Carotid Artery Disease: Is there a New Gold Standard in Therapy?

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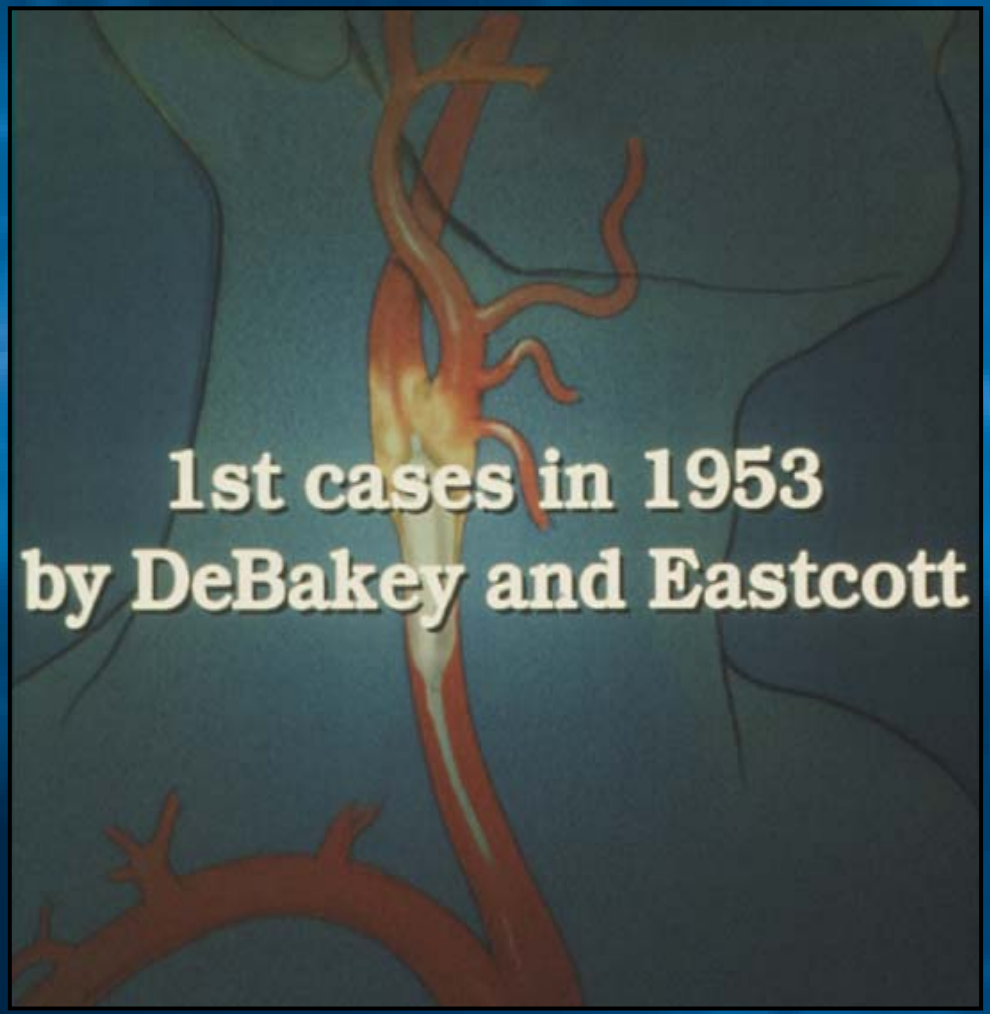
Stroke

- *731,000 strokes each year*
- *160% increase in incidence by the year 2050*

Carotid Endarterectomy



Surgical versus medical therapy

ASYMPTOMATIC	*% Risk reduction*	*SYMPTOMATIC*	*% Risk reduction*
ACAS	**53%**	**NASCET**	**65%**
VA Asymptomatic	**30%**	**VA Symptomatic**	**60%**
CASANOVA	**5%**	**ECST**	**39%**

NASCET: no advantage for stenosis <50%
disadvantage for stenosis <30%

for symptomatic stenoses the periop. risk should be <6% (AHA)

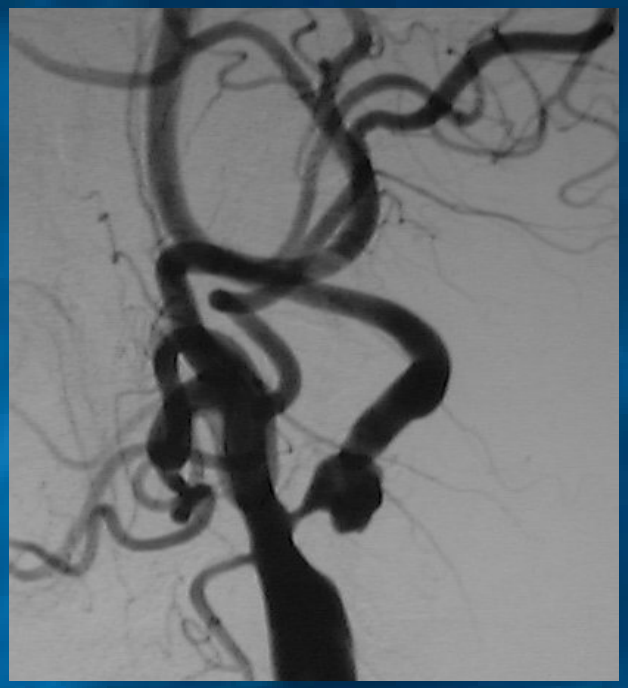
Recommendations:

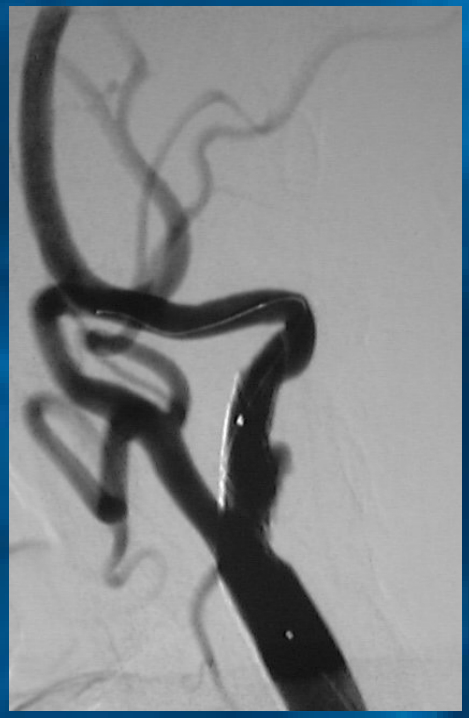
asymptomatic stenosis >70%: recanalization
<70: conservative, repeated

follow-up

symptomatic stenosis >50%: recanalization

Recommendations applicable for PTA/Stent?

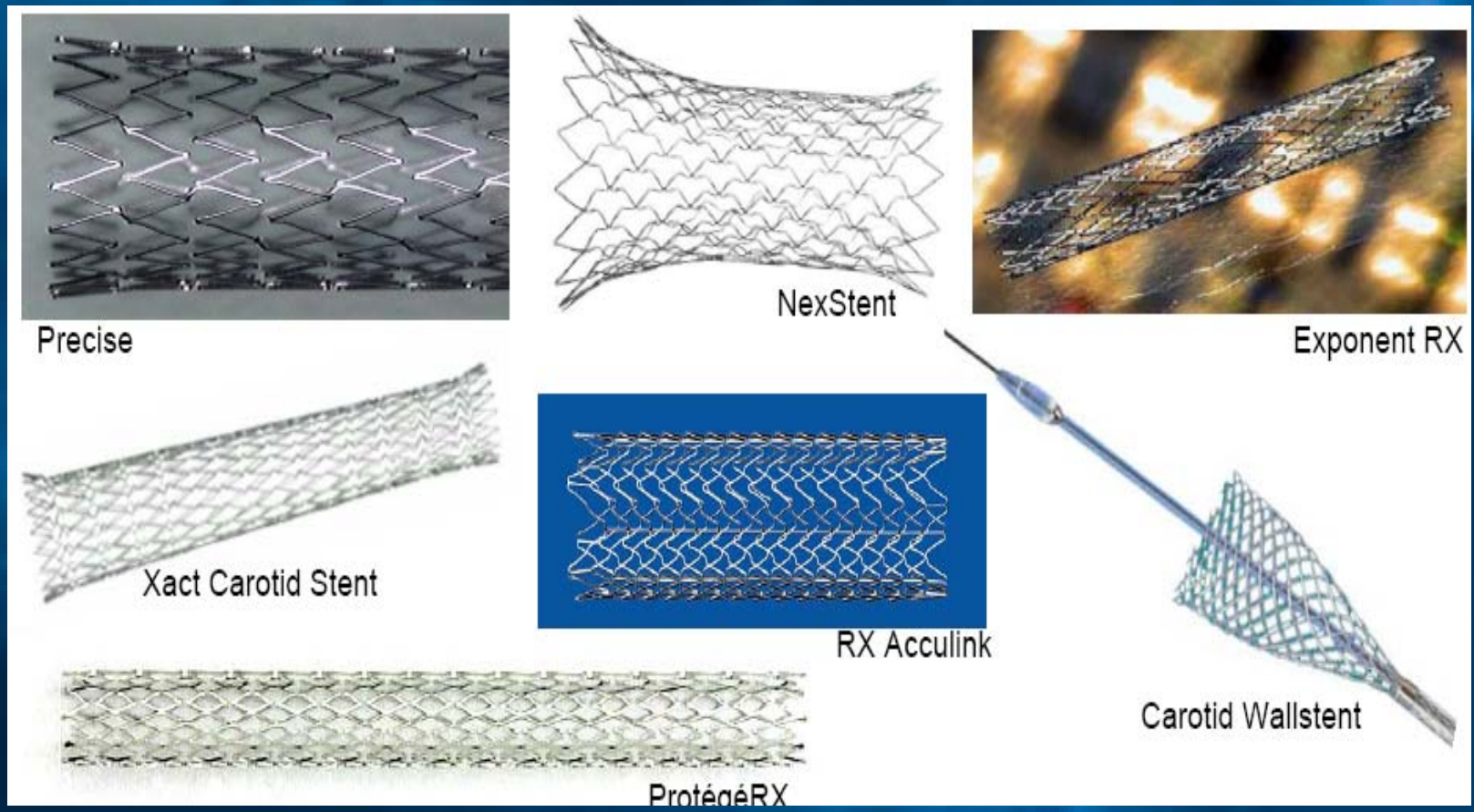




no trials comparing PTA vs medical therapy

is PTA equal to surgery (CEA)?

