09.16.2020 Carotid Artery Stenosis

PRESENTER: KRISTEN RAUE

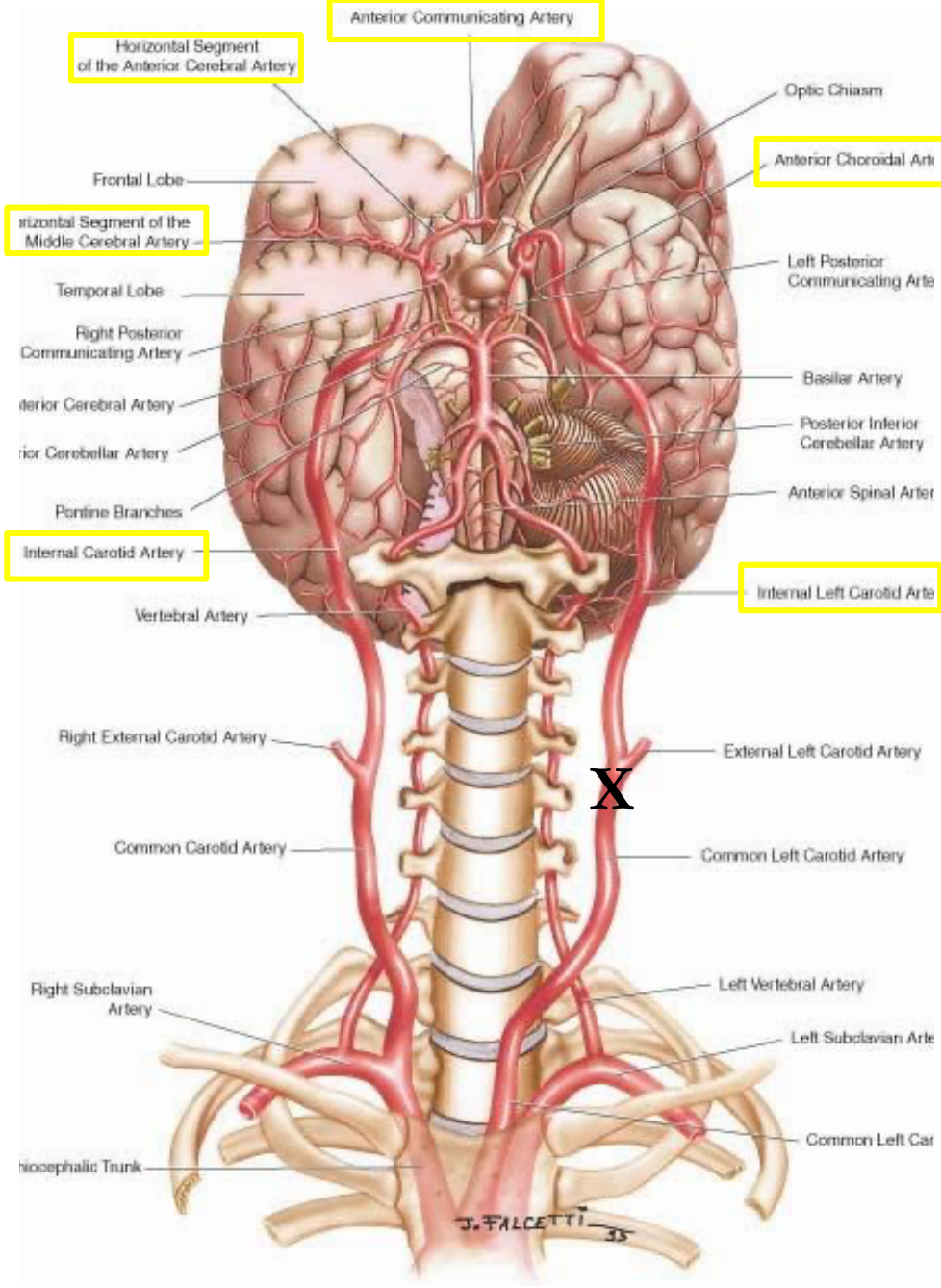
Overview

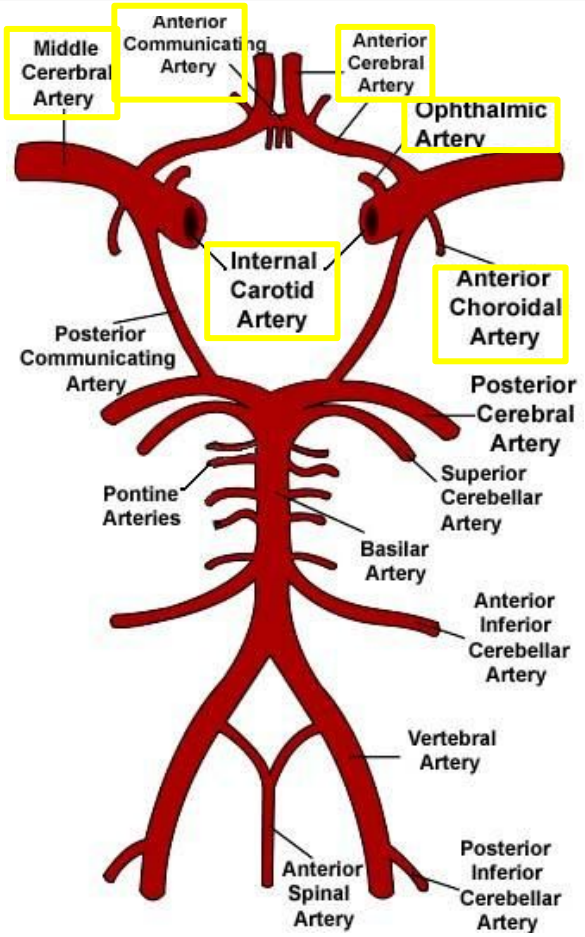
- **Introduction on Carotid Artery Stenosis –** Kristen Raue
- **NASCET Trial –** Kristen Raue
- **CREST Trial –** Jonah Moss

