Contemporary Management of Carotid Disease

"What We Know So Far"

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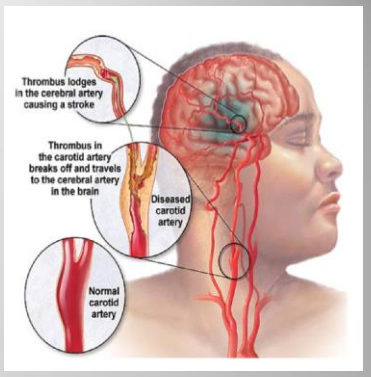
Interventional Cardiology & Endovascular Medicine

Disclosers

NONE

Epidemiology



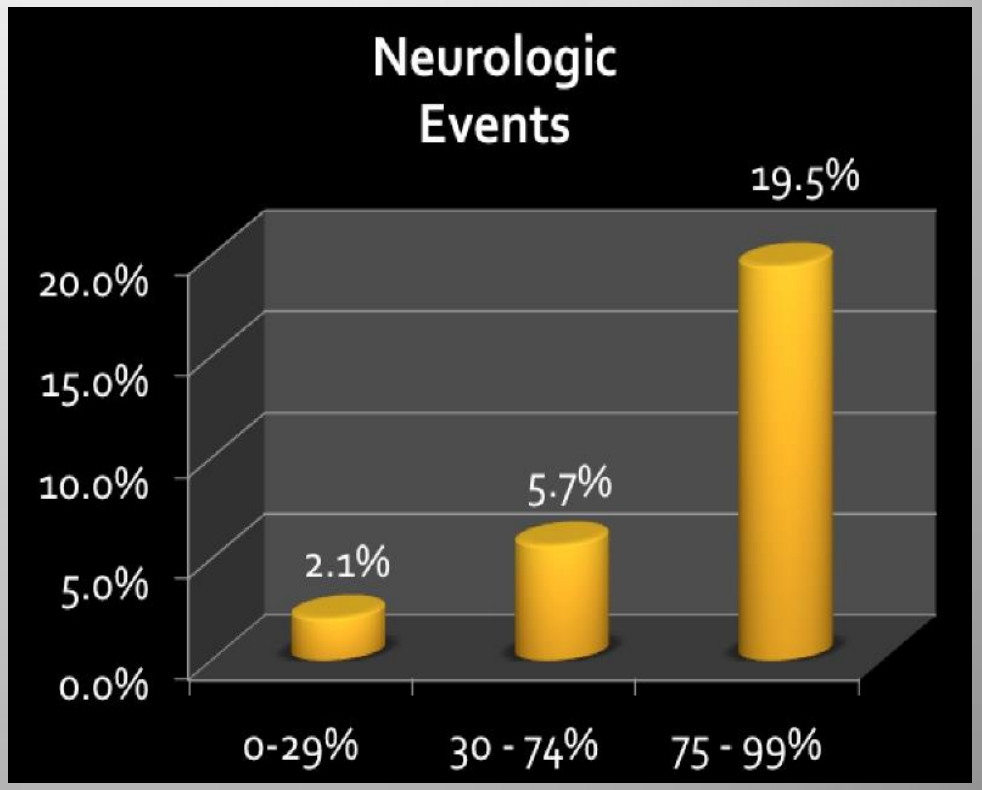
- 80 % of stroke are ischemic
- Approximately 25% of strokes are due to carotid artery disease
- Stroke is the third most common cause of death in the U.S. and the leading cause of serious long-term disability