Carotid Stent types



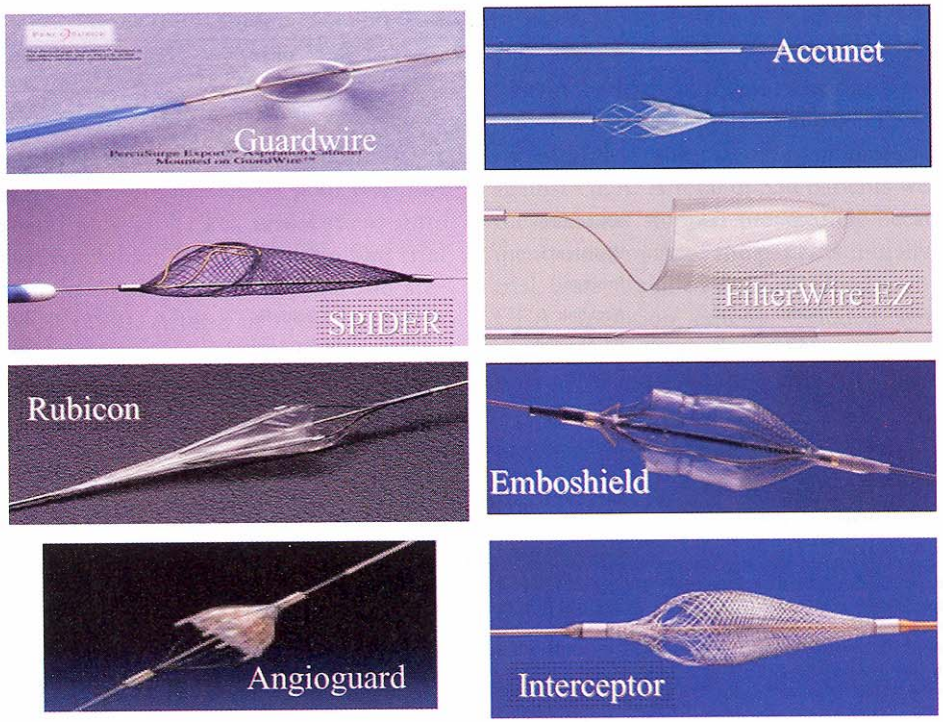
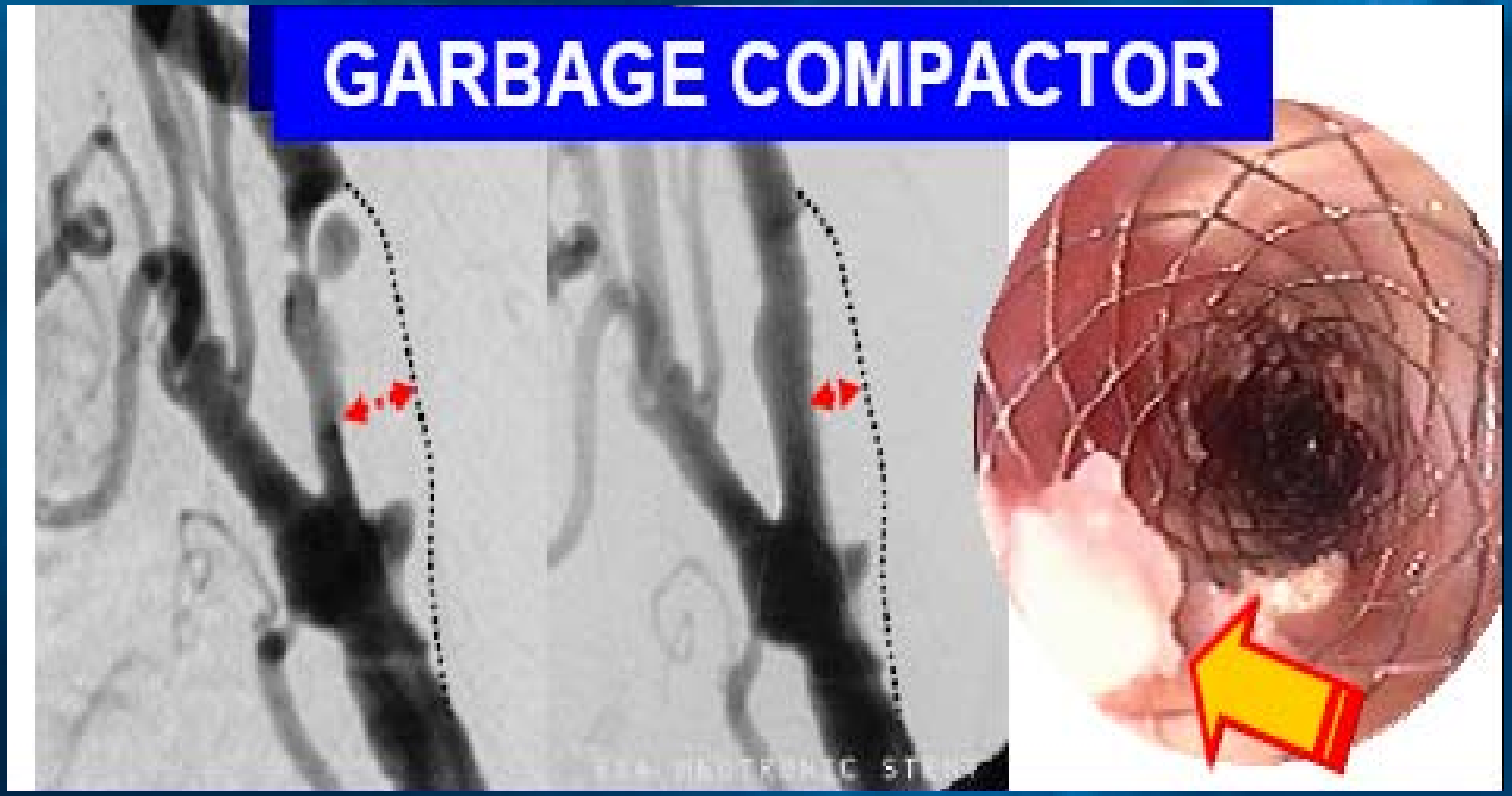


Figure 6. Examples of Filter-Type Embolic Protection Devices

CEA: plaque removal

Stenting: Plaque containment



Let the battles begin

Table 10. Acronyms for CAS Registries and Clinical Trials

ACT	Asymptomatic Carotid Stenosis Stenting vs. Endarterectomy Trial
ARCHeR	Acculink for Revascularization of Carotids in High-Risk Patients
BEACH	Boston Scientific EPI: A Carotid Stenting Trial for High Risk Surgical Patients
CABANA	Carotid Stenting Boston Scientific Surveillance Program
CABERNET	Carotid Artery Revascularization using Boston Scientific EPI Filterwire EX/EZ and the EndoTex NexStent
CAPTURE	Carotid Acculink/Accunet Post Approval Trial to Uncover Rare Events
CaRESS	Carotid Revascularization using Endarterectomy or Stenting Systems
CASES-PMS	Carotid Stenting with Emboli Protection Surveillance-Post-Marketing Study
CREATE	Carotid Revascularization with ev3 Arterial Technology Evaluation
CREST	Carotid Revascularization: Endarterectomy versus Stent Trial
ELOCAS	European Long-term Carotid Artery Stenting Registry
EMPIRE	EMPiRE Embolic Protection with Reversed Flow
EVA-S3	Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis
ICSS	International Carotid Stenting Study (CAVATAS II)
MAVErIC	Evaluation of the Medtronic AVE Self-expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis
MO.MA	Multicenter Registry to Assess the Safety and Efficacy of the MO.MA Cerebral Protection Device During Carotid Stenting
PASCAL	Performance and Safety of the Medtronic AVE Self Expandable Stent in the Treatment of Carotid Artery Lesions
PRINCE	Prospective Investigation of Nitinol Carotid Stent with Embolic Filter
ProCAS	Prospective Registry of Carotid Angioplasty and Stenting
ProCAR	Protégé Stent in the Treatment of Carotid Artery Stenosis with Adjunctive Use of a Filter Embolic Protection Device
RULE-Carotid	Rubicon Filter-Carotid
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy
SECuRITY	Registry Study to Evaluate the NeuroShield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy
SHELTER	Stenting of High-risk Patients with Embolic Removal
SPACE	Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy
VIVA	Vivexx Carotid Revascularization Trial
XACT	Emboshield and Xact Post Approval Carotid Stent Trial

The CAVATAS Trial

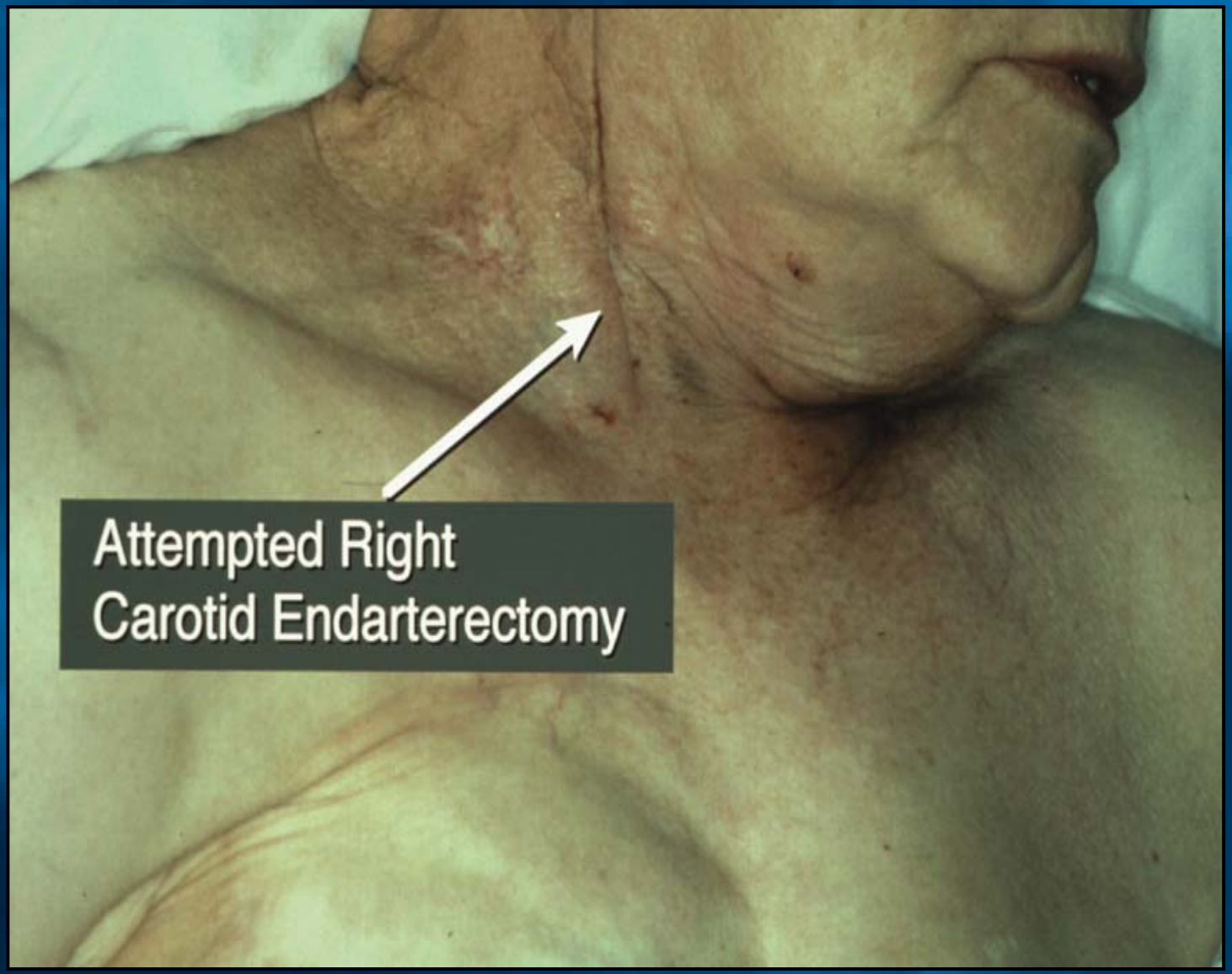
- Enrollment 1992 to 1997
- 504 patients (96% symptomatic) randomized
- Randomized
  - 253 to CEA
  - 251 PTA (*25% stent*)
- Identical medical Rx in both arms
- High medical and surgical risk pts excluded
- 3 year follow up
- No EPD