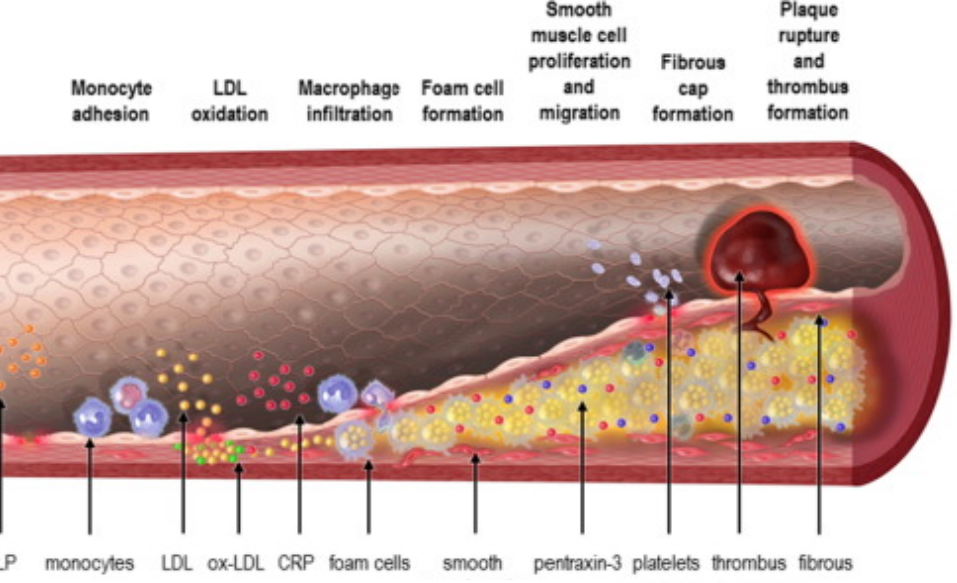
Overview

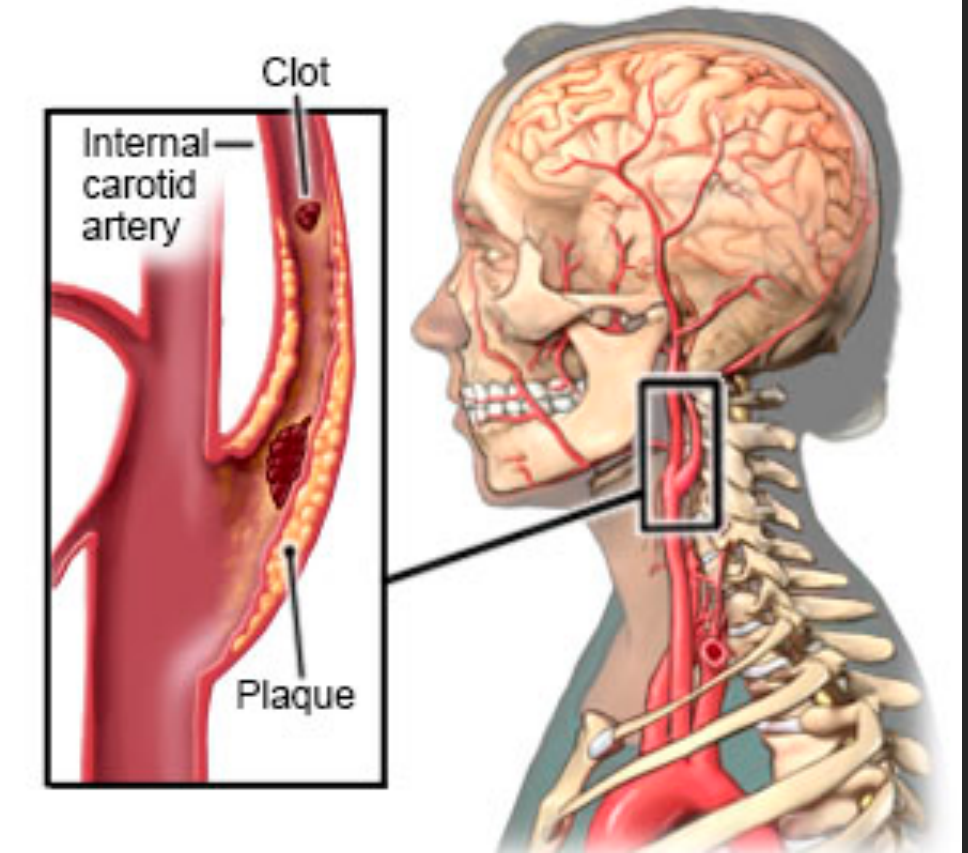
- **Carotid artery stenosis (CAS) is most commonly due to atherosclerosis[1,3]**
- **Atherosclerosis**: build up of cholesterol plaques, or "atheromas," affecting elastic arteries (i.e. carotid) or medium to large muscular arteries (i.e. coronary)[1,3.]
  - Infrarenal abdominal aorta > coronary artery > popliteal artery > carotid artery > circle of Willis
- **Risk factors[2,3]:**
  - Nonmodifiable: genetic abnormalities (e.g. familial hypercholesterolemia), family hx, increasing age, male sex
  - Modifiable: hyperlipidemia (high LDL, low HDL, high Lp(a)), HPTN, obesity, sedentary lifestyle, cigarette smoking, DM, inflammation (high CRP)
- 10-12% of ischemic strokes due to carotid stenosis[2]