Risk of Stroke and Carotid Stenosis

1986 NEJM:
500 patisnts with aymptomatic bruit plus abnormal ultraspund

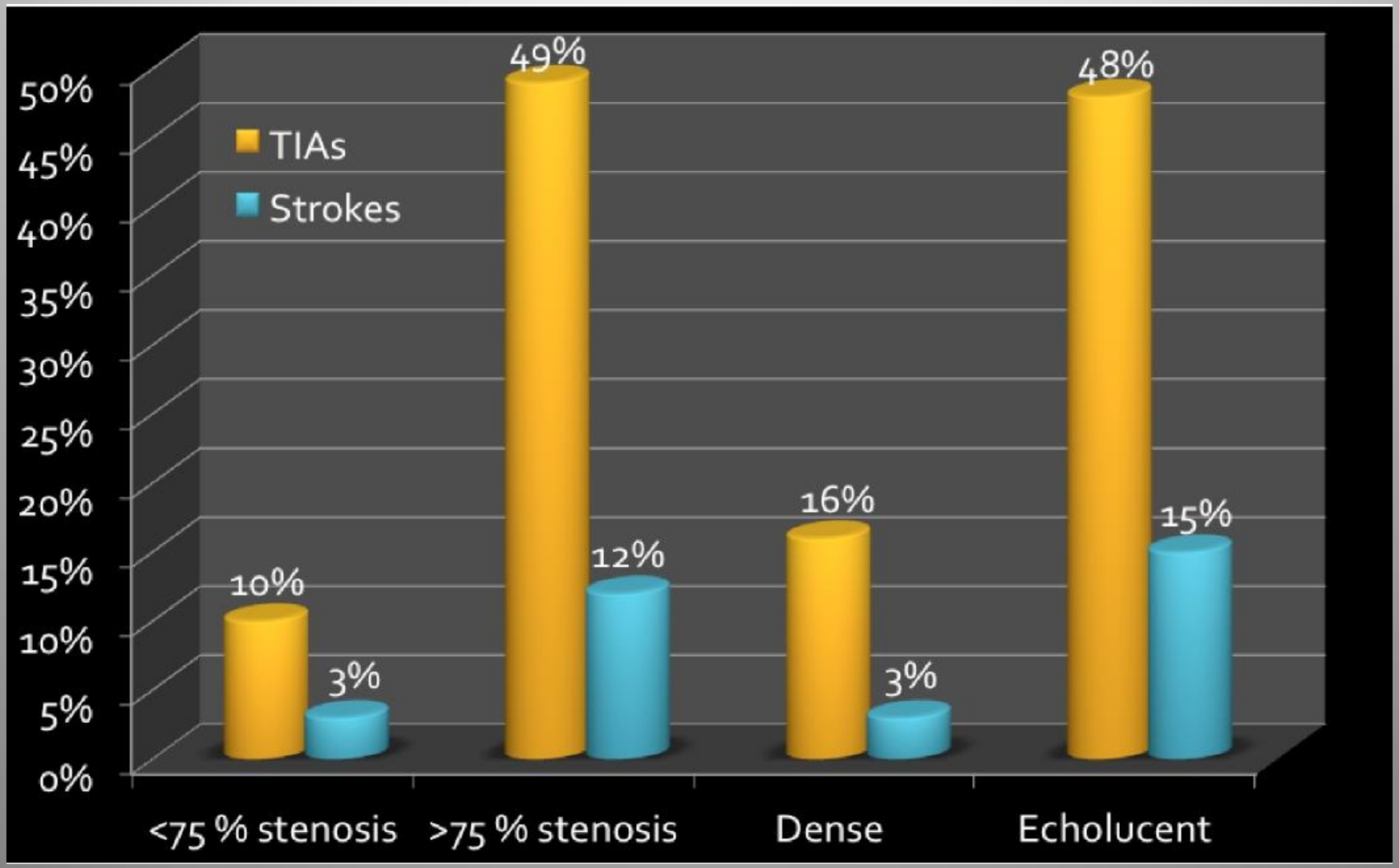
Recorded TIA/Stroke rates

Study period ***4 years***
Mean follow up 26 months



Chambers, et al. N Engl J Med 1986;315: 860-865

Echogenicity

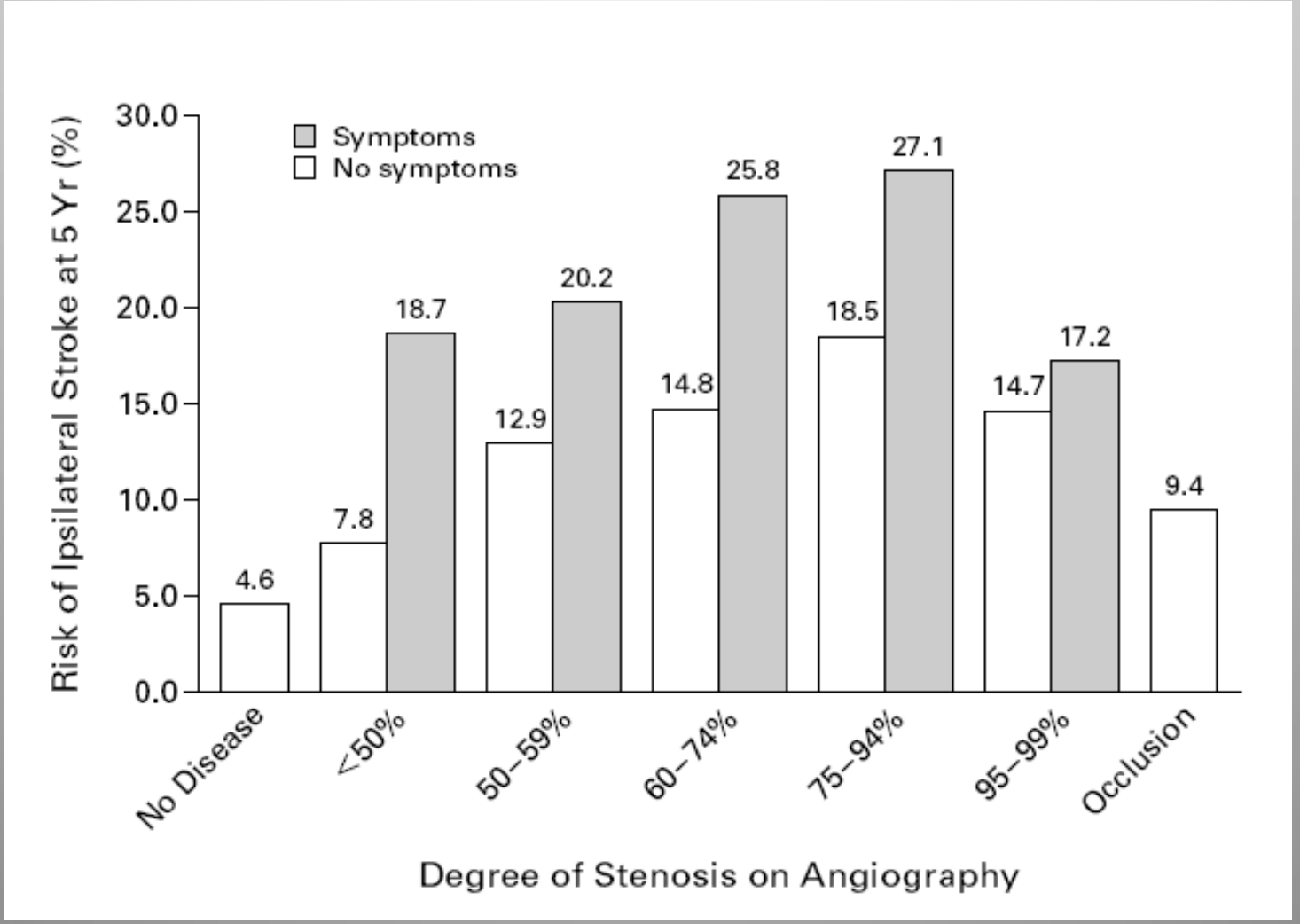


Risk of Stroke and Carotid Stenosis

- Patients with unilateral symptomatic carotid-artery stenosis
- Patients with asymptomatic contralateral stenosis
- The risk of stroke at ***five years*** after study entry in a total of 1820 patients increased with the severity of stenosis

N Engl J Med 2000; 343:1420-1421, Nov 9, 2000.

Risk of Stroke and Carotid Stenosis



Symptoms

- ***Symptomatic patient***
  - Transient Ischemic Attack (TIA)
  - Amaurosis fugax (transient visual loss)
  - Minor non-disabling stroke
  - Cerebral infarction

Fun Facts:

- 35% of patients with a carotid ***bruit*** have >50% carotid stenosis
- Only 50% of patients with significant hemodynamic carotid stenosis have ***a bruit*** noted during physical examination

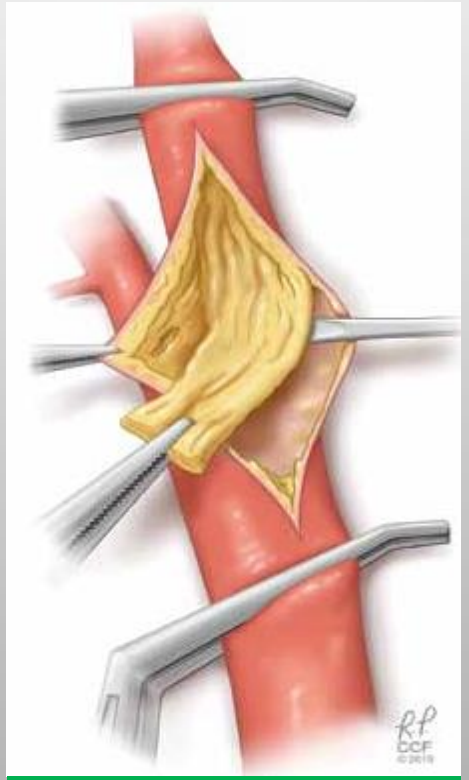
Evaluation

- *Physical Exam*
  - Noting cervical bruits
- *Carotid Duplex Ultrasonography*
  - Most frequent primary test today
- *CT Arteriography (CTA)*
- *MR Arteriography (MRA)*

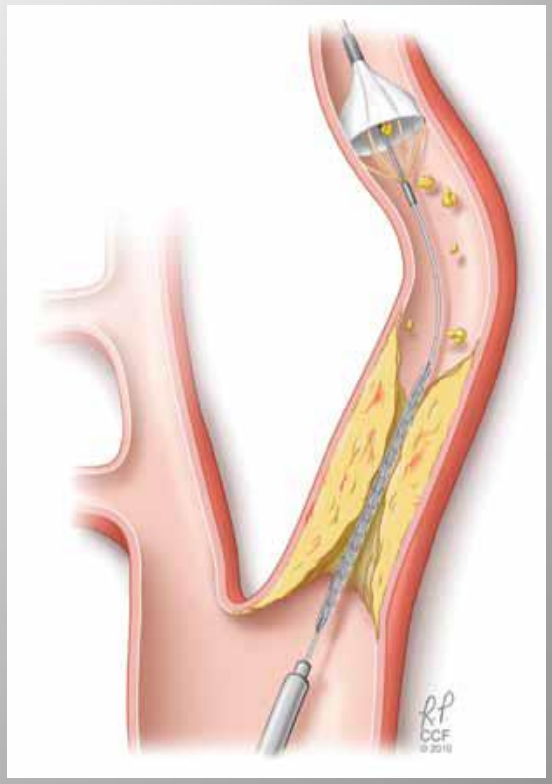
- ***Diagnostic angiography***
  - Considered highly accurate
  - Standard in clinical trials

Treatment Options

Medical therapy



Carotid Endarterectomy



Carotid artery Stenting

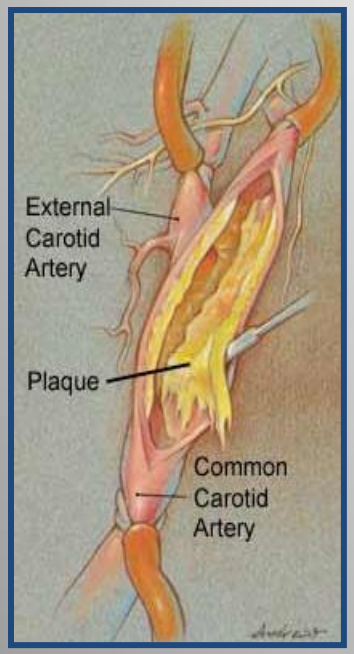
Medical Therapy

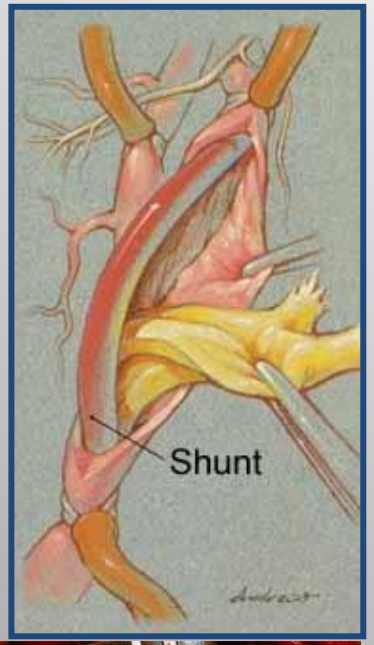
- Rationale:
  - Pathophysiology is thrombosis or atherosclerotic *debris release* from carotid artery plaque
  - Treatment directed toward risk factor reduction and thrombosis prevention, and should be a mainstay of treatment post procedure
- Optimal medical therapy includes:
  - Risk Factor Modification
  - Medications
- Medical therapy should be first course of therapy for:
  - Asymptomatic patients with <60% stenosis
  - Symptomatic patients with <50% stenosis