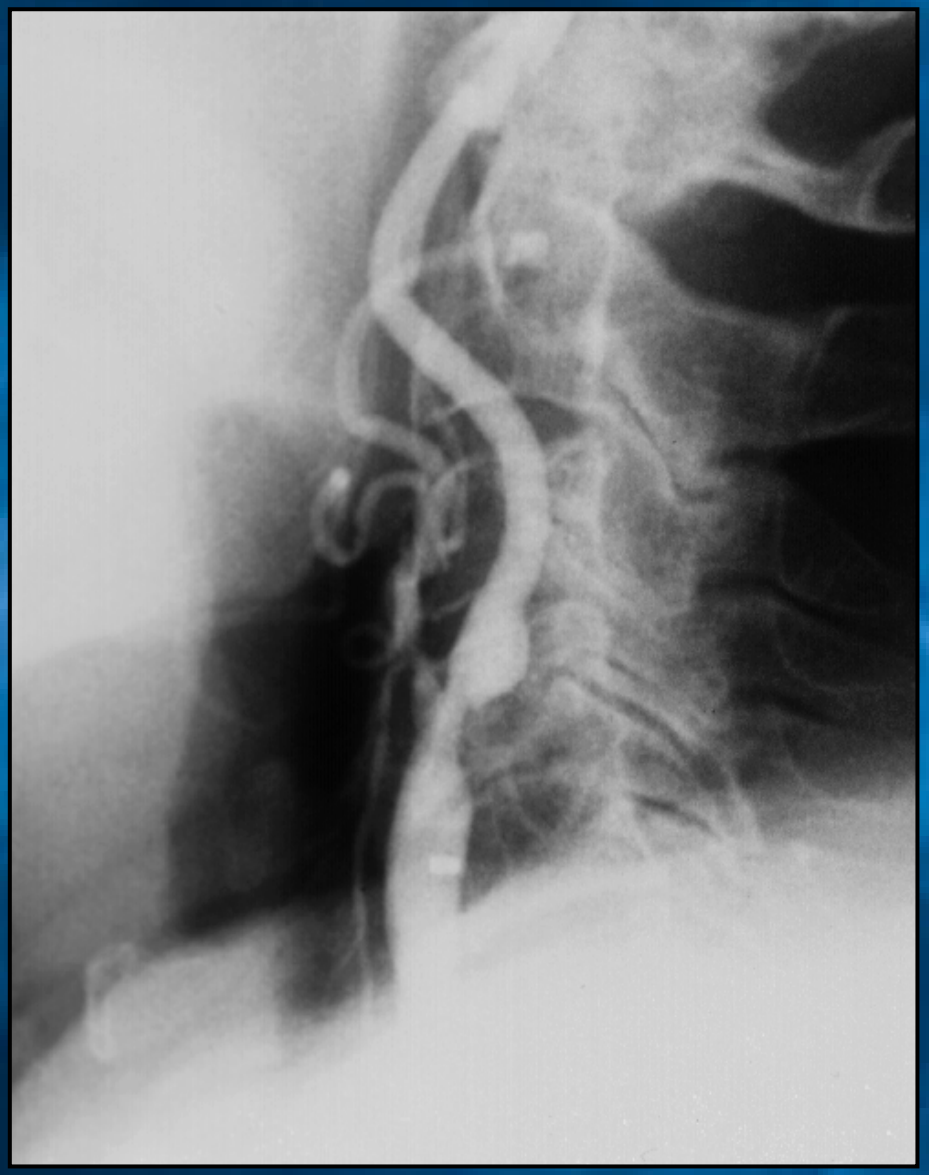
Lancet 2001;357:1729

CAVATAS

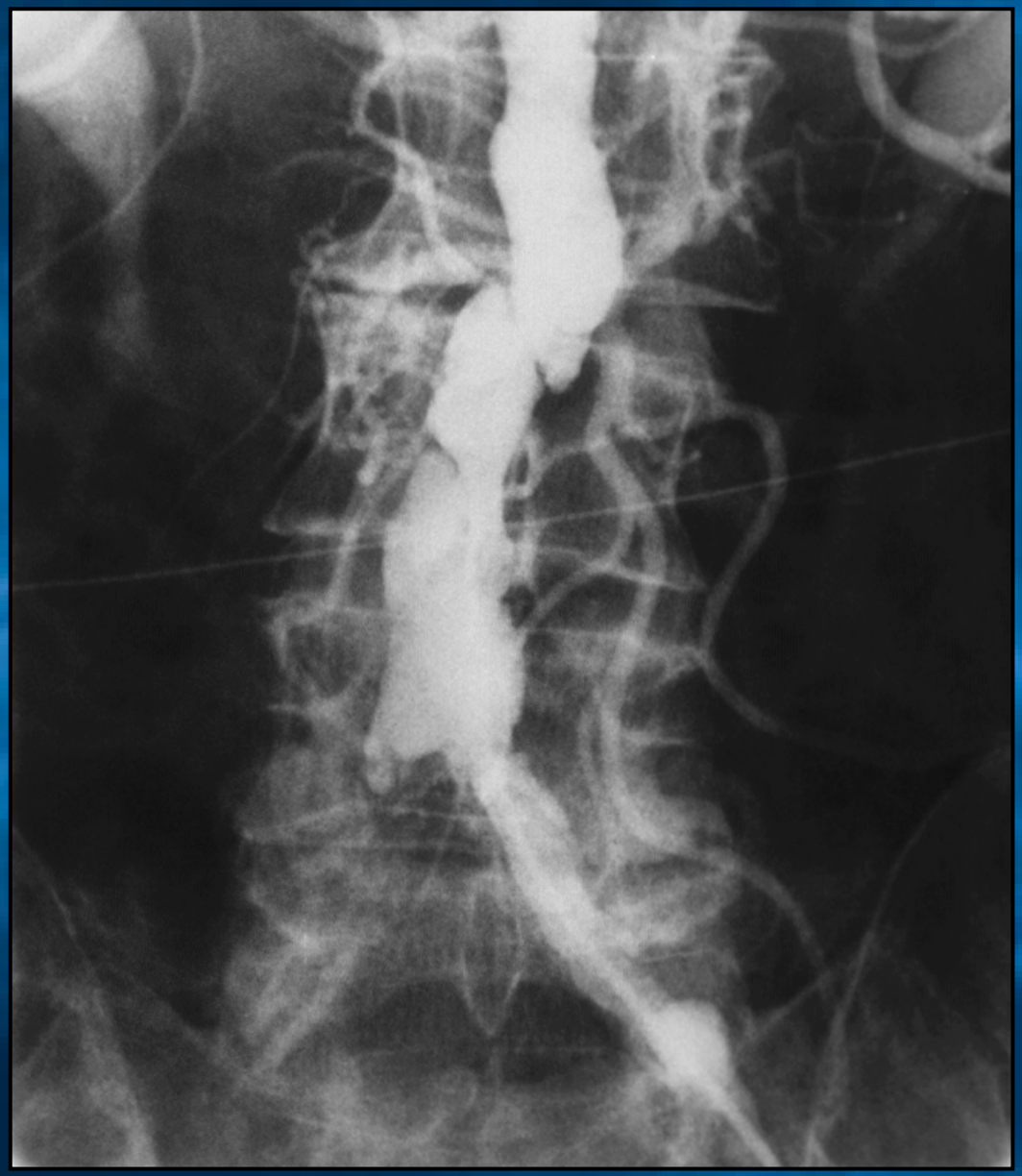
	PTA (n= 251)	CEA (n=253)	p-value
30d Death (%)	3	2	NS
30d Disabl Stroke (%)	4	4	NS
30d MI	0	1	NS
30d Non-disabl stroke (%)	4	4	NS
30d Death±disabl stroke (%)	6	6	NS
30d Death ± any stroke (%)	10	10	NS
3-Yr Dth±disabl stroke (%)	14	14	NS

Lancet 2001;357:1729


Attempted Right
Carotid Endarterectomy



D.D.H.
8-22-00



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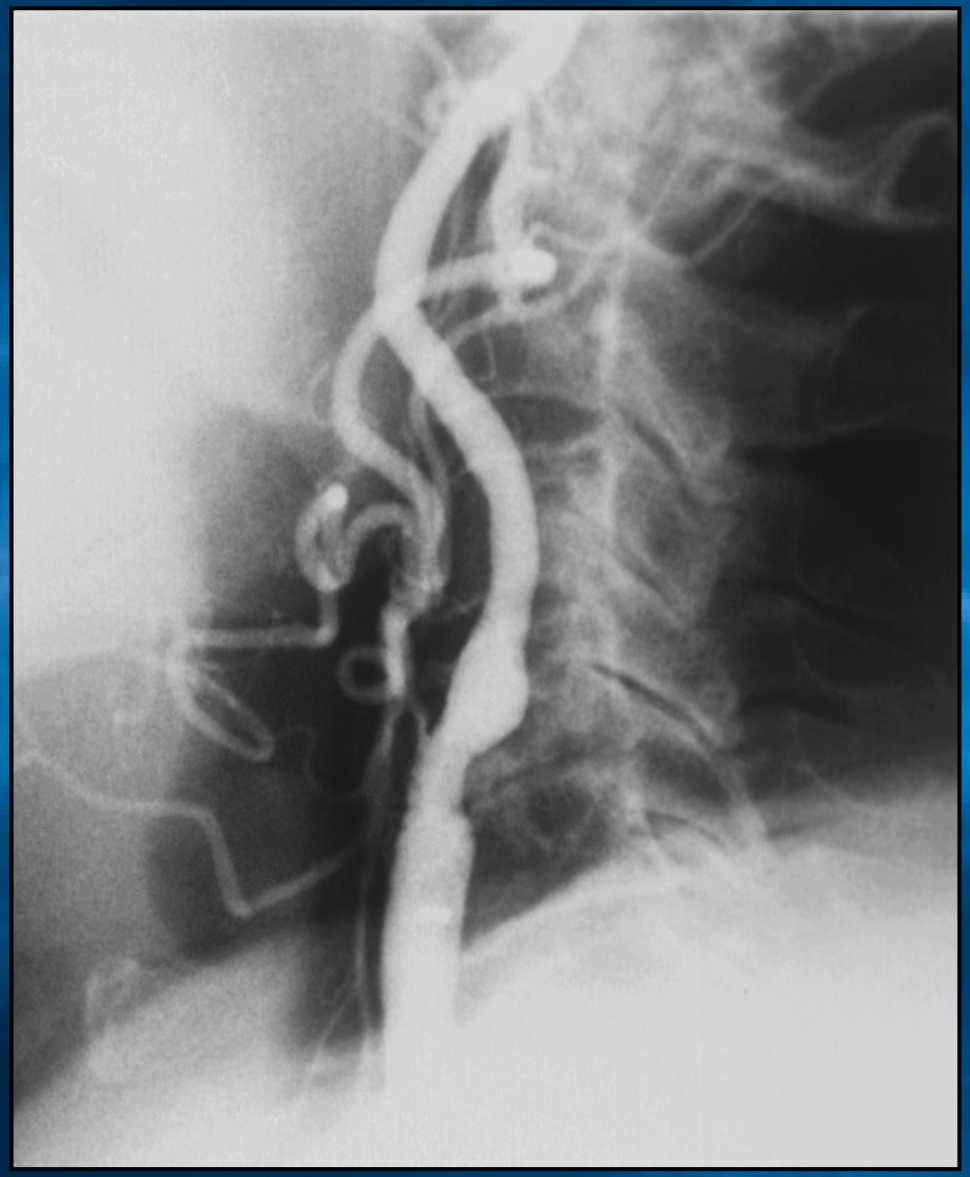


D.D.H.
8-22-00

Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (The SAPPHIRE Study)