Relevant Anatomy: Head & Neck Vasculature









Pathogenesis

Stages of atherosclerotic disease[1,3]:

1) Endothelial cell dysfunction
2) Macrophage and LDL accumulation
3) Foam cell formation
4) Fatty streak
5) Smooth muscle cell migration (PDGF and FGF)
6) Smooth muscle cell proliferation
7) ECM deposition and formation of fibrous plaque
8) Complicated atheroma
9) **Complications: myocardial infarction, cerebral infarction*, transient ischemic attack (TIA)*, aneurysm, peripheral vascular disease**

Clinical Presentation

- **Acute onset of transient ischemic attacks (TIAs) or ischemic stroke with carotid symptoms within the previous six months**[2,4]
  - **TIAs:** neurologic dysfunction self-resolving within 24hrs due to a low flow state (repetitive, stereotyped) or an embolus (vascular territory, amaurosis fugax)
  - **Ischemic stroke**
    - Contralateral homonymous hemianopsia, hemiparaylsis, hemisensory loss
    - Aphasia | Visuospatial neglect, constructional apraxia, dysprosody
  - **Ocular Ischemia/Infarction** (absent pupillary light response | Arterial occlusion, retinal ischemia)
  - **Atypical –** unilateral limb shaking, transient monocular visual loss w/ bright light, syncope
  - **Carotid bruit** may be heard on PE[2,3]
- Patients may be asx but display stenosis upon imaging[5]

Clinical Evaluation

- **Dx imaging:** cerebral angiography (gold standard), carotid duplex ultrasound (CDUS), transcranial doppler, MRA or CTA[2]
  - **Measuring stenosis on imaging*:**
    - **North American Symptomatic Carotid Endarterectomy Trial (NASCET)=** (diameter at most stenotic portion/diameter of normal ICA) x 100%
    - **European Carotid Surgery Trial (ECST)=** (diameter at most stenotic portion/estimated diameter of original ICA) x 100%
    - **Common Carotid (CC)=** (diameter at most stenotic portion/diameter at proximal CCA) x 100%
  - **Measuring stenosis on U/S:** carotid index (peak internal carotid artery velocity/common carotid artery velocity) >4
- **Baseline ipsilateral stroke risk:** age, sex, severity of CAS, type of presenting sx event, time since last sx event, carotid plaque morphology[2]

*50% stenosis with NASCET = 65% stenosis w/ ECST and CC. 70% stenosis with NASCET = 82% stenosis with ECST and CC

Carotid artery stenosis assessed by magnetic resonance angiography

A magnetic resonance angiogram (MRA) in the same patient who underwent carotid duplex ultrasonography shows marked narrowing and stenosis at the origin of the right internal carotid artery (arrow).
Courtesy of Jonathan Kruskal, MD.

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Treatment for Asymptomatic Patients

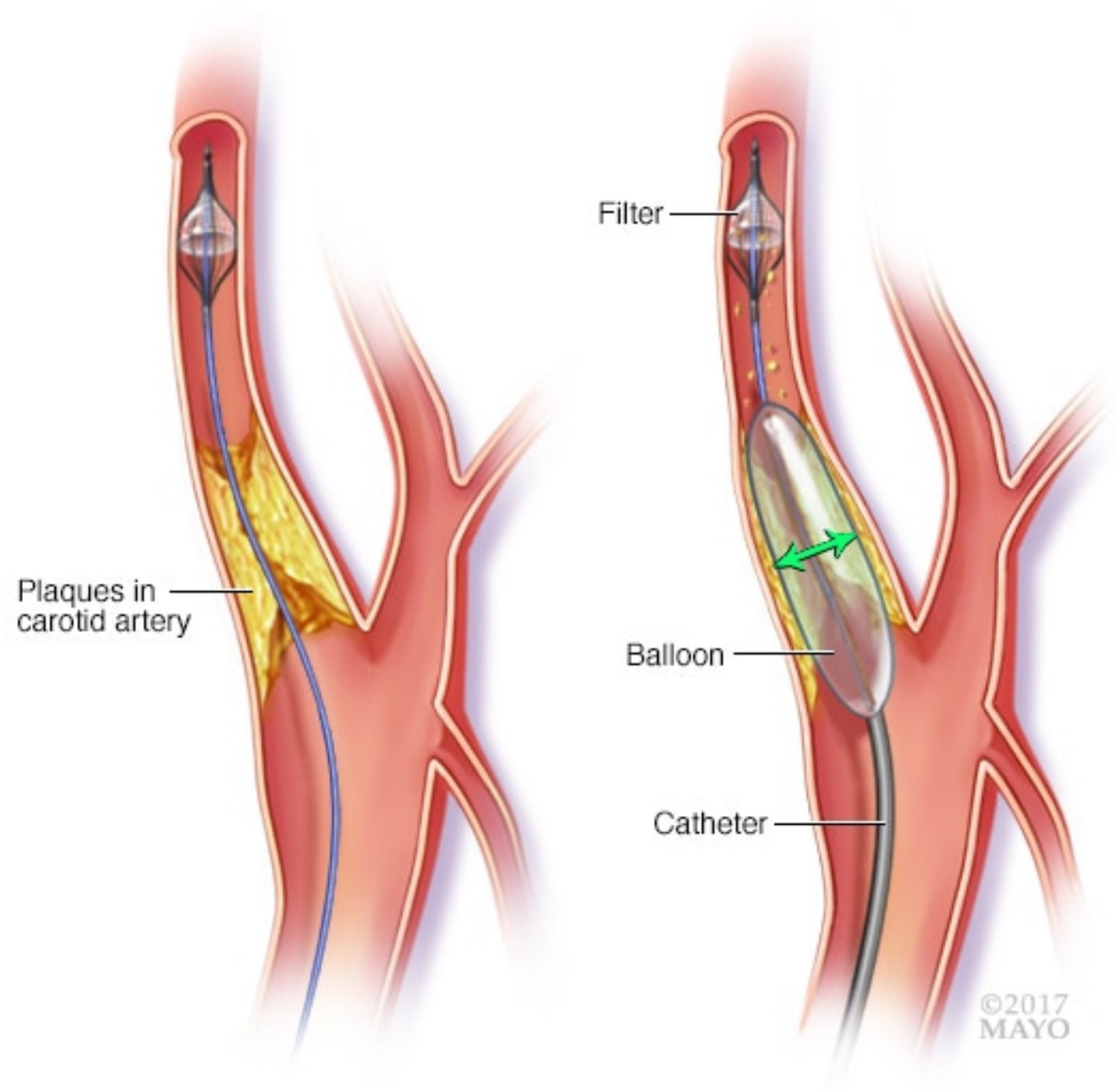
- **Annual risk of ipsilateral stroke 0.5-1% with stenosis ≥ 50%**
  - **Stenosis < 60%**
    - **Medical Management** – statin, antihypertensive(s), antiplatelet agents, lifestyle modifications
  - **Stenosis 60-99%**
    - **Surgical Management: carotid endarterectomy (CEA) or carotid artery stenosis (CAS)**
      - **CEA** – life expectancy ≥ 5 years & perioperative risk stroke/death < 3%
        - VA Trial – ARR 1.0% over 4 years
        - ACAS – ARR 3.0% over 2.7 years
        - ACST – ARR 3.1% over 3.4 years
      - Evidence CAS and CEA provide similar long-term outcomes