Medical Therapy

- Goals
  - Reduce the risk of future stroke
  - Control progression of carotid atherosclerosis
- Strategies to achieve goals
  - Antiplatelet or Anticoagulation therapy
  - Antihypertensive therapy
  - Statin therapy to lower serum cholesterol
  - Aggressive glycemic control
  - Quit smoking
  - Limit alcohol consumption
  - Diet and exercise
  - Duplex ultrasound monitoring for patients with stenosis of 50% or more

Carotid Endarterectomy (CEA)





Surgical procedure to ***<u>remove plaque</u>*** from the carotid artery

Goal: reduce future stroke risk

Gold standard therapy in patients at low surgical risk but who require reestablishment of blood supply and removal of plaque to prevent embolization

The superiority of CEA with medical therapy in comparison to medical therapy alone has been demonstrated in randomized prospective studies for two classes of Carotid Artery Disease patients:

- Symptomatic patients with stenosis >50%
- Asymptomatic patients with stenosis >75%

CEA vs. Medical Therapy
NASCET: North American Symptomatic Carotid Endarterectomy Trial

Design	Prospective, Multicenter, Randomized Controlled Trial
Stratification	Endarterectomy + Medical Care (n=616) vs. Medical Care Alone (n=596)
Hypothesis	To test the potential benefit of CEA in patients with moderate or severe stenosis; standard risk patients

Subjects:	Randomized 1,212
Sites:	50 (US and Canada)

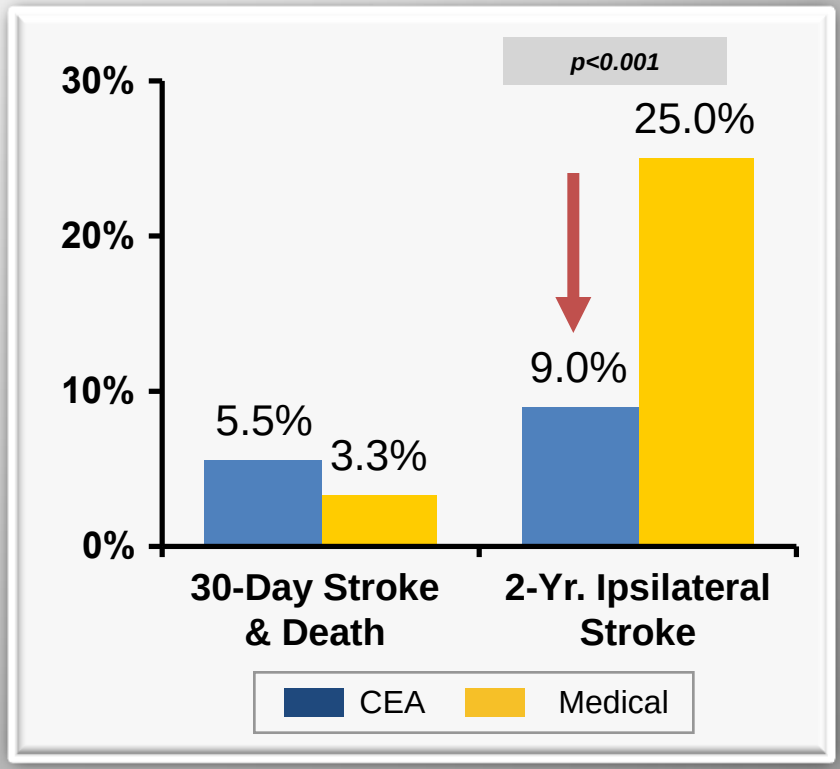
Primary Endpoint:	Ipsilateral stroke
Follow-up:	30 days, 1 year, & 2 years

- **Patients stratified according to degree of stenosis:**
  - **moderate (<70%)**
  - **severe (70-99%)**
- **Trial demonstrated clear benefits from CEA relative to medical therapy with aspirin in symptomatic patients at standard risk for surgery.**

NASCET Collaborators. *Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High Grade Carotid Stenosis* **N Engl J Med 1991; 325:445-53**

NASCET Results

- Results
  - ***Symptomatic patients with ≥ 70%*** carotid stenosis derived substantial long term benefit from CEA
    - Medical event rate: close to 26%
    - CEA event rate 9%
  - ***Symptomatic patients with moderate stenosis (50 – 69%)***, benefited much less (p = 0.045)
  - ***Patients with <50%*** stenosis showed no benefit from CEA
  - Safety monitoring committee stopped trial early for patients with 70 – 99% stenosis after ***significant benefit*** became apparent



NASCET Collaborators. *Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High Grade Carotid Stenosis* **N Engl J Med 1991; 325:445-53**

CEA vs. Medical Therapy
ACAS: Asymptomatic Carotid Atherosclerosis Study

Design	Prospective, Multicenter, Randomized Controlled Trial
Stratification	CEA + aspirin & risk factor reduction (n=825) vs. aspirin & risk factor reduction alone (n=834)
Hypothesis	To determine whether the addition of carotid endarterectomy to aggressive medical management can reduce the incidence of cerebral infarction in patients with asymptomatic carotid artery stenosis

Subjects:	Randomized 1,662 (follow-up on 1,659)
Sites:	39 (US and Canada)
Enrollment End:	1993

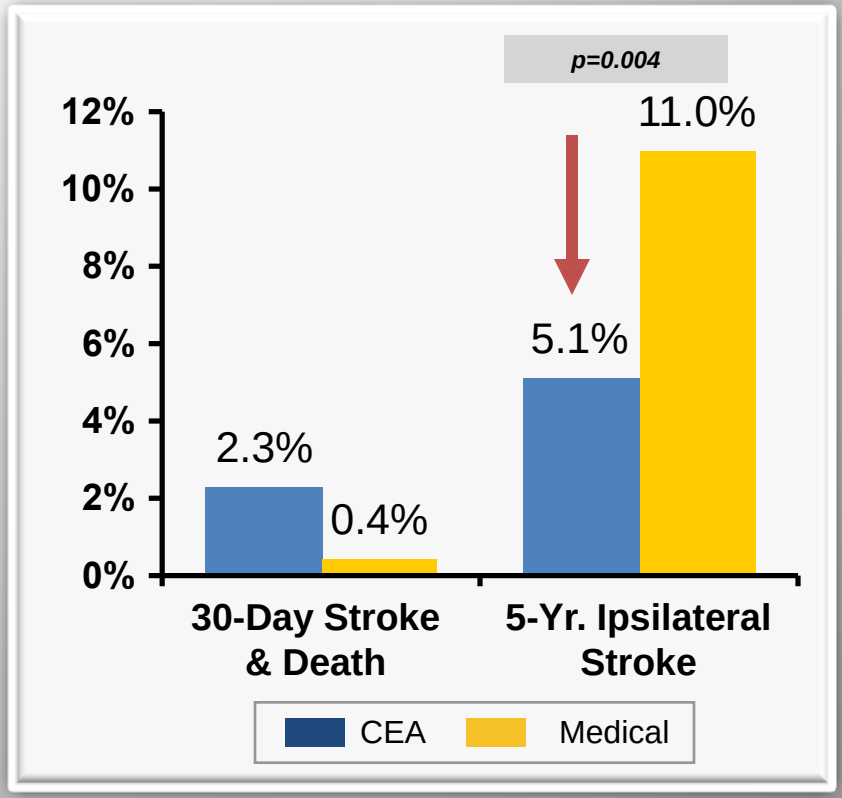
Primary Endpoint:	30-day perioperative stroke or death plus subsequent stroke ipsilateral to the treated carotid artery
Follow-up:	30 days, 1 year, & 2 years

Trial demonstrated clear benefits from CEA relative to medical therapy with aspirin in symptomatic patients at standard risk for surgery.