AHA Scientific Sessions

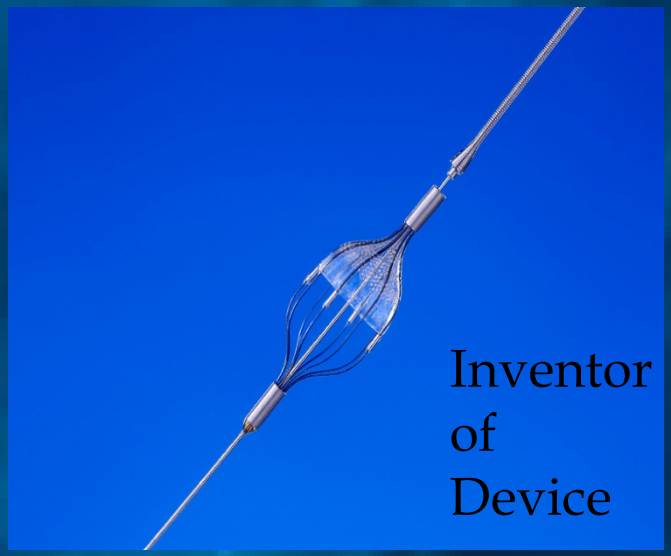
November 19, 2002

Cordis

a Johnson & Johnson company

Device Specifications

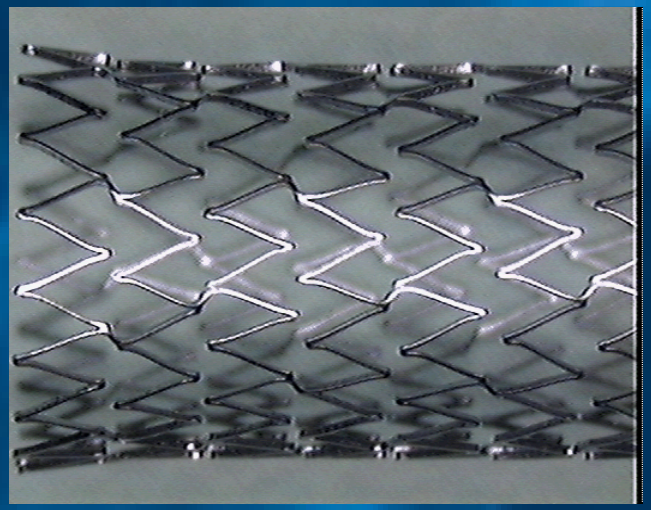
ANGIOGUARD™



.014" Emboli Prevention Guidewire

Filter pore size 100 microns

PRECISE™



Nitinol Self-Expanding Stent

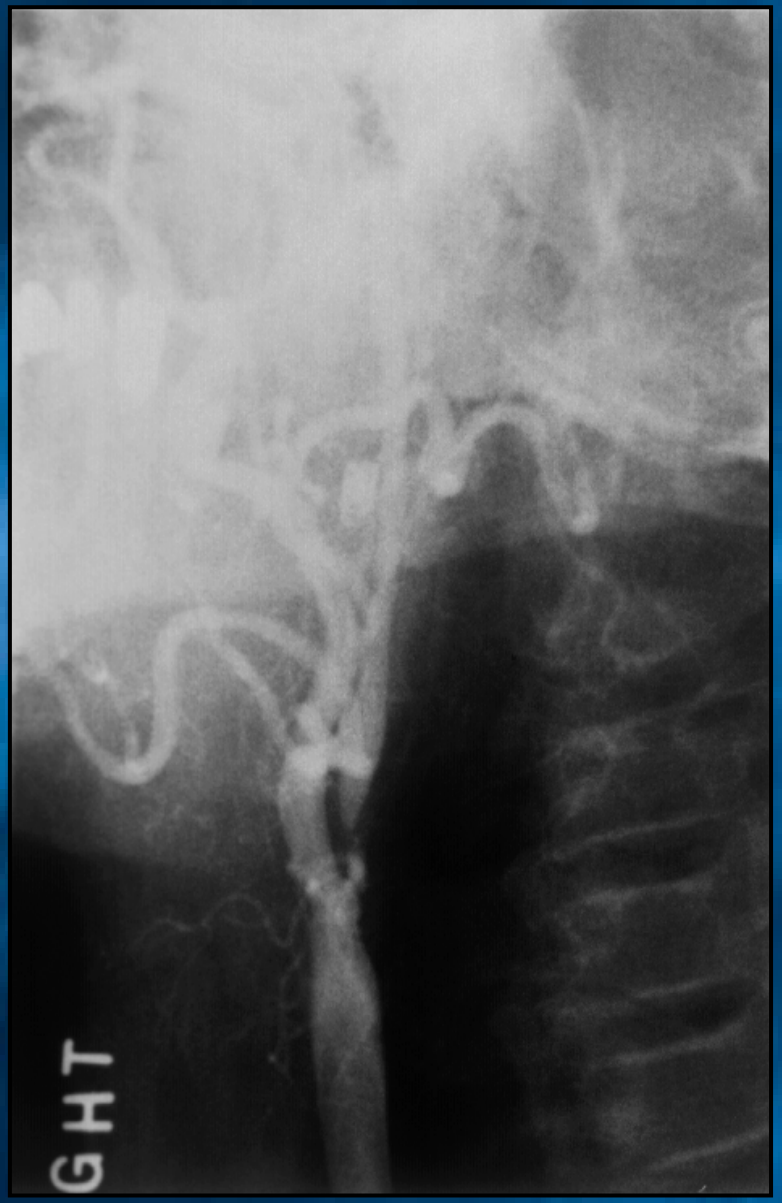
5.5 & 6 French Delivery Systems

Cordis
a Johnson & Johnson company

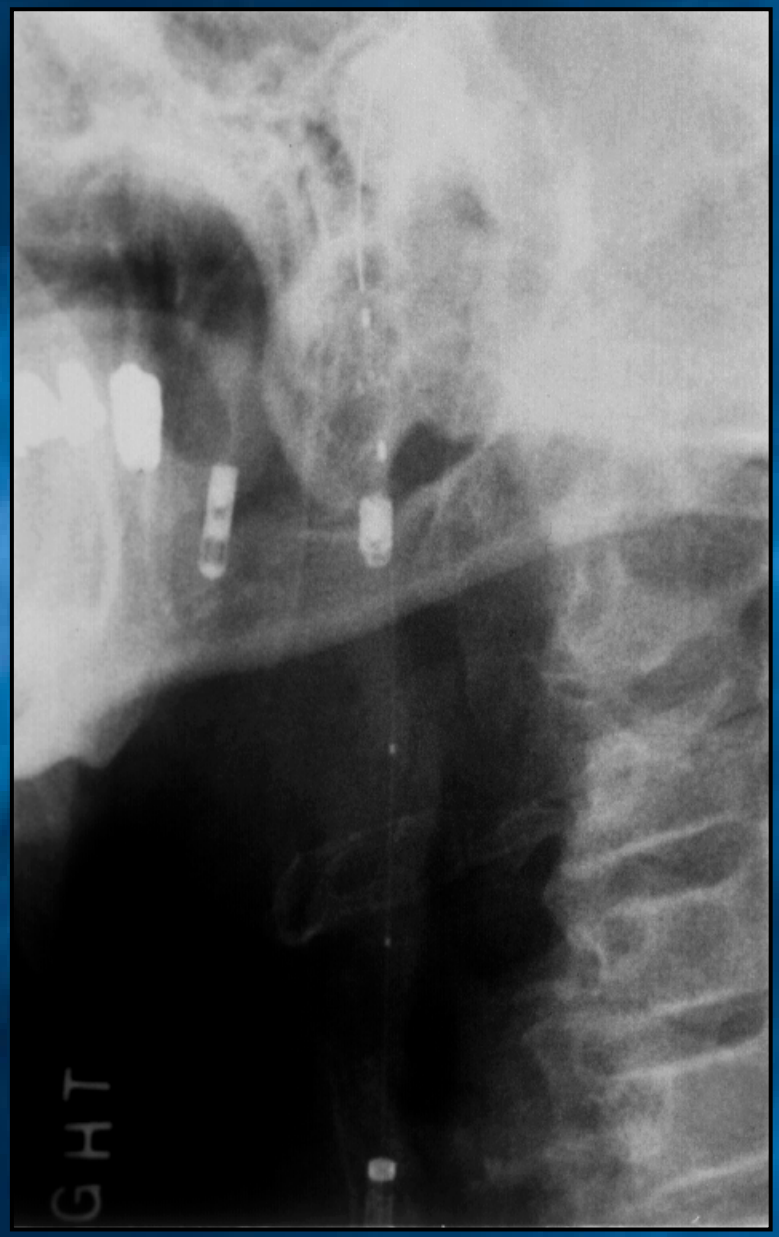
Equipoise and carotid therapy?

"The ethics of clinical research requires equipoise---a state of genuine uncertainty within the expert medical community regarding the comparative merits of each treatment arm in a trial."

Equipoise and the ethics of clinical research.
Freedman B. N Engl J Med 1987 Jul 16;317(3):141-5



C.S.W.
8-22-00



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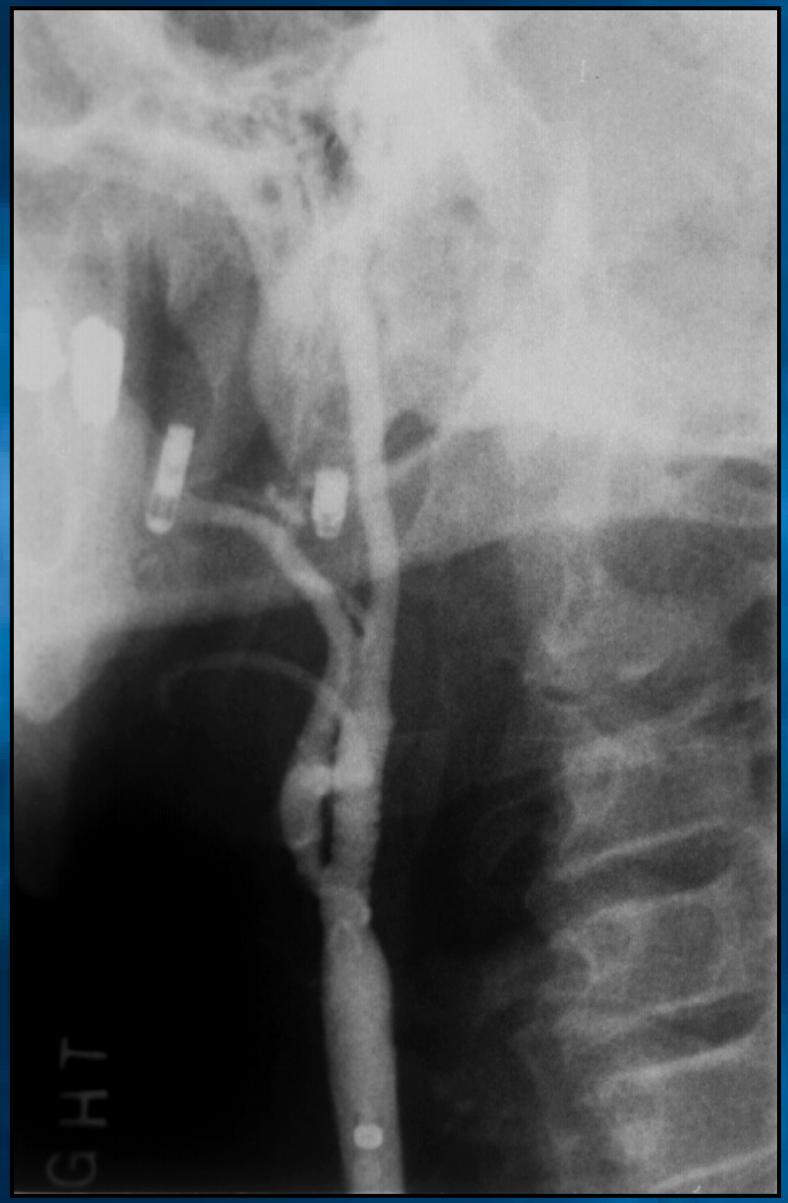

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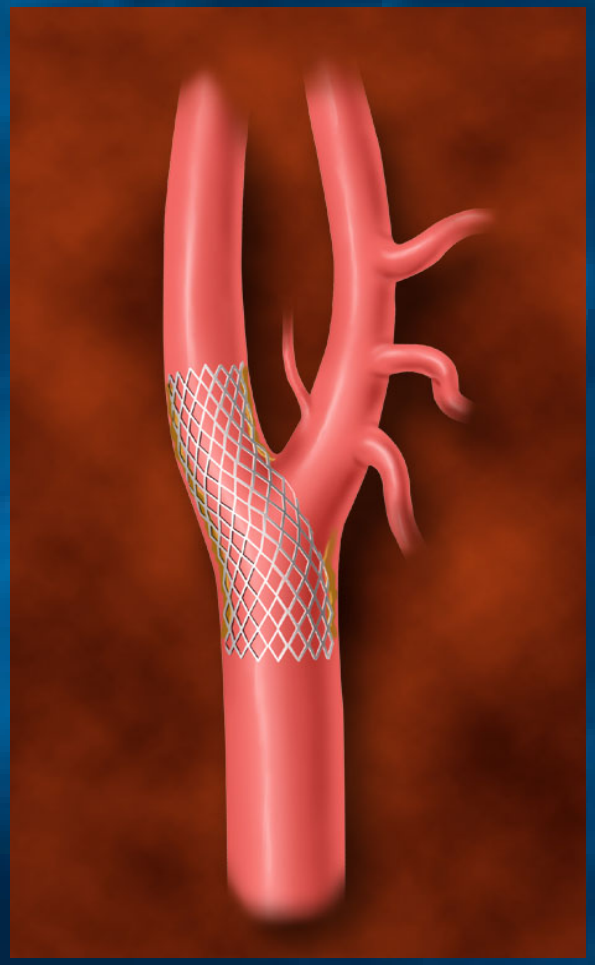
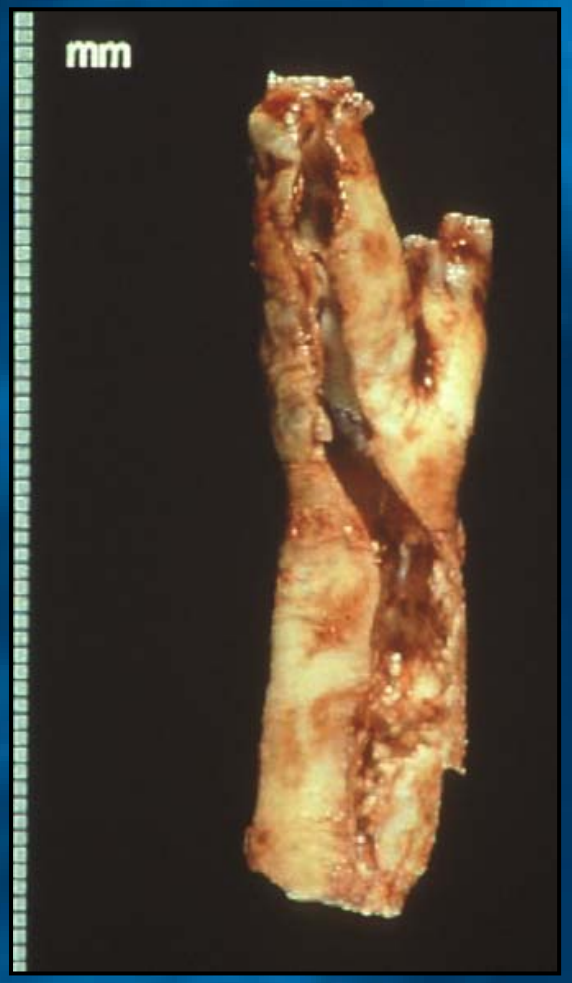
WHO WON?