Treatment for Symptomatic Patients

- **Stenosis < 50% – medical management**
- **Stenosis 50-69%** (perioperative risk stroke/death < 6%)
  - Men w/ life expectancy ≥ 5y – CEA
  - Women – medical management
- **Stenosis 70-99% – CEA (or CAS)**
  - **CEA** – surgically accessible, no prior ipsilateral CEA or overt anesthesia risks
    - Risks greatest in first 48hrs after onset compared to 3-14 days
  - **CAS** – not suitable to surgery, radiation-induced stenosis, anesthesia risks (unclear if CAS>CEA)
- **Complete occlusion – medical management**

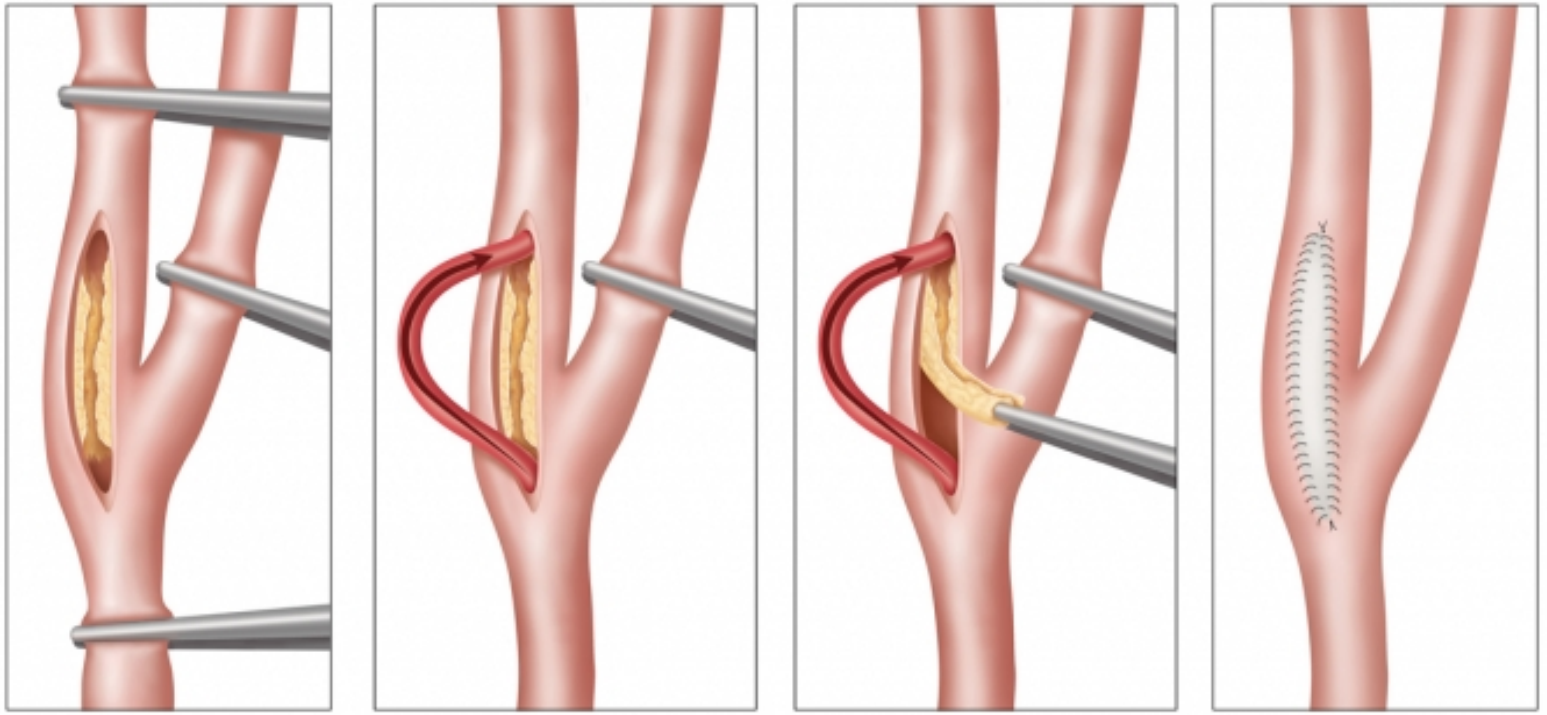
Surgical Intervention- Carotid Artery Stenting (CAS)[6]

