease on MRI

Age related white matter change score

Any Stroke

Disabling Stroke

Fatal or Disabling Stroke

Lancet Neurol 2013; 12: 866–72
Carotid Stenosis Management

• CEA is of proven value for symptomatic carotid stenosis > 50% and CAS is an alternative especially under age 70
• Choice of intervention depends on age, degree of stenosis and other co-morbidities
• Risks for CEA and CAS have declined, but the optimal treatment for Asx stenosis is unclear
• Stroke risk predictors for Asx stenosis include plaque echolucency, thrombus, and MRI subclinical markers
• Medical therapy has improved for ICA stenosis and includes antiplatelets, statins, and aggressive risk factor modification
BACK UP SLIDES
Ongoing Trials for Carotid Stenosis CREST-2 Registry: Objective

• The C2R CAS Registry (C2R) will promote rapid initiation and completion of enrollment in the CREST-2 trial

• Asymptomatic patients
  – Patient age ≥18 and ≤80
  – ≥70% stenosis, standard surgical risk for CEA
  – ≥70% stenosis, high anatomic/physiologic risk for CEA

• Symptomatic patients
  – Patient age ≥18 and ≤80
  – ≥70% stenosis, standard surgical risk for CEA
  – ≥50%-69% stenosis, high anatomic/physiologic risk for CEA
1993–2003, 3120 asymptomatic patients with carotid stenosis >60% were randomized to CEA and deferral of any CEA and followed for up to 5 years
Pooled Analysis of Three Trials

- Three large trials of symptomatic stenosis
  - NASCET, ECST, and VA309
- Any stroke or operative death
- Key point:
  - Benefit is realized quickly

Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial


http://dx.doi.org/10.1016/S0140-6736(10)60239-5
Meta-analyses of the relative risk of stroke or death after CAS and CEA according to the 9 potential risk factors.

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<th>N</th>
<th>n1/N1</th>
<th>n0/N0</th>
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<th>Psig</th>
<th>I², % (Phet)</th>
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<td>17/485</td>
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<td>0.89</td>
<td>0 (0.84)</td>
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Touzé E et al. Stroke. 2013;44:3394-3400