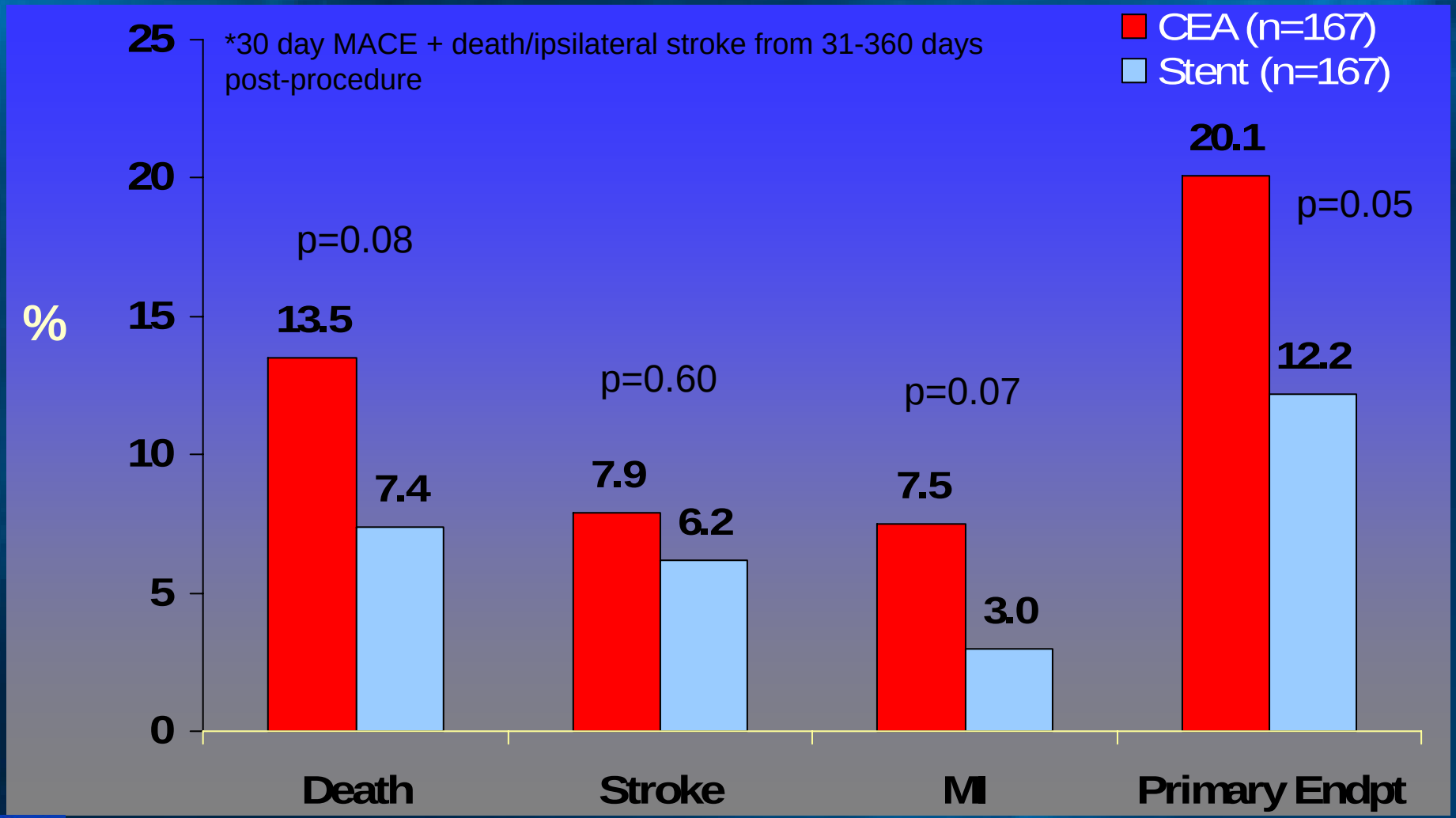




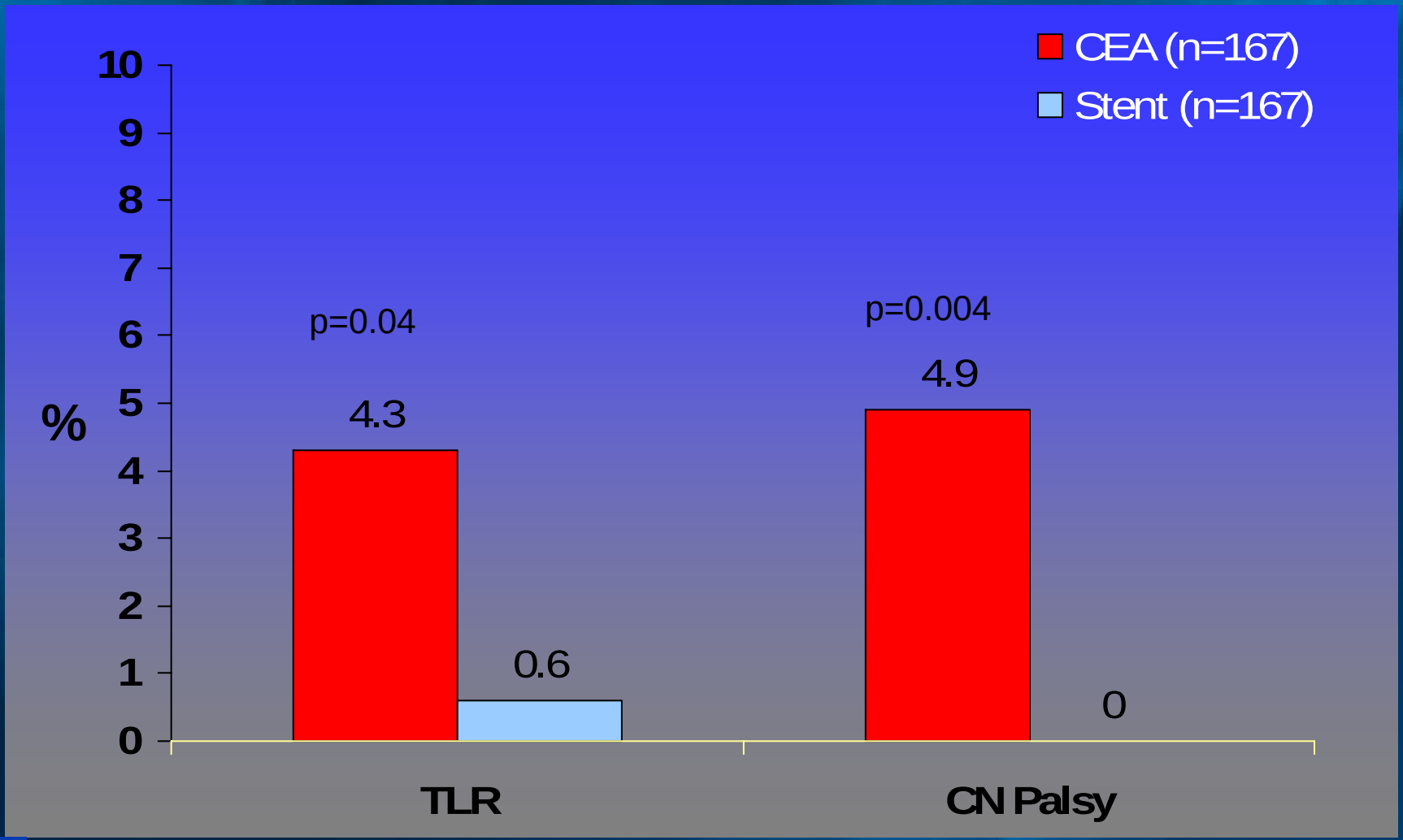
5.8%

12.6%

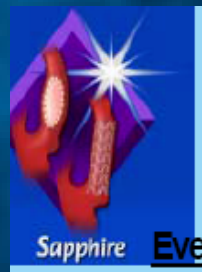
SAPPHIRE
360-Day Primary Endpoint



SAPPHIRE
Other Outcomes at 360 Days



CAS versus CEA - SAPPHIRE



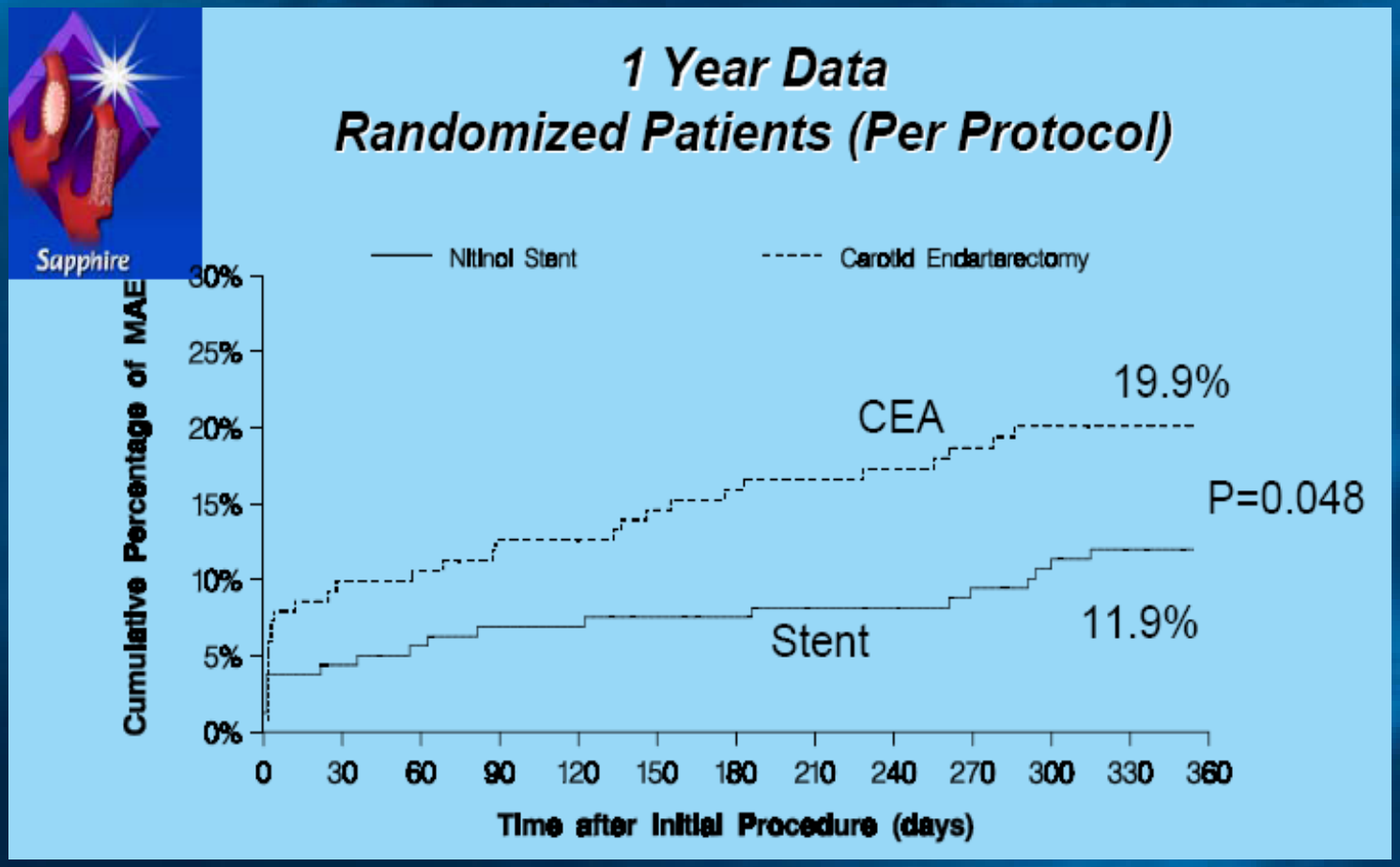
1 Year Data
Randomized Patients (Per Protocol)

Events	Stent (159 pts)	CEA (151 pts)	p Value
Death:	11 (6.9%)	19 (12.6%)	0.12
Stroke:	9 (5.7%)	11 (7.3%)	0.65
Major Ipsilateral:	0 (0.0%)	5 (3.3%)	0.03*
Major Non-Ipsilateral:	1 (0.6%)	1 (0.7%)	>0.99
Minor Ipsilateral:	6 (3.8%)	3 (2.0%)	0.50
Minor Non-Ipsilateral:	3 (1.9%)	3 (2.0%)	>0.99
MI (Q or NQ)	4 (2.5%)	12 (7.9%)	0.04*
Q-Wave MI	0 (0.0%)	2 (1.3%)	0.24
Non-Q Wave MI	4 (2.5%)	10 (6.6%)	0.10

Yadav et al., NEJM 2004; 351: 1493

84% asymptomatic high risk stenoses, what about symptomatic stenoses in normal risk patients?