1) Percutaneous vascular access is obtained via the common femoral artery*
2) Guide wire and sheath are placed. Embolic protection device is utilized.
3) CAS is pre-dilated;
4) Carotid stent is positioned and deployed using an angioplasty balloon
5) Imaging to ensure proper placement and deployment
6) Embolic protection device, guide wire, and sheath are removed



Surgical Intervention- Carotid Endarterectomy (CEA)[7]

1) Neck incision
2) Stabilization of rostral ICA and ECA and caudal CCA
3) Longitudinal or transverse arteriotomy performed at carotid bifurcation
4) Shunt placed
5) Carotid plaque removed
6) Arteriotomy is closed by suture or carotid patch



Summary

- Common presentation: elderly male with hx of HPTN, hyperlipidemia, DM, obesity and/or smoking[1,2,3,4,5]
- CAS is commonly due to atherosclerosis, which can result in TIA or stroke[1,3]
- ICA supplies the ipsilateral anterior brain, including the ACA, Acomm, MCA, ophthalmic, and lenticulostriate arteries
- Cerebral angiogram is gold standard for imaging, although CDUS or MRA are more commonly used as less invasive[2]
- Three methods can be utilized for measuring stenosis (NASCET, ECST, CC)[2]
- Asymptomatic disease with ≥ 60% stenosis are surgical candidates[2,4,5]
- Symptomatic disease with ≥ 50% stenosis are surgical candidates[2,4,5,6,7]

References

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North American Symptomatic Carotid Endarterectomy Trial (NASCET)

PRESENTER: KRISTEN RAUE

Overview

ORIGINAL ARTICLE

Benefit of Carotid Endarterectomy in Patients with Symptomatic Moderate or Severe Stenosis

Henry J.M. Barnett, M.D., D. Wayne Taylor, M.A., Michael Eliasziw, Ph.D., Allan J. Fox, M.D., Gary G. Ferguson, M.D., R. Brian Haynes, M.D., Richard N. Rankin, M.D., G. Patrick Clagett, M.D., Vladimir C. Hachinski, M.D., David L. Sackett, M.D., Kevin E. Thorpe, M.Math., Heather E. Meldrum, B.A., et al., for the North American Symptomatic Carotid Endarterectomy Trial Collaborators*

The NEW ENGLAND JOURNAL of MEDICINE

Purpose

P- For patients with moderate or severe stenosis, …

I- does carotid artery endarterectomy (CAE)

C- as opposed to medical management

O- result in better outcomes as measured by reduced risk of an ipsilateral stroke and/or stroke-related death?

Eligibility

INCLUSION CRITERIA

- Provide informed consent
- <80 years of age at time of enrollment
- Sx of ipsilateral transient ischemic attacks or a nondisabling stroke within 180 days of enrollment
- Stenosis <70% as measured via angiogram*

EXCLUSION CRITERIA

- Did not provide informed consent
- ≥80 years of age at time of enrollment
- Lack of angiographic visualization of sx artery
- Intracranial stenosis of more clinical significance than carotid stenosis
- Total internal carotid artery occlusion or carotid stenosis of less than 30%
- Comorbid condition with life-expectancy of <5 years
- Debilitating stroke in region of interest
- Nonatherosclerotic carotid disease
- Cardiac lesions likely to cause cardioembolism
- Hx of ipsilateral endarterectomy

Methods

- **Randomized controlled trial** with four-step assessment of outcome events
  1. Participating neurologist and surgeon
  2. Study center neurologists
  3. Blinded steering committee member
  4. Blinded external adjudicators
- **Primary endpoint** = fatal or nonfatal stroke ipsilateral to sx carotid artery within 30-days post-operation or 32-days post-randomization in pts assigned to medical therapy
- Prior to patient enrollment, **providers** at 106 centers were assessed for demonstration for procedural competency and ability to follow through with study requirements

Methods ctd.

- **Clinical evaluations w/ baseline + 1, 3, 6, 9, and 12 mo with every 4 mo thereafter**
  - Blood pressure
  - Heart rate, rhythm, and murmurs
  - 12-point functional status assessment of ability to perform daily activities of living
  - Documentation of hx of vascular disease, DM, HPTN, angina perctoris, MI, intermittent claudication, cigarette status, employment status, current medications/change in medications
  - Blood tests: CBC, PT, BUN, creatinine, fasting/random glucose, fasting cholesterol, HDL, LDL, and triglycerides
  - 12-lead ECG
  - Imaging including angiogram, CT, D/US,
- **Treatment groups**
  - **Carotid endarterectomy** (CAE) **versus medical management** consisting of antiplatelets (ASA, recommended 1300 mg/day), antihypertensives, antilipidemic drugs and/or cardiac drugs
  - Moderate stenosis (50-69%) and low-moderate stenosis (<50%)

Results

- Moderate stenosis (50-69%)
  - CAE reduces risk of ipsilateral stroke and death
- Low-moderate stenosis (<50%)
  - CAE does NOT reduce risk of ipsilateral stroke and/or death

TABLE 2. FAILURE RATES AT FIVE YEARS OF FOLLOW-UP, ACCORDING TO THE EVENT DEFINING TREATMENT FAILURE, IN PATIENTS WITH MODERATE STENOSIS.