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *Endarterectomy for Asymptomatic Carotid Artery Stenosis*. JAMA 1995;273:1421-1428

ACAS Results

- ***30-day stroke and death*** rate was higher in the CEA group: 2.3% vs. 0.4%
- Absolute risk reduction of 5-year ipsilateral stroke was 5.9 %
- 1.2% stroke risk from pre-op angiogram



Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *Endarterectomy for Asymptomatic Carotid Artery Stenosis*. **JAMA 1995;273:1421-1428**

NASCET/ACAS Trials Summary

- NASCET/ACAS were key trials that set up ***CEA as the standard of care*** for carotid disease vs. Medical Management

- Established AHA recommendations for ***perioperative stroke risk***
  - Symptomatic ≥ 70% stenosis < 6% (Peri-operative Stroke & Death risk)
  - Asymptomatic ≥ 60% stenosis <3% (Peri-operative Stroke & Death risk)

- ***No Octogenarians*** (80 years old) enrolled in these studies

- ***30 day results*** not as definitive as long term results for absolute risk reduction for stroke

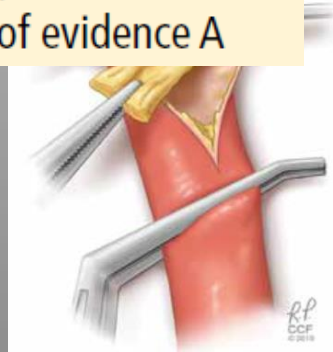
- ACAS and NASCET are ***NORMAL-RISK*** trials and cannot be directly compared to the high-risk CAS trials

NASCET Committee: Stroke 22 (6) 711-720, 1991; NASCET Committee: **JAMA 273 (18): 1421-1428, 1995.**

Carotid Endarterectomy (CEA)

American Heart Association and American Stroke Association recommendations on carotid endarterectomy for carotid stenosis

	RECOMMENDATION	LEVEL OF RECOMMENDATION
Symptomatic stenosis		
High-grade (≥ 70%)	Carotid endarterectomy performed by a surgeon with a perioperative morbidity rate < 6%	Class I Level of evidence A
Moderate (≥ 50% and < 70%)	Carotid endarterectomy, depending on patient-specific factors such as age, sex, comorbidities, and severity of initial symptoms	Class I Level of evidence A
Mild (< 50%)	No indication for endarterectomy	Class I Level of evidence A
Asymptomatic stenosis		
High-grade (≥ 60%)	Endarterectomy performed by a surgeon with a perioperative morbidity and mortality rate < 3%	Class I Level of evidence A



Carotid Endarterectomy (CEA)

- Anatomical limitations for CEA

Carotid Artery Stenting (CAS)

- Carotid artery stenting is a less invasive alternative to CEA
  - Goal to reduce future stroke risk
- Components of CAS include
  - Stent
    - Stabilizes and “traps” the plaque
    - Reduces the flow pressures on the plaque
    - Increases blood flow
  - Embolic Protection Device (EPD)
    - Designed to prevent embolization of debris released during a stenting procedure

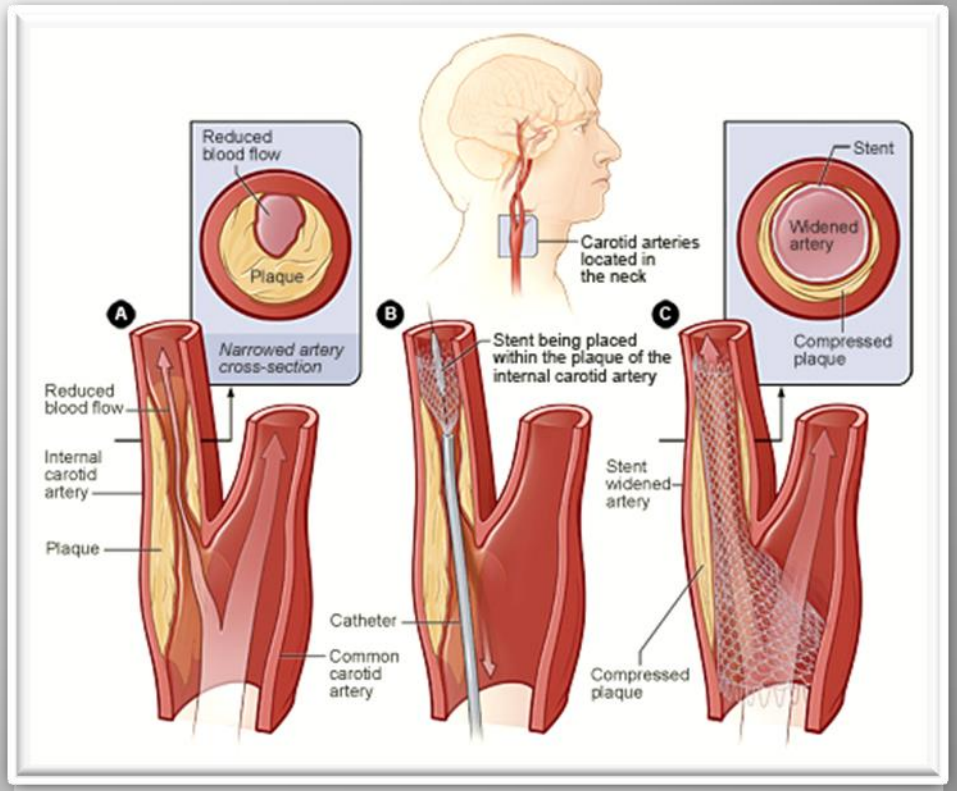
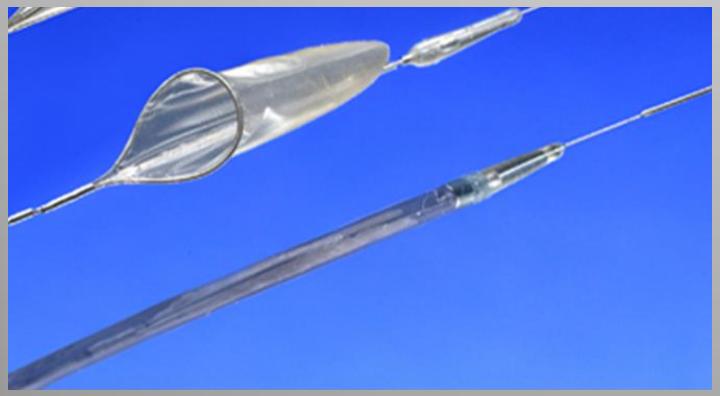


Image courtesy of the NHLBI

Embolic Protection

- DEP devices
  - Filters
    - Porosity 100-150 µm
  - Distal occlusion
  - Flow reversal



Carotid Stenting

Carotid Stenting

CEA vs. CAS
CREST: Carotid Revascularization Endarterectomy vs. Stenting Trial

Design	Prospective, Multicenter, Randomized Controlled Trial
Stent/EPD	CEA (n=1240) vs. CAS: (n=1262)
Hypothesis	1. Superiority – Hazard Ratio for CAS vs. CEA with multi-year follow-up (NIH Analysis) 2. Non-inferiority – CAS is not worse than CEA at 1 year follow-up (FDA analysis)

Subjects:	Lead-in Randomized	1,564 2,522
Sites:	117 (108 US, 9 Canada)	
Follow-up:	1 mo, 6 mos, every 6 mos for 4 years	

Enrollment:	First Patient	Dec 00
	Lead-in completed	Apr 08
	Randomized completed	Jul 08
	First data presented	Feb 10

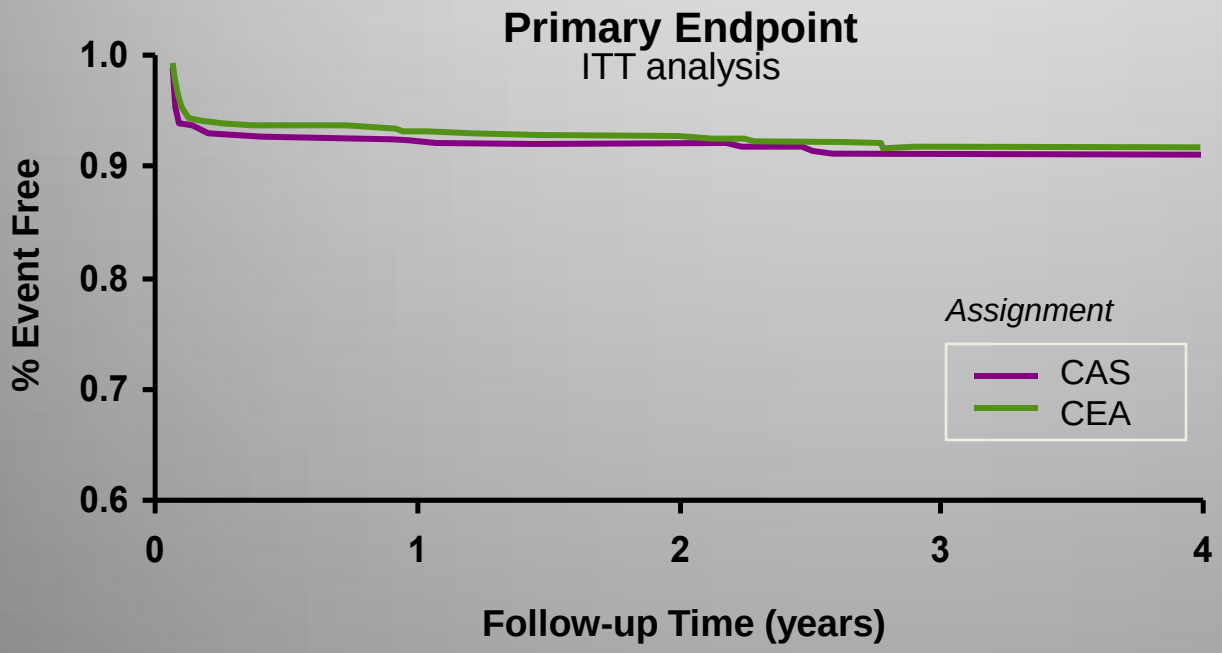
- CREST represents the largest, most rigorous, prospective randomized trial to show both stenting and surgery are safe and effective.
- Both CAS and CEA treatment groups had very low event rates confirming safety and effectiveness.
- CAS was proven non-inferior to CEA for the primary endpoint, and death, stroke, or MI at 30 days