CAS versus CEA - SAPPHIRE



3 years

CEA: 30.3%

CAS: 25.5%

Comparison of ACAS and NASCET to SAPPHIRE

The Patients enrolled into the Sapphire Trial were at high risk for surgery –
ACAS and NASCET Patients were carefully selected as low risk surgical candidates

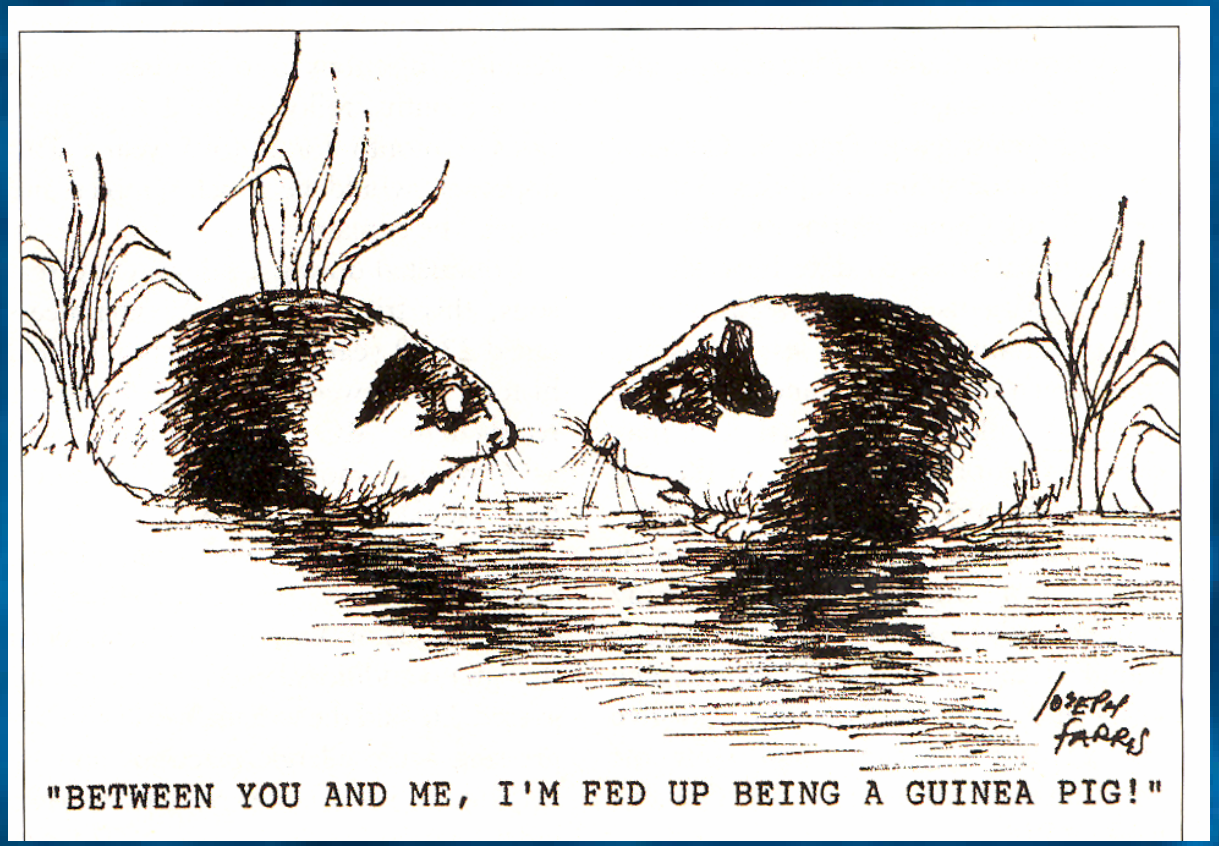
ACAS	NASCET	SAPPHIRE
Patients were *Excluded* if they HAD any of the following high risk factors: • Previous CEA • Unstable Angina • Congestive Heart Failure • Previous Stroke • Renal Insufficiency • Respiratory Insufficiency • Previous neck surgery or radiation treatment • Major surgery within past month • Age >79 years Also excluded: • Symptomatic Patients	Patients were *Excluded* if they HAD any of the following high risk factors: • Previous CEA • Unstable Angina • MI (within 6 months) • Previous neck surgery • Major surgery within past month • Age >79 years Also excluded: • Asymptomatic Patients	*Patients were Included if they HAD one of the following high risk factors:* • Congestive Heart Failure • Open Heart Surgery w/in 6 weeks • Recent MI (>24 hrs, < 4 weeks) • Unstable Angina • Coexistent Severe Coronary Artery Disease • Severe Pulmonary Disease • Contralateral Carotid Occlusion • Contralateral Laryngeal Palsey • Post Radiation Treatment • Previous CEA recurrent Stenosis • High Cervical ICA Lesions • Severe Tandem Lesions • CCA Lesions below the Clavicle • > 80 years of age Also excluded: • Asymptomatic Patients

The published MAE rates for ACAS and NASCET were 30-day results – and did not include MI (SAPPHIRE 30-day MAE results included patients with MI's) At 30 days, the MAE rates were:

ACAS	NASCET	SAPPHIRE Stent	SAPPHIRE CEA
2.3%	5.8%	4.4% - 3.8% without MI's	9.9% - 4.6% without MI's

Despite the fact that the SAPPHIRE Patients were High Risk Patients, there is no significant difference in 30 day MAE rates when both the Stent and CEA cohorts are compared to both ACAS and NASCET.

NOTE: This represents investigational data. Carotid stenting is not an FDA approved procedure



"BETWEEN YOU AND ME, I'M FED UP BEING A GUINEA PIG!"

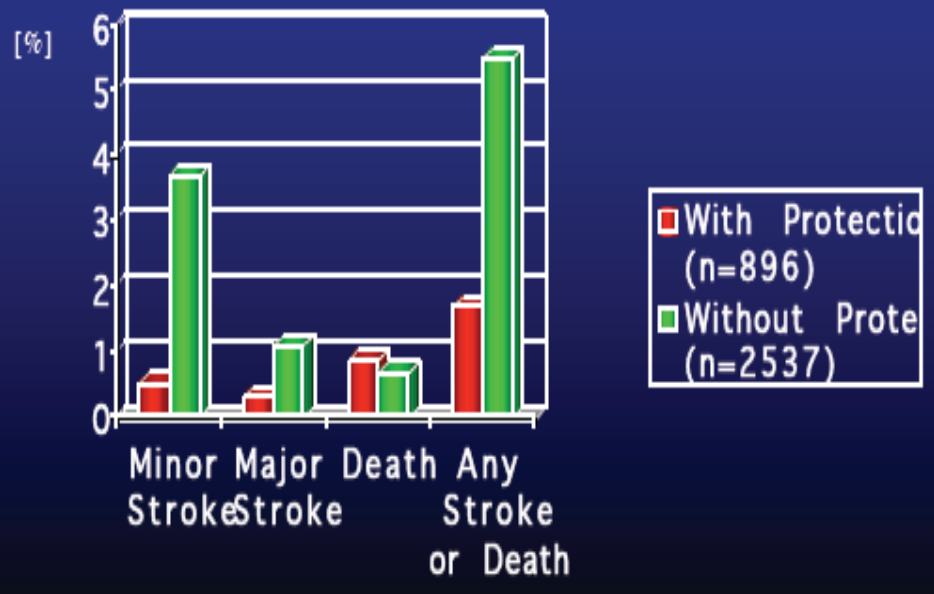
Trial data

- Total multi-center US carotid stent trial data reported (to date):
  - 3338
- Total multi-center US endarterectomy data (NASCET and ACAS):
  - 3179

Why embolic protection?

Protection or not?

Early Outcome of Carotid Angioplasty and Stenting With and Without Cerebral Protection Devices (Metaanalysis)
Kastrup A;Stroke 2003;34:813-819



German CAS Registry

Participating Centers 36

Interventions 2,147 (100.0 %)

	CP	no CP
minor stroke	1.3 %	1.5 %
major stroke	0.7 %	1.3 %
total	2.0 %	2.8 %

Risk reduction 30%

SAPPHIRE

Provide nationwide evidence-based clinical data on patients who are high-risk with severe carotid disease…