EVENT DEFINING TREATMENT FAILURE*	MEDICAL THERAPY	SURGICAL THERAPY	RELATIVE REDUCTION IN RISK	ABSOLUTE REDUCTION IN RISK†	P VALUE‡	NUMBER NEEDED TO TREAT§
	no. of first events (failure rate)¶		percent			
Stenosis 50–69%						
No. of patients	428	430				
Any ipsilateral stroke	80 (22.2)	57 (15.7)	29	6.5±3.0	0.045	15
Disabling ipsilateral stroke	24 (7.2)	11 (2.8)	61	4.4±1.7	0.054	23
Any stroke	113 (32.3)	85 (23.9)	26	8.4±3.5	0.026	12
Any disabling stroke	34 (10.3)	20 (5.3)	49	5.0±2.1	0.070	20
Any stroke or death from any cause	156 (43.3)	120 (33.2)	23	10.1±3.8	0.005	10
Any disabling stroke or death from any cause	86 (25.2)	64 (18.3)	27	6.9±3.2	0.032	14
Stenosis <50%						
No. of patients	690	678				
Any ipsilateral stroke	110 (18.7)	89 (14.9)	20	3.8±2.3	0.16	26
Disabling ipsilateral stroke	27 (4.7)	27 (4.6)	3	0.1±1.3	0.95	1000
Any stroke	151 (26.2)	148 (25.7)	2	0.5±2.7	0.88	200
Any disabling stroke	43 (8.0)	51 (8.7)	—	−0.7±1.7	0.56	—
Any stroke or death from any cause	209 (37.0)	208 (36.2)	2	0.8±3.0	0.97	125
Any disabling stroke or death from any cause	113 (21.9)	120 (21.7)	1	0.2±2.6	0.70	500

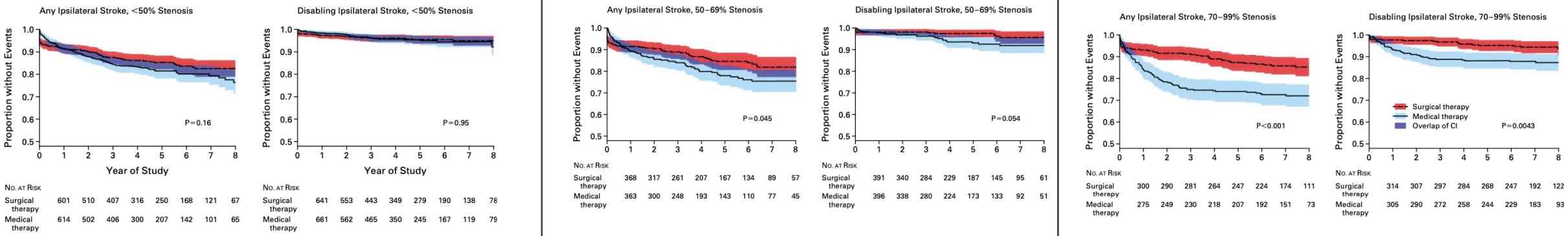
*Events used to calculate the treatment-failure rate include all strokes (at any site) and all deaths from any cause between randomization and the 30th day after surgery for surgically treated patients and during the 32-day period beginning with randomization for medically treated patients.

†Plus–minus values are percent reductions ±SE. The negative number indicates an increase in risk.

‡P values are derived by comparison of the survival curves by the Mantel–Haenszel chi-square test.

§The number needed to treat is the number of patients who would have to be treated with endarterectomy for one outcome event to be prevented at five years. For ipsilateral stroke at two years, the number needed to treat is 20 for patients with stenosis of 50 to 69 percent and 48 for patients with stenosis of <50 percent. For patients with 70 to 99 percent stenosis, the number needed to treat is eight at both two and five years.

¶Failure rates, expressed as percentages, were derived from Kaplan–Meier estimates of survival at five years.



CAE yields greater event-free survival benefit with increasing degree of stenosis