Lal BK, Brott TG. The Carotid Revascularization Endarterectomy vs. Stenting Trial completes randomization: Lessons learned and anticipated results. **J Vasc Surg 2009**; 50:1224-1231

CREST Primary Endpoint: Stenting and Surgery Found to be Equally Durable

Any death, stroke or MI within the perioperative period plus ipsilateral stroke out to 4 years

CAS	CEA	Hazard Ratio	P-value
7.2%	6.8%	HR = 1.11; 95% CI: 0.81-1.51	0.51



Peri-procedural period defined per protocol as 30 days post-procedure for all patients receiving assigned therapy within 30 days from randomization, or 36 days after randomization for all patients not receiving assigned treatment within 30 days

Clark, CREST Presentation at International Stroke Conference on **February 26, 2010**

CREST
Peri-procedural Findings

Outcome	CEA %	CAS %	p value
Periprocedural stroke+MI+death	4.5	5.2	0.38
Periprocedural stroke	2.3	4.1	0.01
- Major ipslateral stroke	0.3	0.9	0.09
- Minor ipsilateral stroke	1.4	2.9	0.009
Periprocedural MI	2.3	1.1	.03
Periprocedural death	0.3	0.7	0.18
Periprocedural cranial nerve injury	4.8	0.3	.001

win

win

win

Thomas G. Brott N Eng Journal of Med 20

Pre-specified Secondary Analysis by Symptomatic Status:
Peri-procedural period

Death, Stroke, MI

	CAS	CEA	HR	P-value
Asymptomatic	3.5%	3.6%	HR = 1.02; 95% CI: 0.55-1.86	0.96
Symptomatic	6.7%	5.4%	HR = 1.26; 95% CI: 0.81-1.96	0.30

Death, Stroke

	CAS	CEA	HR	P-value
Asymptomatic	2.5%	1.4%	HR = 1.88; 95% CI: 0.79-4.42	0.15
Symptomatic	6.0%	3.2%	HR = 1.89; 95% CI: 1.11-3.21	0.019

Peri-procedural death, stroke rates for both CAS and CEA meet AHA guidelines in both asymptomatic and symptomatic patients

Brott TG., et al Stenting Compared to Endarterectomy for Treatment of Carotid Artery Stenosis. New England Journal of Medicine 2010; 363 11-23

CREST
4 years Findings

Outcome	CEA %	CAS %	p value
4 years stroke+MI+death	6.8	7.2	0.51
4 years stroke	2.3	2	0.085

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Pre-specified Secondary Analysis by Symptomatic Status:

Peri-procedural period plus ipsilateral stroke out to 4 years

Death, Stroke, MI

	CAS	CEA	HR	P-value
Asymptomatic	5.6%	4.9%	HR = 1.17; 95% CI: 0.69-1.98	0.56
Symptomatic	8.6%	8.4%	HR = 1.08; 95% CI: 0.74-1.59	0.69

Death, Stroke

	CAS	CEA	HR	P-value
Asymptomatic	4.5%	2.7%	HR = 1.86; 95% CI: 0.95-3.66	0.54
Symptomatic	8.0%	6.4%	HR = 1.37; 95% CI: 0.90-2.09	0.14

No evidence of a difference for either treatment by symptomatic status

Brott TG., et al Stenting Compared to Endarterectomy for Treatment of Carotid Artery Stenosis. New England Journal of Medicine May 2010

CREST Findings
Age

Younger patients have better outcome with CAS while older patients have better outcome with CEA

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120 days ***stroke and death risk***

Age <70 yrs : CAS – 5.8% CEA – 5.7%

Age >70 yrs : CAS – 12% CEA – 5.9%

Arterial tortuosity and calcification in elderly prones to catheter provoked cerebral emboli

Bonati LH Lancet 2010

CEA vs. CAS

Carotid Endarterectomy (CEA)		Carotid Artery Stenting (CAS)	
Pros	***Cons***	***Pros***	***Cons***
↓ Periprocedural stroke	↑ MI	↓ Periprocedural MI	↑ Periprocedural stroke
	↑ Cranial nerve injury	No cranial nerve injury	
	↑ Wound infection	↓ Wound infection	
	Required GA	No GA required	
	Longer recovery	Minimally invasive	

So, What is the Optimal Strategy?

Matching Patient to Intervention

Treatment decisions depends on patient-specific factors

Risk factors for CEA

Risk factors for CAS

Medical

Surgical / Anatomical

Risk Factors for CEA

Medical Risk Factors

- ☐ CHF and left ventricular dysfunction
- ☐ Unstable angina or recent MI (<30 days)
- ☐ Coronary artery disease (CAD)
- ☐ Open heart surgery needed within 6 weeks
- ☐ Severe pulmonary dysfunction

- risk of worse outcome
- Similar stroke and death rate between low and high risk patient

Mozes J Vasc Surg 2004

Risk factors for CEA

Surgical / Anatomical risk factors

Surgical Factors

- ☐ Restenosis after prior CEA
- ☐ Previous ablative neck surgery (e.g. radical neck dissection, laryngectomy)
- ☐ Previous neck irradiation
- ☐ Contralateral vocal cord paralysis
- ☐ Tracheostomy