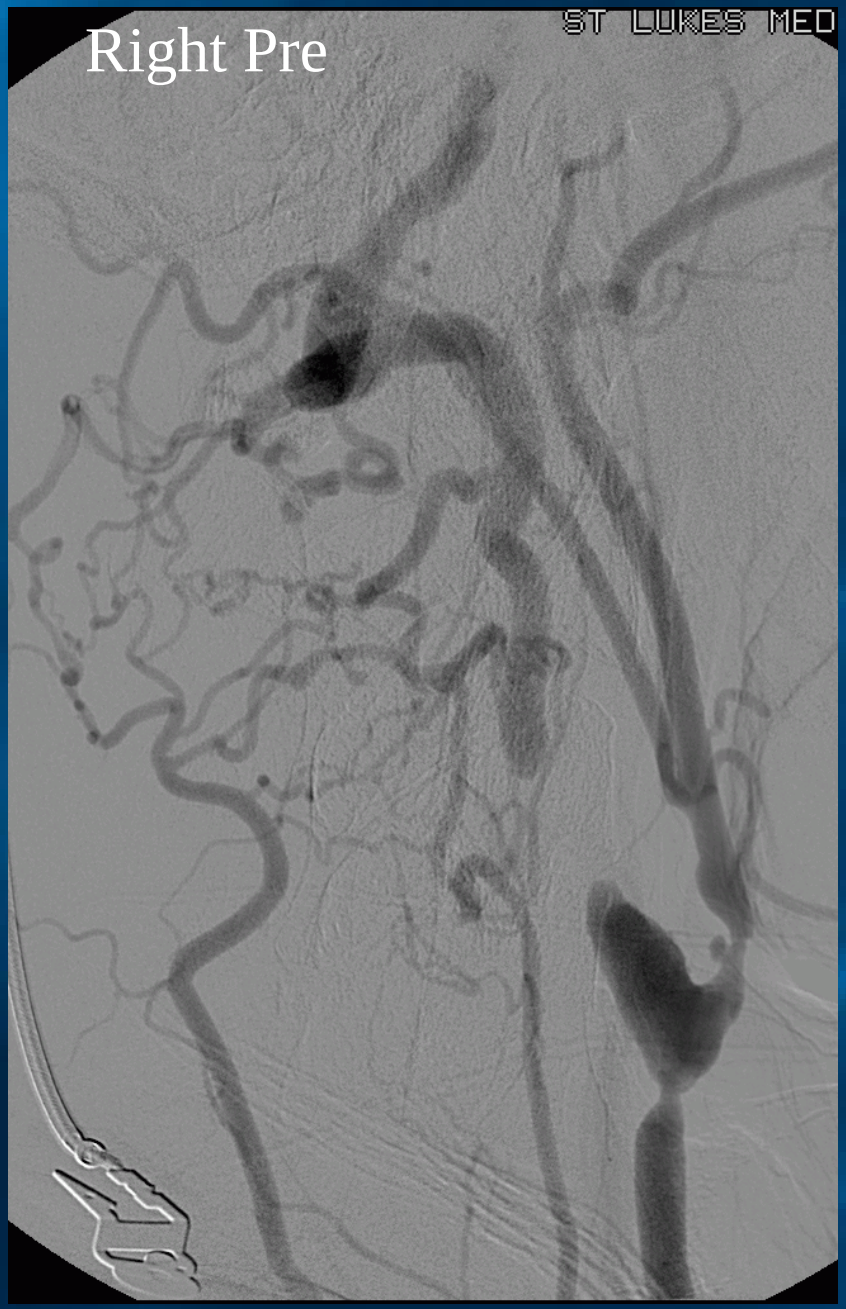
Patient History

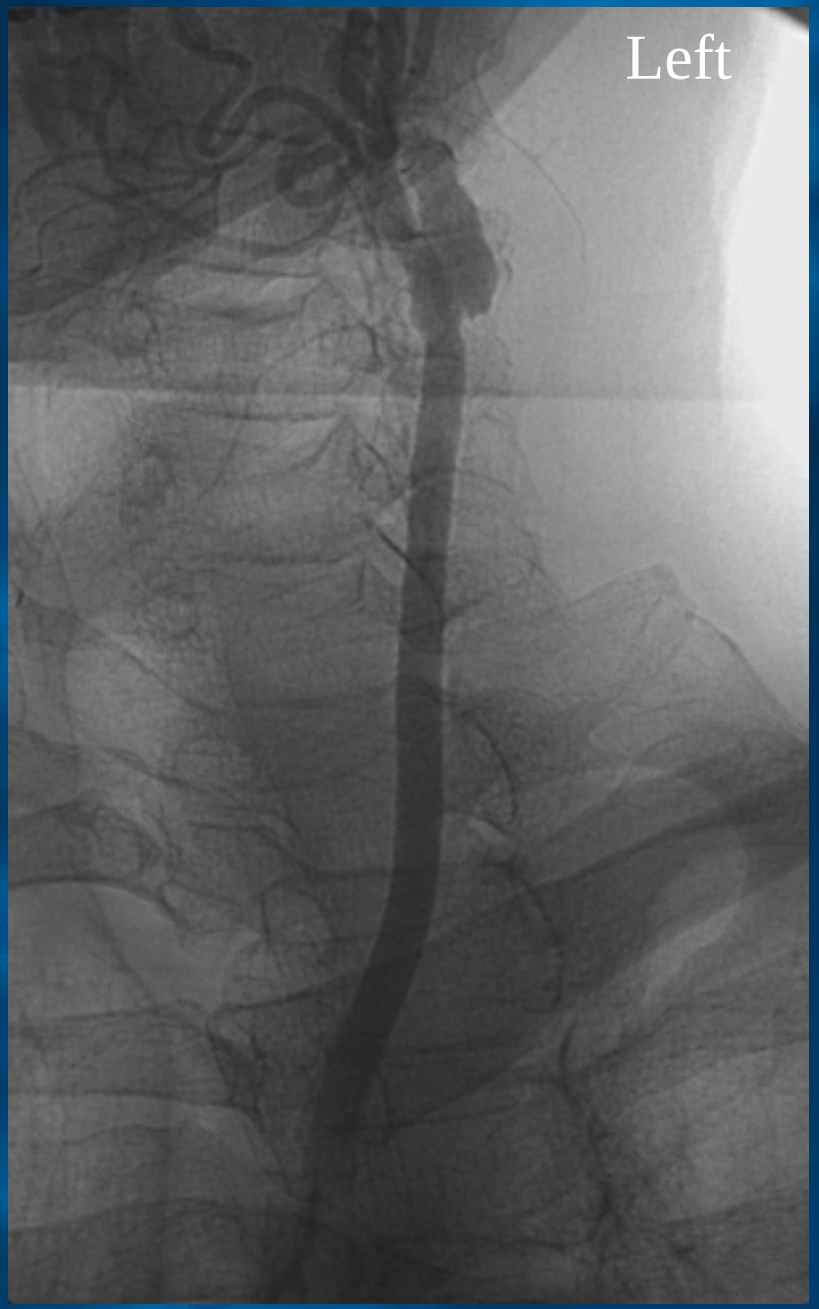
- *55 yo male*
  - *No carotid symptoms*
  - *Prior neck radiation for unknown carcinoma*
  - *Surveillance CT initially performed 2/2006 showed severe bilateral carotid disease; repeat CT performed 2/2007 showed no significant changes*

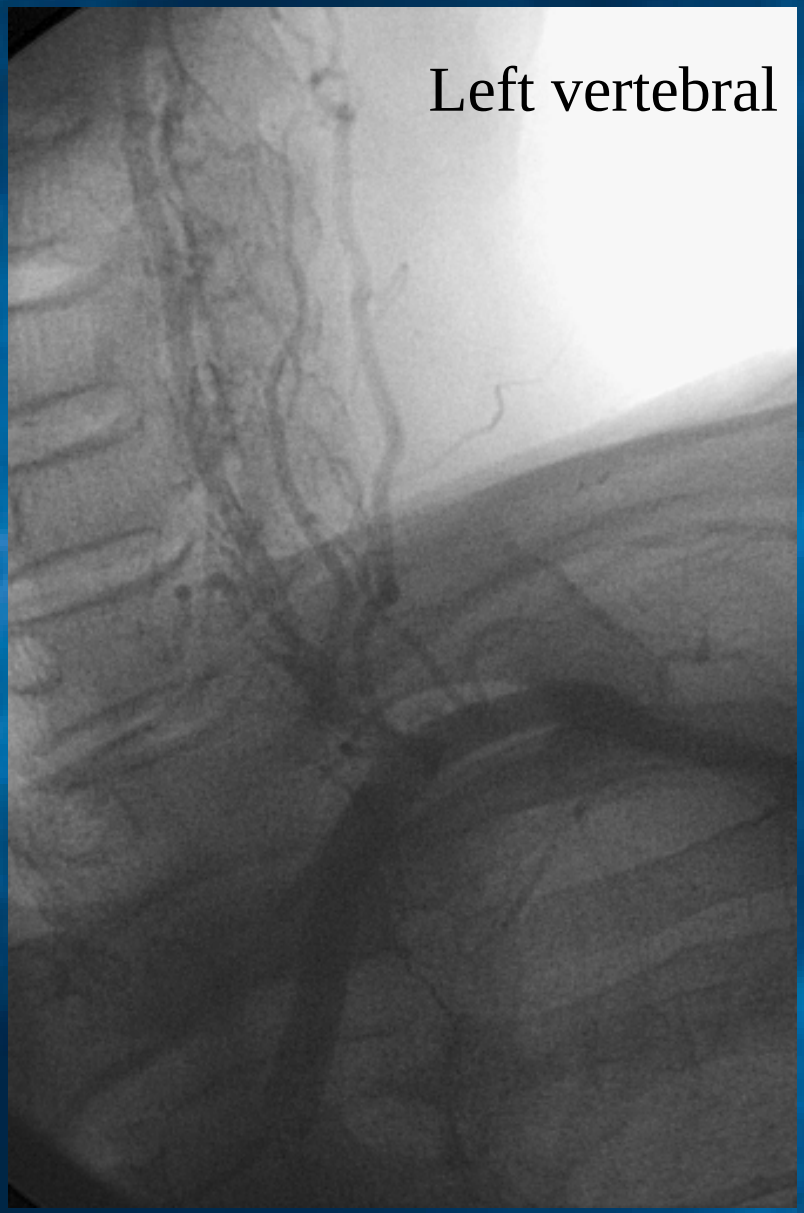
CTA Feb 2007

What are we waiting for??

- *Bilateral occluded ICA's*
- *Patent circle of Willis*
- *<95% stenosis distal right CCA with >90% ECA stenosis*
- *Occluded right vertebral artery at origin*
- *Patent small left vertebral artery*
- *Collateral circulation thought to derive from external carotid arteries*

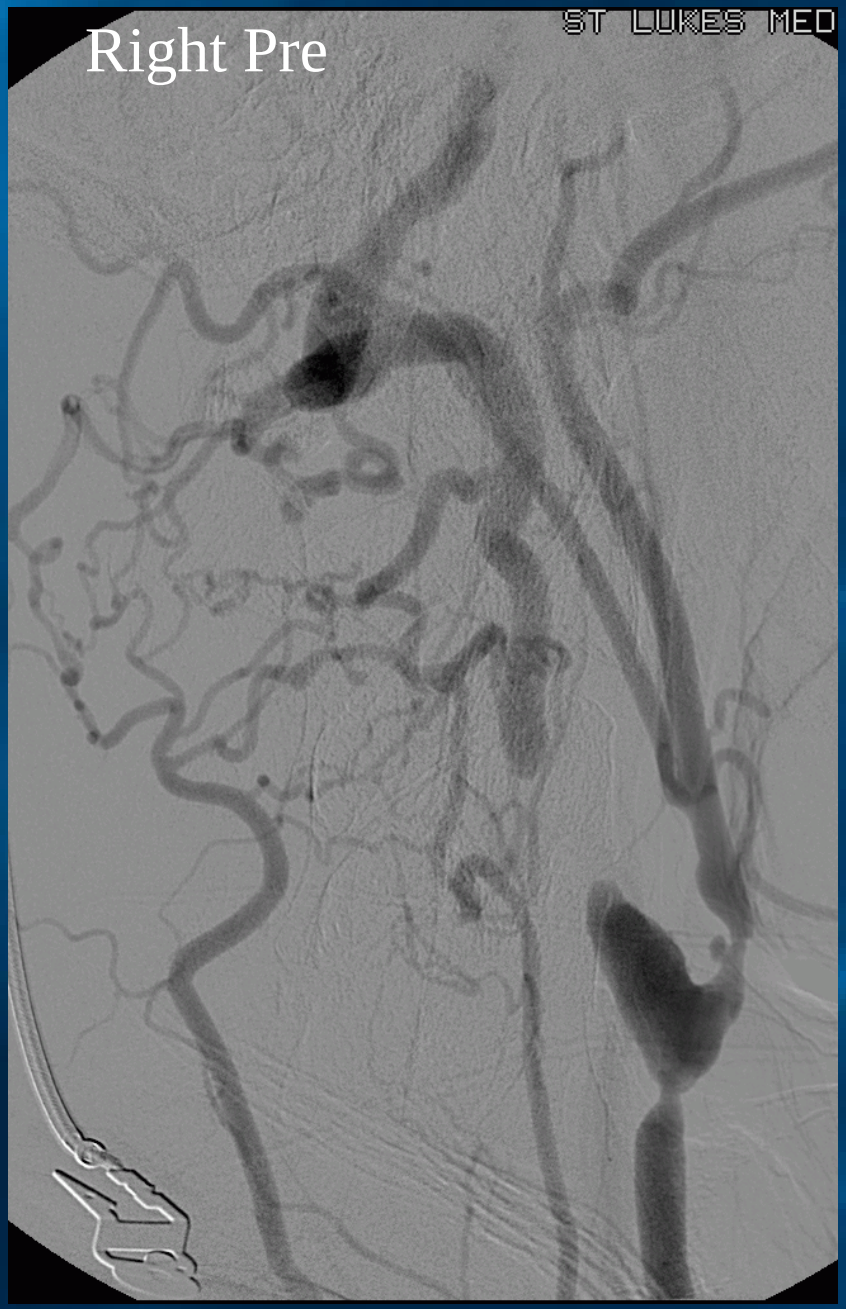

Right Pre
ST LUKES MED


Left


Left vertebral

Strategy

- *Medical therapy*
- *Endarterectomy*
- *Six-pack and a fishing pole*
- *Scratch your head*
- *PTA/Stent*
  - *Embolic protection?*
  - *Consent / risks?*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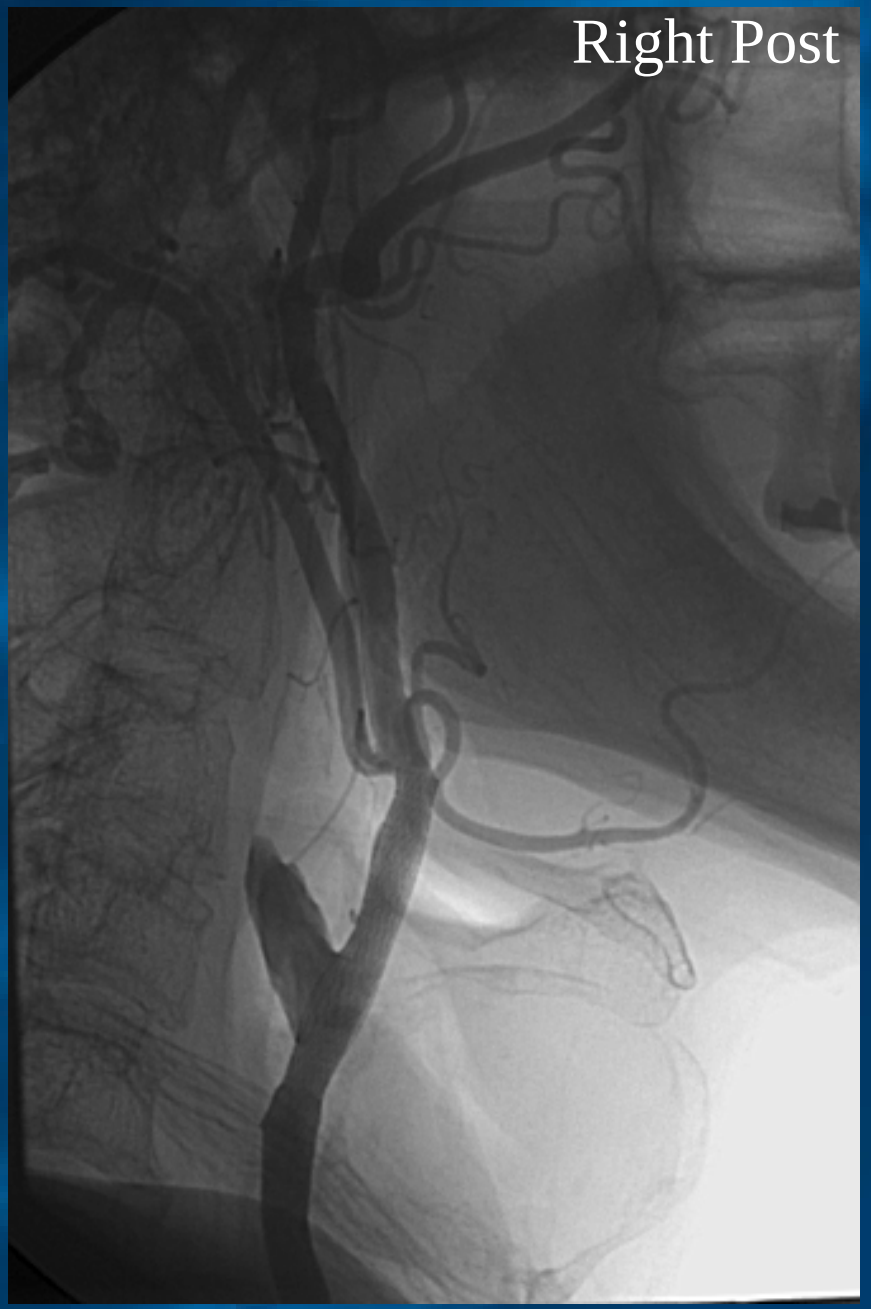

Right Post

Carotid stenting is inferior to carotid endarterectomy

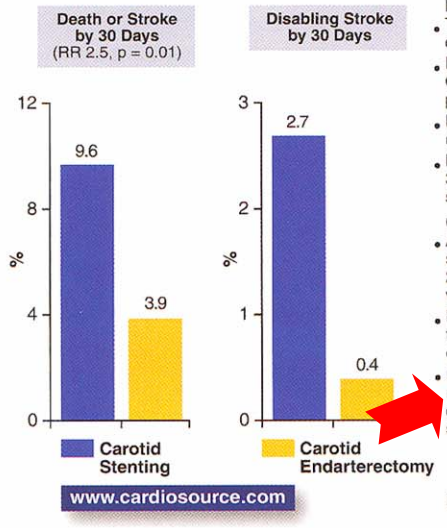
Mas JL, Chatellier G, Beyssen B, et al, for the EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006; 355:1660–1671.