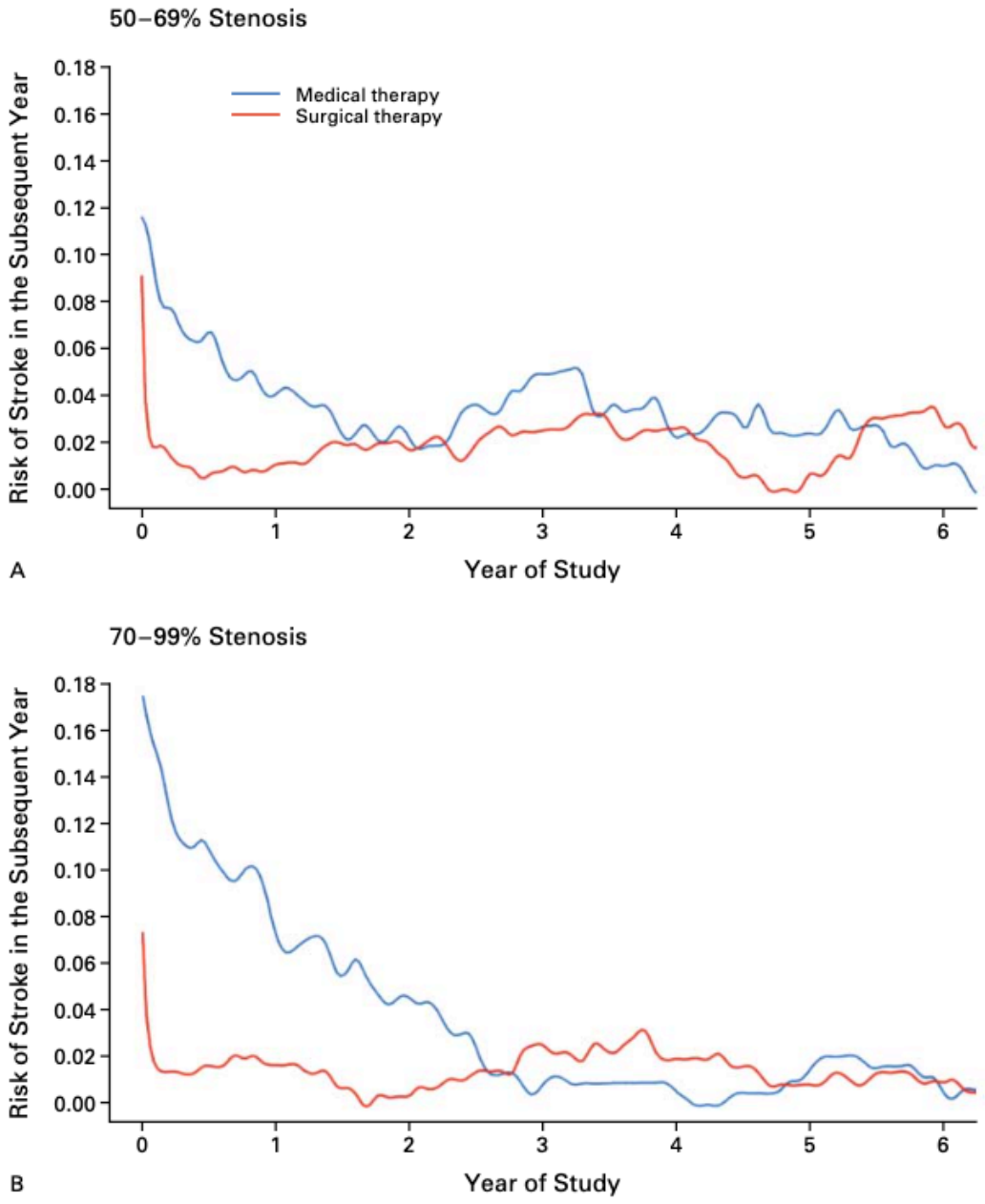


Figure 2. Change in the Risk of Ipsilateral Stroke over Time, According to Severity of Stenosis and Treatment Group.
The curves show the risk of an ipsilateral stroke over the next year among patients who had not had an ipsilateral stroke since randomization. Separate calculations were made every 10 days from randomization to the sixth year of follow-up for patients with stenosis of 50 to 69 percent at base line (Panel A) and those with stenosis of 70 to 99 percent at base line (Panel B).

Risk of ipsilateral stroke over time

- Medical patients have a higher risk of ipsilateral stroke initially and for the first 2-3 years; risk eventually becomes like surgical patients (~2 %/yr)
- Surgical patients demonstrate a rapid decrease in risk of ipsilateral stroke post-operatively; effect is maintained 6-years post-op.

For patients with moderate stenosis, cause of death and type/severity of stroke at randomization and 5-years do NOT differ between medical and surgical groups

TABLE 3. DEATHS AMONG PATIENTS WITH MODERATE STENOSIS, ACCORDING TO CAUSE AND TREATMENT GROUP.

CAUSE OF DEATH	MEDICAL THERAPY (N=1118)	SURGICAL THERAPY (N=1108)
	no. of patients (%)	
Stroke	24	30
Myocardial infarction	35	32
Other ischemic heart disease	36	34
Sudden death	17	23
Other cardiovascular disease	11	11
Cancer	45	33
Respiratory disease	23	10
Other cause	40	45
Total	231 (20.7)	218 (19.7)

TABLE 4. TYPE AND SEVERITY OF FIRST STROKES AFTER RANDOMIZATION AMONG PATIENTS WITH MODERATE STENOSIS, ACCORDING TO TREATMENT GROUP.

TYPE OF STROKE	MEDICAL THERAPY (N=1118)			SURGICAL THERAPY (N=1108)		
	NONDISABLING	DISABLING	FATAL	NONDISABLING	DISABLING	FATAL
	no. of patients					
Ipsilateral hemispheric stroke	126	33	6	94	18	7
Ipsilateral retinal stroke	21	0	0	14	0	0
Contralateral hemispheric stroke	39	13	6	48	12	6
Contralateral retinal stroke	7	0	0	5	0	0
Vertebrobasilar stroke	29	6	3	32	10	3
Subarachnoid hemorrhage	0	0	0	0	0	1
Total	222	52	15	193	40	17

TABLE 5. TYPE OF FIRST IPSILATERAL STROKE OR OTHER EVENT AT FIVE YEARS OF FOLLOW-UP IN PATIENTS WITH MODERATE STENOSIS, ACCORDING TO TREATMENT GROUP.*

EVENT	MEDICAL THERAPY (N=1118)	SURGICAL THERAPY (N=1108)
	no. (%)	
Large-artery hemispheric stroke		
Nonhemorrhagic stroke	121 (63.7)	96 (65.8)
Hemorrhagic infarction	7 (3.7)	6 (4.1)
Large-artery retinal stroke	19 (10.0)	14 (9.6)
Subtotal of events originating in carotid artery	147 (77.4)	116 (79.5)
Lacunar stroke	13 (6.8)	6 (4.1)
Cardioembolic stroke	16 (8.4)	7 (4.8)
Primary intracerebral or subarachnoid hemorrhage	1 (0.5)	4 (2.7)
Death not due to stroke†	1 (0.5)	5 (3.4)
Subtotal of events not originating in the carotid artery	31 (16.3)	22 (15.1)
Uncertain‡	12 (6.3)	8 (5.5)
Total	190 (100.0)	146 (100.0)

*Values for events include all strokes (at any site) and deaths (from any cause) during the 30 days after surgery for surgically treated patients and during the 32 days after randomization for the medically treated patients.