↑ Local complications

- Infection
- Nerve injury
- Cervical haematoma
- Wound dehiscence

Risk Factors for CEA

Surgical / Anatomical risk factors

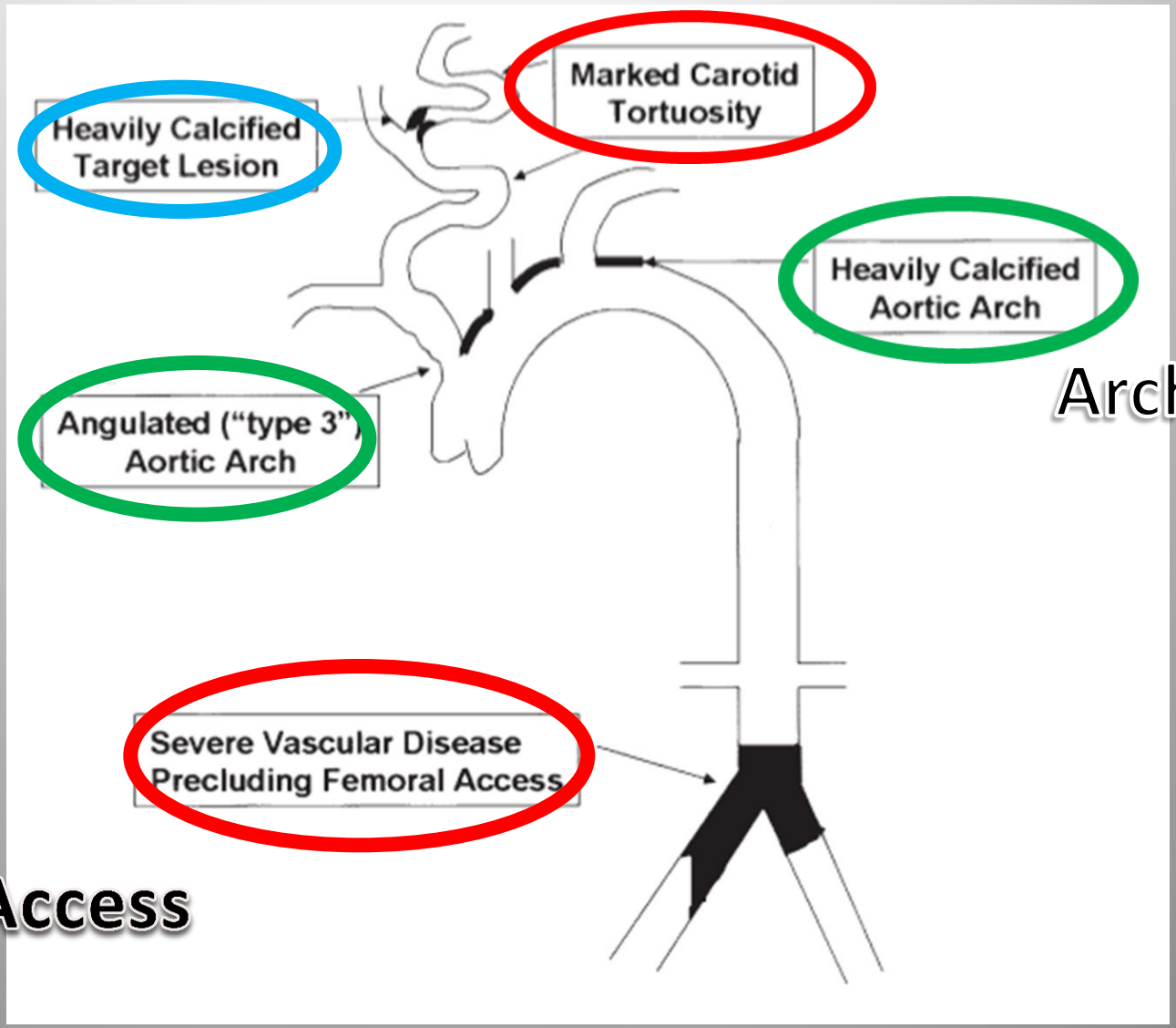
Anatomical Factors

- ☐ High carotid bifurcation (above C2)
- ☐ Extension of atherosclerotic lesion into intracranial ICA or proximal CCA below clavicle

→ ↑ Intraoperative or Peri-operative stroke

Risk Factors for CAS

Target Vessel



Individualized Management

Optimal treatment selection specific for each patient

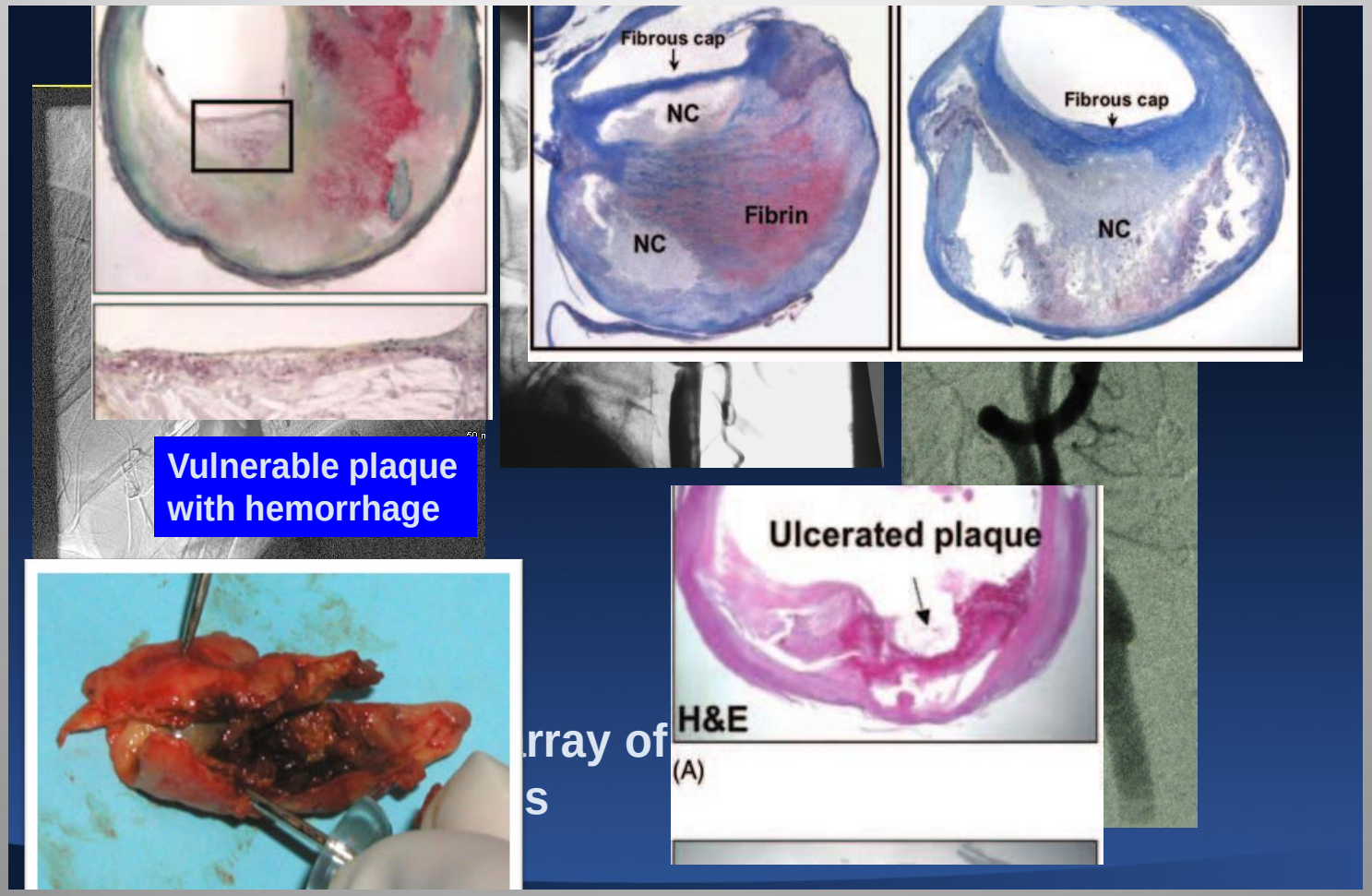
Lowest morbidty rate

Most favorable outcomes

What's on the Horizon?

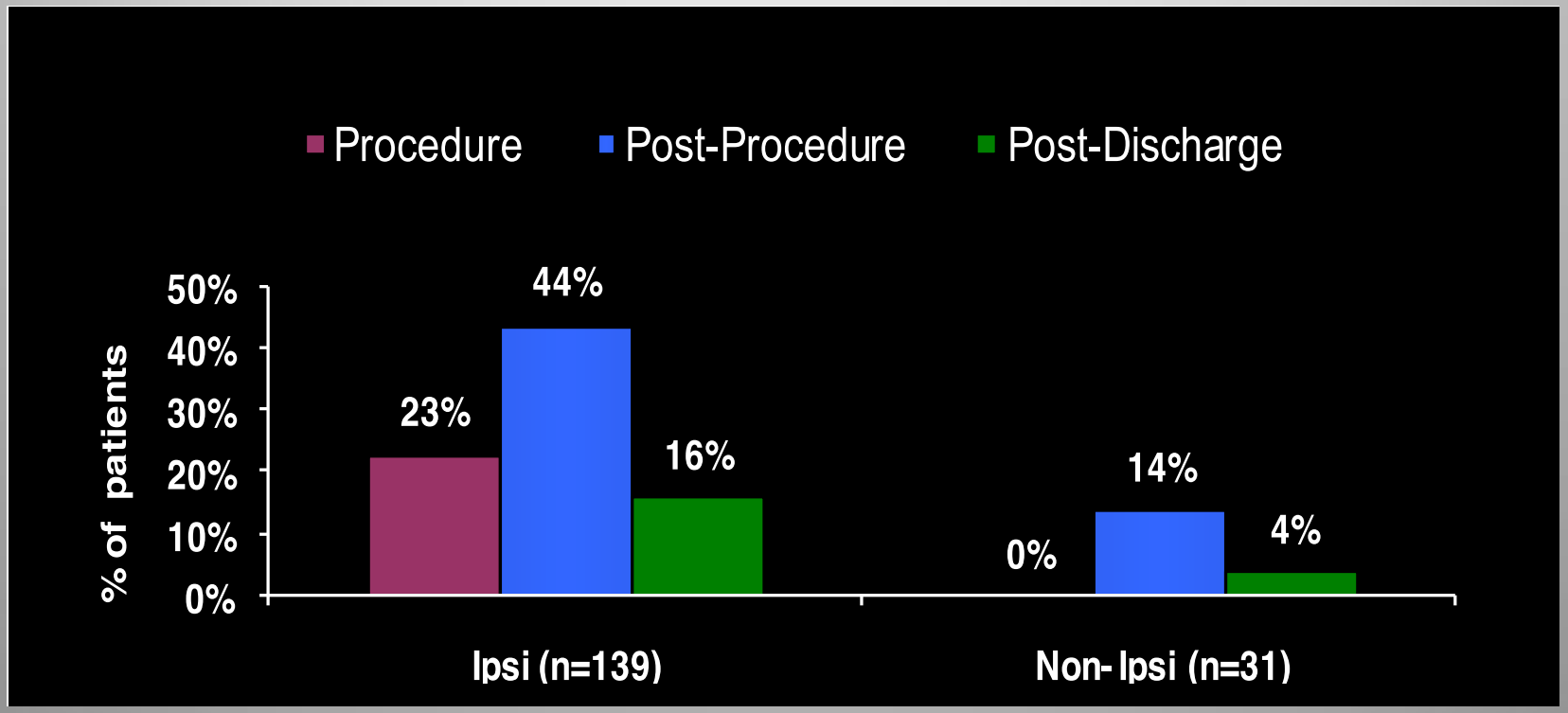
Plaque Imaging

Do All Plaques Behave the Same?