Guidelines *& Trials*

Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S)

EVA-3S

Trial Design: EVA-3S was a randomized trial of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) in patients with symptomatic carotid artery stenosis ≥60%. Primary endpoint was death or stroke within 30 days of treatment.



Results

- Trial stopped early after hazard observed with carotid stenting over endarterectomy
- Death or stroke more than double in CAS group vs. CEA group (Figure), regardless of use of cerebral protection with stenting or physician experience
- Death or stroke remained ↑ with CAS at 6 months (11.7% vs. 6.1%, p = 0.02)
- Nonfatal stroke ↑ CAS group (8.8% vs. 2.7%, RR 3.3, 95% CI 1.4-7.5, p = 0.004), including disabling stroke (Figure)

Conclusions

- Among patients with symptomatic carotid artery stenosis, treatment with CAS was associated with 2.5 times higher rate of death or stroke by 30 days vs. CEA
- For every 17 patients treated with stenting rather than endarterectomy, 1 additional stroke or death occurred
- Based on these findings and other recent large randomized trials, CEA, and not CAS, should be considered optimal treatment for carotid artery stenosis

N Engl J Med 2006;355:1660-71

EVA 3-S

Unprotected CAS – trial suspended

Trial restarted with protected CAS

Trial suspended October 2005 (527 patients enrolled)

Procedural stroke risk 9.6% (CAS) vs. 3.9% (CEA) (primary endpoint)

New Engl J Med 2006; 355: 1660-71

Concerns: complication rate very high (unusual)
some interventionalists performed their first CAS during trial
under coaching

EVA-3S

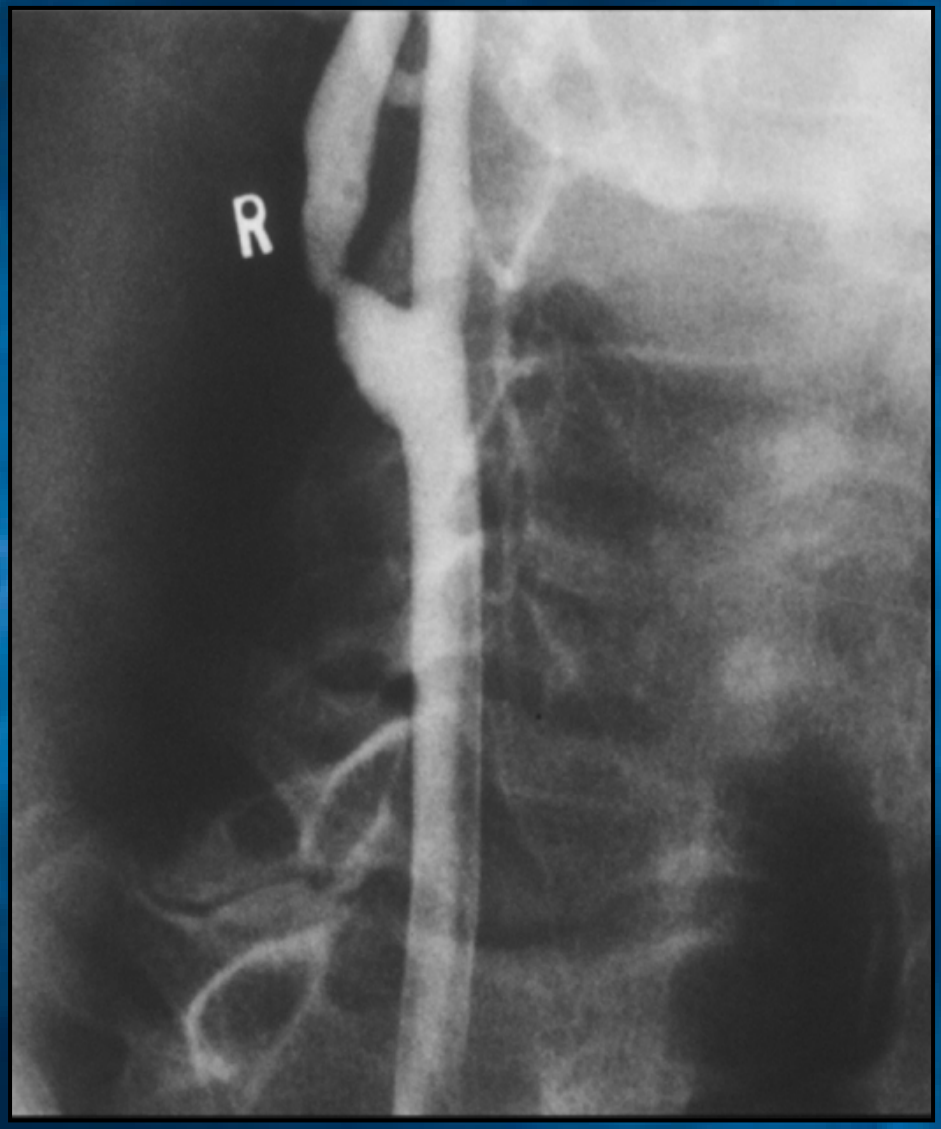
- *1.8 patients enrolled per center in the 5 years the study took*
- *2.4% didn't even receive Heparin or similar agents during the procedure.*
- *Most of the operators were vascular surgeons with no previous interventional experience*

Same procedure again!!

Randomized Study of Carotid Angioplasty and Stenting versus Carotid Endarterectomy: A Stopped Trial

Naylor AR; J Vasc Surg 1998;28:326-34

- Endarterectomy 10 pts
  No complications
- Carotid Angioplasty 7 pts
  5 strokes (3 disabling)
- Trial stopped, first stent implantations of trialists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What did we learn from EVA-3S?

Three years into the trial… the investigators thought embolic protection might be important.

What did we learn from EVA-3S?

Three years into the trial the investigators thought ASA/Plavix should be begun 3 days before.

What did we learn from EVA-3S?

They felt 5 cases done investigators was adequate training.

What did we learn from EVA-3S?

Some sites randomized patients with the 1st enrollment of treatment.

What did we learn from EVA-3S?

They treated 85.4% of the enrolled patients with ASA/Plavix.

What did we learn from EVA-3S?

5 % of patients had failure of carotid stenting and had to have CEA.

What did we learn from EVA-3S?

The median carotid stenting time was 70 minutes.

SPACE The Final Frontier???

SPACE-Trial

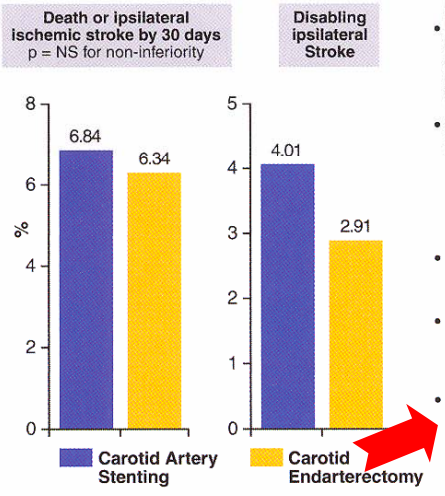
- *Prospective multicenter trial*
- *Inclusion criteria: >70% symptomatic stenosis*
- *Primary endpoints: stroke & death in 30 days*
- *Secondary endpoints: stroke & death after 1 year*
- *Trial powered to 1.900 patients – stopped after 1.200*
- *Non-inferiority trial – margin set at 2.5%*

Guidelines & Trials

Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE)

SPACE

Trial Design: SPACE was a randomized trial of carotid artery stenting (CAS) (n=605) or carotid endarterectomy (CEA) (n=595) in patients with symptomatic carotid artery stenosis. Primary endpoint was ipsilateral ischemic stroke or death through 30 days, evaluated for non-inferiority.



Results

- Primary endpoint failed to meet non-inferiority criteria in both ITT analysis (Figure; absolute difference 0.51%, 90% CI 1.89%-2.91%) and per protocol analysis (6.95% for CAS vs 5.64% for CEA, absolute difference 1.32%)
- All secondary endpoints fell in favor of CEA, including disabling ipsilateral stroke or death (4.67% for CAS vs 3.77% for CEA, OR 1.25); disabling ipsilateral stroke (Figure, OR 1.39); any stroke (7.51% for CAS vs 6.16% for CEA, OR 1.24); and procedural failure (3.17% for CAS vs 2.05% for CEA, OR 1.56)
- Results similar in subgroup of patients treated with embolic protection devices in CAS group

Conclusions

- Among patients with symptomatic carotid artery stenosis, treatment with carotid artery stenting failed to demonstrate non-inferiority compared to carotid endarterectomy at 30 day follow-up
- Given these findings and those of other recent trials, carotid endarterectomy – not carotid artery stenting – should be considered optimal treatment for carotid artery stenosis

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SPACE

- *No MI Endpoint.*
- *No contralateral CVA endpoint.*
- *Procedure failure 3%?*
- *Why antiplatelet agents in only 79%?*
- *Why EPD's in only 27%?*
- *Why are no Cardiologists involved?*
- *Lots of low volume centers.*

SPACE

Why would a patient select a more invasive procedure for symptomatic carotid therapy if the outcomes were the same?

Conclusion From the Two Studies

- ***Failure to adequately treat patients with dual agents is unacceptable.***
- ***The procedure needs to be performed by an experienced operator.***
- ***The use of embolic protection is mandatory and if the use of embolic protection is not possible because of anatomy, the patient might be better off with CEA or other medical therapy.***

CEA: plaque removal

Facts on carotid Stenting

- ***ASA/Plavix should be given for 5 days prior.***
- ***Embolic Protection is essential***
- ***In 2007 the interventionist should have done a minimum of 100 carotid angio's and 25 carotid interventions before performing a CAS procedure.***
- ***The filter time should be less than 20 minutes.***

FUTURE CAROTID THERAPY

- From The Pharmaceutical Perspective -

- recently developed statins and anti-platelet agents are a start
- why only treat focal areas of disease when atherosclerosis is known to be a systemic disease?
- we need to look beneath the surface of plaque and address the underlying pathophysiology of atherosclerosis & inflammation

Perhaps there is a new battle brewing.

Carotid Artery Disease: Is there a New Gold Standard in Therapy?

Carotid Artery Disease: Is there a New Gold Standard in Therapy?

Conclusion

- ***We do know high risk patients are helped with CAS and EPD compared to CEA.***
- ***What about > 80 year old patients?***
- ***Experience, use of EPD, use of antiplatelet agents, and technique are crucial in CAS (and CEA).***
- ***We don't know about low risk patients… CEA or CAS.***
- ***If CAS is found to be equivalent to CEA in low risk patients it will be the patient preferred procedure of choice.***

Conclusion

- *CREST, ICSS, and ACT I need to be completed.*
- *These low risk trials will give us direction to determine whether the treatment of carotid disease has truly changed.*
- *Perhaps there is a role for a trial of aggressive medical therapy compared to CEA and CAS similar to the COURAGE trial.*