†This category includes only deaths from causes other than stroke in the 30 days after endarterectomy for surgically treated patients and the 32 days after randomization for the medically treated patients.

‡Computed tomography was not performed in these cases.

Risk Factors

Risk factors that doubled the perioperative risk of stroke or death

- Contralateral carotid occlusion (RR, 2.3; 95% CI, 1.1-5.1)
- Left-sided carotid disease (RR, 2.3, 95% CI, 1.4-3.8)
- Prescribed <650 mg/day ASA (RR, 2.3; 95% CI 1.3-3.9)
- No past hx of MI or angina (RR, 2.2; 95% CI 1.3-3.8)
- Lesion elsewhere identified by CTA or MRA ipsilateral to stenosed artery (RR, 2.0; 95% CI 1.2-3.1)
- Dx of DM (RR, 2.0; 95% CI, 1.2-3.1)
- Diastolic BP > 90 mmHg (RR, 2.0; 95% CI, 1.1-3.3)

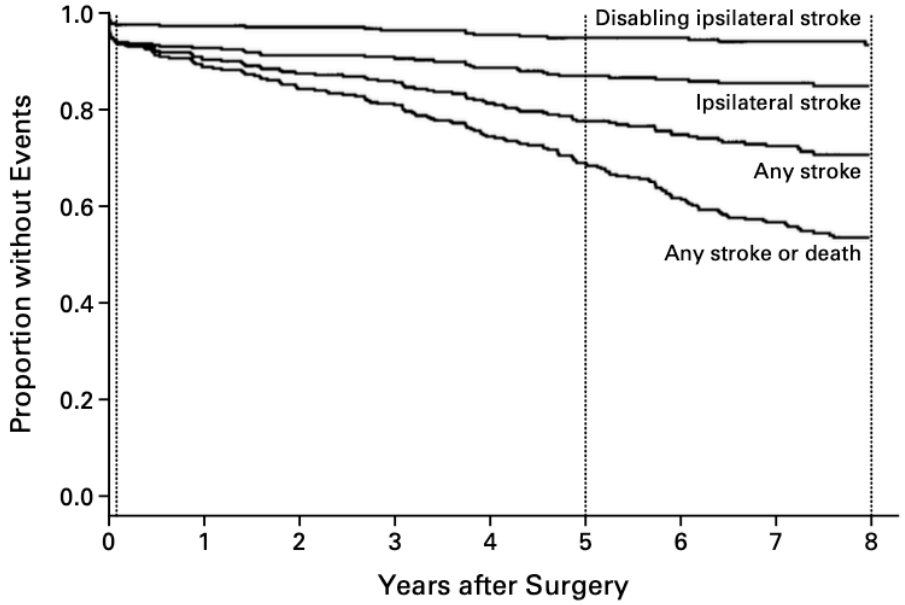
Sex and age did not impact risk

Beneficial factors

- Factors that demonstrated greater long-term benefit from CAE
  - Male sex (male, NNT=12 any stroke, NNT=16 disabling stroke | female, NNT= 67 any stroke, NNT=125 disabling stroke)
  - Recent stroke (NNT=10 any stroke, NNT=13)
  - Recent hemispheric sx (NNT= 11, NNT= 16)
  - >650 mg/day ASA (NNT= 7, NNT= 14)

Risk of adverse events 8-years post-CAE for patients with severe stenosis

- Risk of disabling stroke is minimal and stays minimal 8-years post-CAE
- Risk of ipsilateral stroke increases to 15.2% 8 years post-op
- Approximately 29.4-46.6% of patients with severe stenosis who underwent CAE can expect to have a stroke or be deceased 8-years post-op



Risk of Event (%)	30 days	5 years	8 years
Disabling ipsilateral stroke	2.1	5.1	6.7
Ipsilateral stroke	5.8	13.0	15.2
Any stroke	5.8	22.3	29.4
Any stroke or death	5.8	31.0	46.6

Figure 3. Kaplan–Meier Curves for Event-free Survival after Endarterectomy among 326 Patients with Severe Stenosis. The curves show the probability of avoiding an event, according to four different definitions of an outcome event, among patients with 70 to 99 percent stenosis who underwent carotid endarterectomy. Point estimates are shown for the risk of each event at 30 days, 5 years, and 8 years after surgery. The risk of disabling ipsilateral stroke at 30 days includes all perioperative deaths and disabling strokes. The risks of ipsilateral stroke, any stroke, and any stroke or death include all perioperative deaths and all strokes of any type.

Limitations

- Results cannot be extrapolated to asx CAS
- Limited to high skill of participating surgeons. Caution: CAE only proves beneficial if risk of perioperative stroke/death is <2%
- Difficulty in comparison to previous studies utilizing other methods of stenosis as they overestimate degree of stenosis. Additionally, best compared to studies utilizing angiography to measure stenosis rather than duplex U/S or other non-invasive studies
  - NASCET= diameter at most stenotic portion/diameter of normal ICA x 100%
  - ECST= diameter at most stenotic portion/estimated diameter of original ICA x 100%
  - CC= diameter at most stenotic portion/diameter of proximal CCA x 100%

Summary

- Patients with severe stenosis (70-99%) are great candidates for CAE
- Patients with moderate stenosis (50-69%) benefit less from CAE
  - Patients should be first started on medical therapy
  - CAE may be beneficial if sx reoccur
- Patients with stenosis of <50% are poor candidates for CAE