Understanding Peri-Procedureal Strokes

Not all strokes appear on the day of the procedure



Understanding Peri-Procedureal Strokes

Delayed neurologic Events 1-30 days

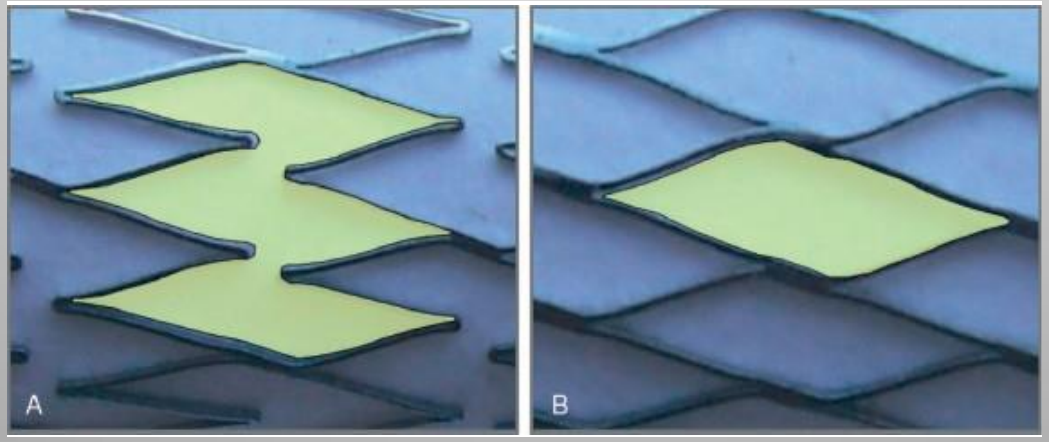
Open vs. Closed Cell design

	Total population		
	Patients	All events	Post-procedural events
Open cell	937	39	32
Closed cell	2242	51	29
Total	3179	90	61
Cell type			
Open cell		4.2%	3.4%
Closed cell		2.3%	1.3%
Total	3179	2.83%	1.9%

2/3 of neuro events were delayed (1-30d)

Stent Design

Open vs. Closed cell



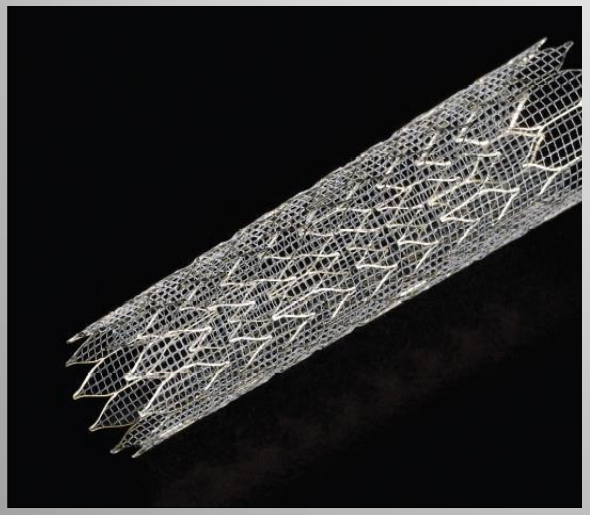
What is The Optimal Carotid Stent?

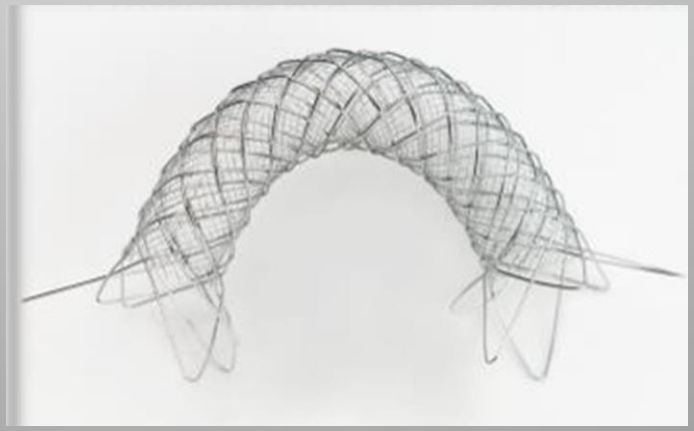
- **Needs to offer:**
  - Scaffolding
  - Lesion Containment
  - Conformability
  - Visibility
  - Ease of use
  - Low profile

New Mesh Stent Design

- Gore
- Terumo
- InspireMD

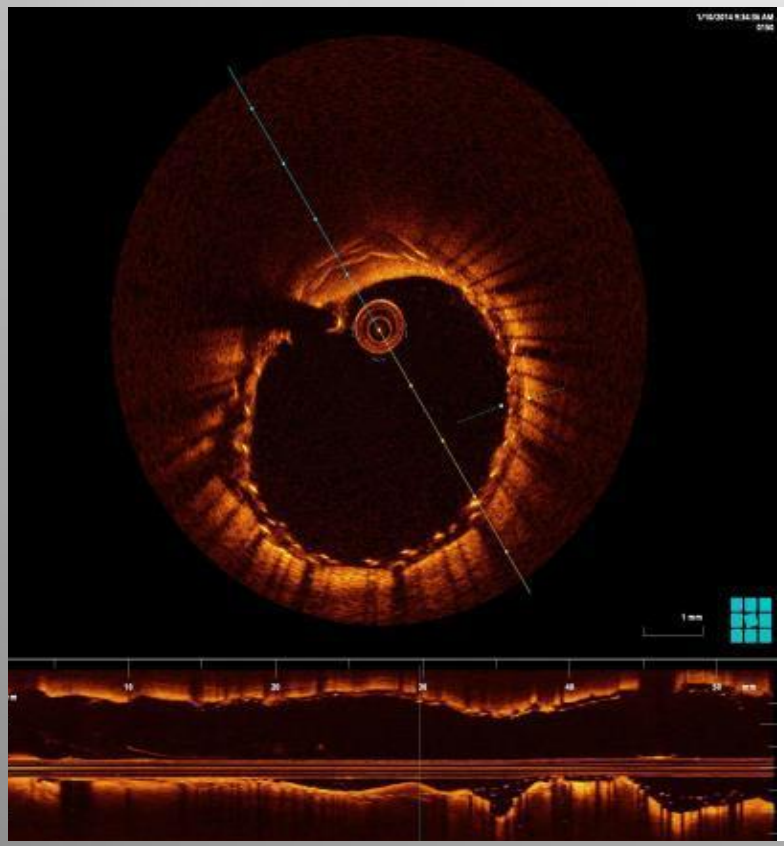
New Mesh Stents

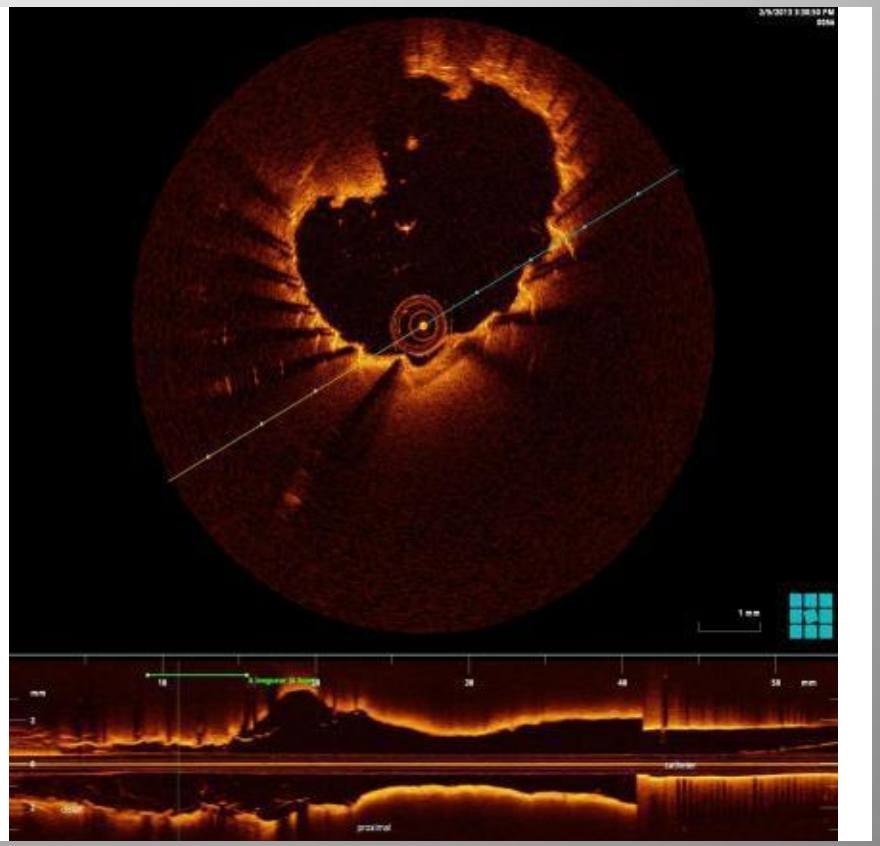




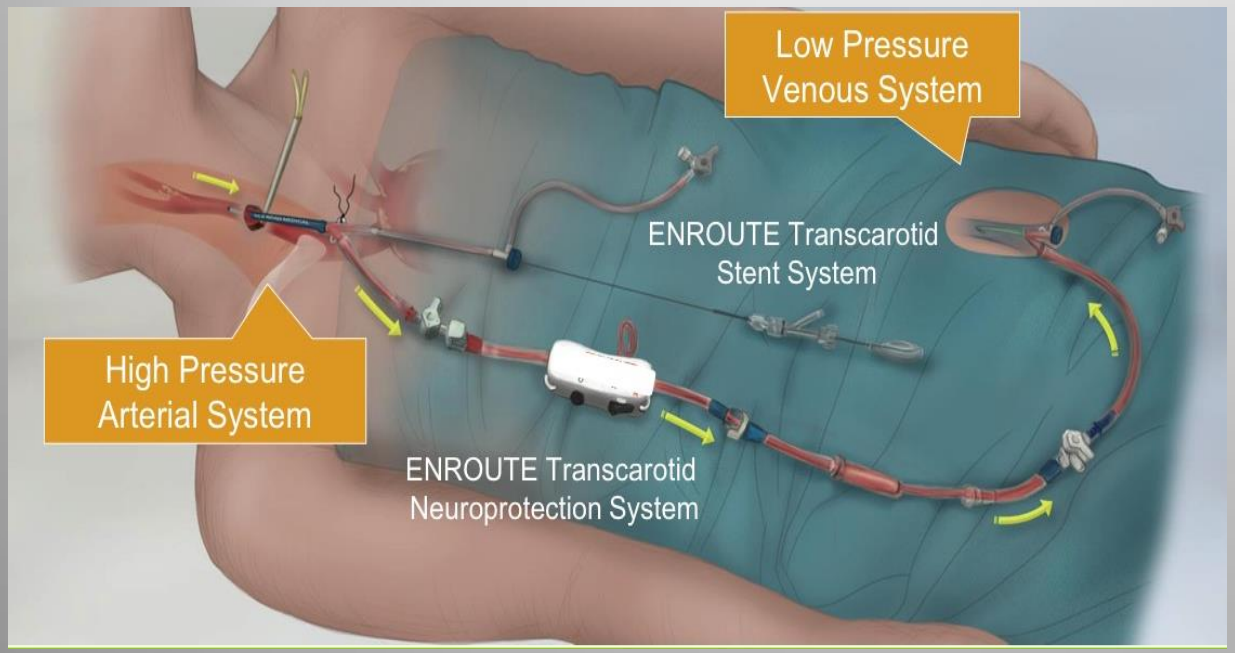
Plaque Protrusion - OCT

Mesh vs Closed cell stent





Direct Carotid Access
High Rate Flow Reversal-TCAR

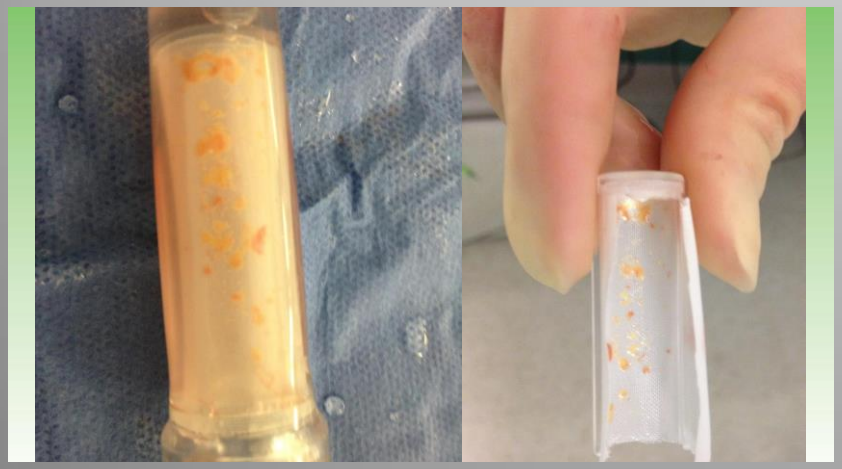


- Avoid the arch
- “CEA-like” neuroprotction
- Less manipulation

Roadster Outcomes

High Surgical Risk	Pivotal Group, ITT (n=141)		Pivotal Group, PP (n=136)	
S/D/MI*	5	3.5%	4	2.9%
Major Stroke	0	0%	0	0%
Minor Stroke	2	1.4%	1	0.7%
Death	2	1.4%	2	1.5%
MI	1	0.7%	1	0.7%
Stroke & Death	4	2.8%	3	2.2%
Cranial Nerve Injury (CNI)	1	0.7%	1	0.7%
CNI Unresolved at 6 Mos	0	0%	0	0%

TCAR



New Technologies in CAS

- Mesh-covered carotid stents likely to add benefit in terms of reducing not only clinical events but also surrogate DWI lesions
- Double-filtration and TCAR is already showing benefit both clinically (TCAR), and using DWI surrogates
- Patient CAS outcomes—already good—should improve further

CREST-2

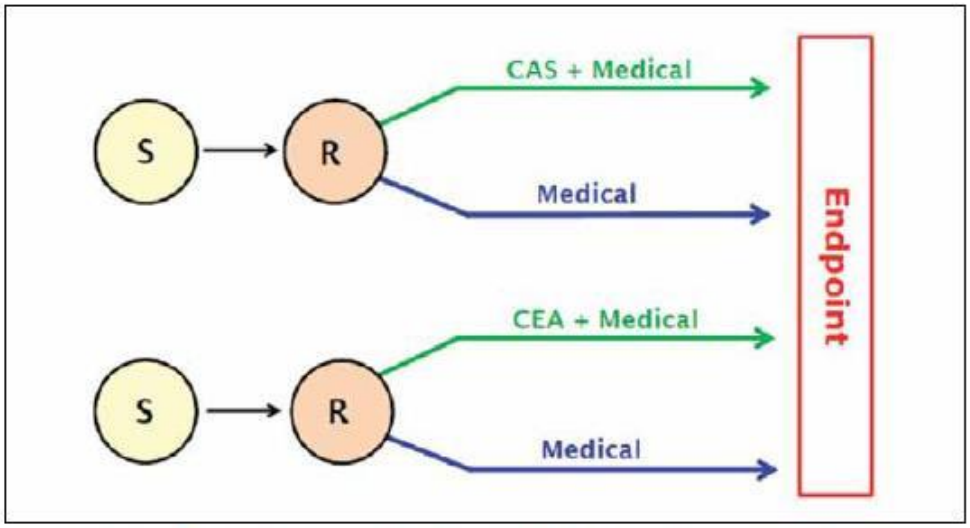


Figure 1. CREST-2 parallel study design. Endpoint = stroke and death in first 30 days and ipsilateral stroke thereafter up to 4 years. S, screening; R, randomization.

Asymptomatic carotid disease

Examining CAS and CEA in the context of intensive medical therapy

2018 Kettering Cardiology Colloquium

Thank You

Cell:937-765-2330

Questions???