Carotid Stenting for Asymptomatic Carotid Stenosis - Will ACT 1 Change Anything?

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Presenter Disclosure Information

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

- ***QuantumCor, Major Stock Holder/Medical Director;***
- ***Radius Medical, Avinger and Claret Medical, Major Stock Holder;***
- ***PQ ByPass, Founder and Major Stock Holder;***
- ***CSI, Stockholder;***
- ***Spectranetics, Abbott, Medtronic, Bard, Abiomed, Honorarium;***
- ***Medtronic, Abbott, AngioScore, Speaker;***
- ***Acist Medical Systems Grant; and***
- ***Verve Medical, Inc., Major Stockholder***
- ***Founder, Arizona Medical Systems***
- ***Owner/Inventor, ORACLE Thrombus Removal System***

Patents *-- RF, Snares, Wires, Balloon Catheters, Covered Stents, Devices for Arterial Venous Connection, Devices for LV and RV Closure, Vascular Access Patents*

Stroke

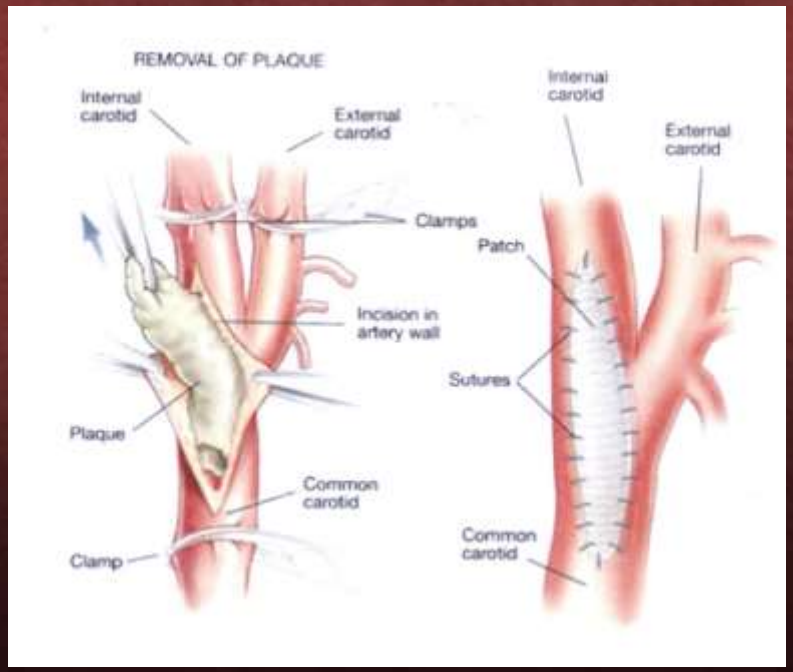
- 3rd leading cause of death
  - -- Estimated 164,000 deaths per year
  - · Leading cause of long term disability
- ~30% of strokes are due to extracranial cerebrovascular disease

CEA: Historical Considerations

- CEA (Carotid EndArterectomy)
- First performed by DeBakey in 1953

  -- ~1 million performed from 1974-1985

  - Uncertainty remained regarding efficacy of operation



Endarterectomy, Stenting, or Neither for Asymptomatic Carotid-Artery Stenosis

J David Spence, MD, and A Ross. Naylor, MD

In the United States, more than 90% of carotid artery interventions are performed in asymptomatic patients. What about other countries?

Germany and Italy 60%
Canada and Australia 15%
Denmark 0%

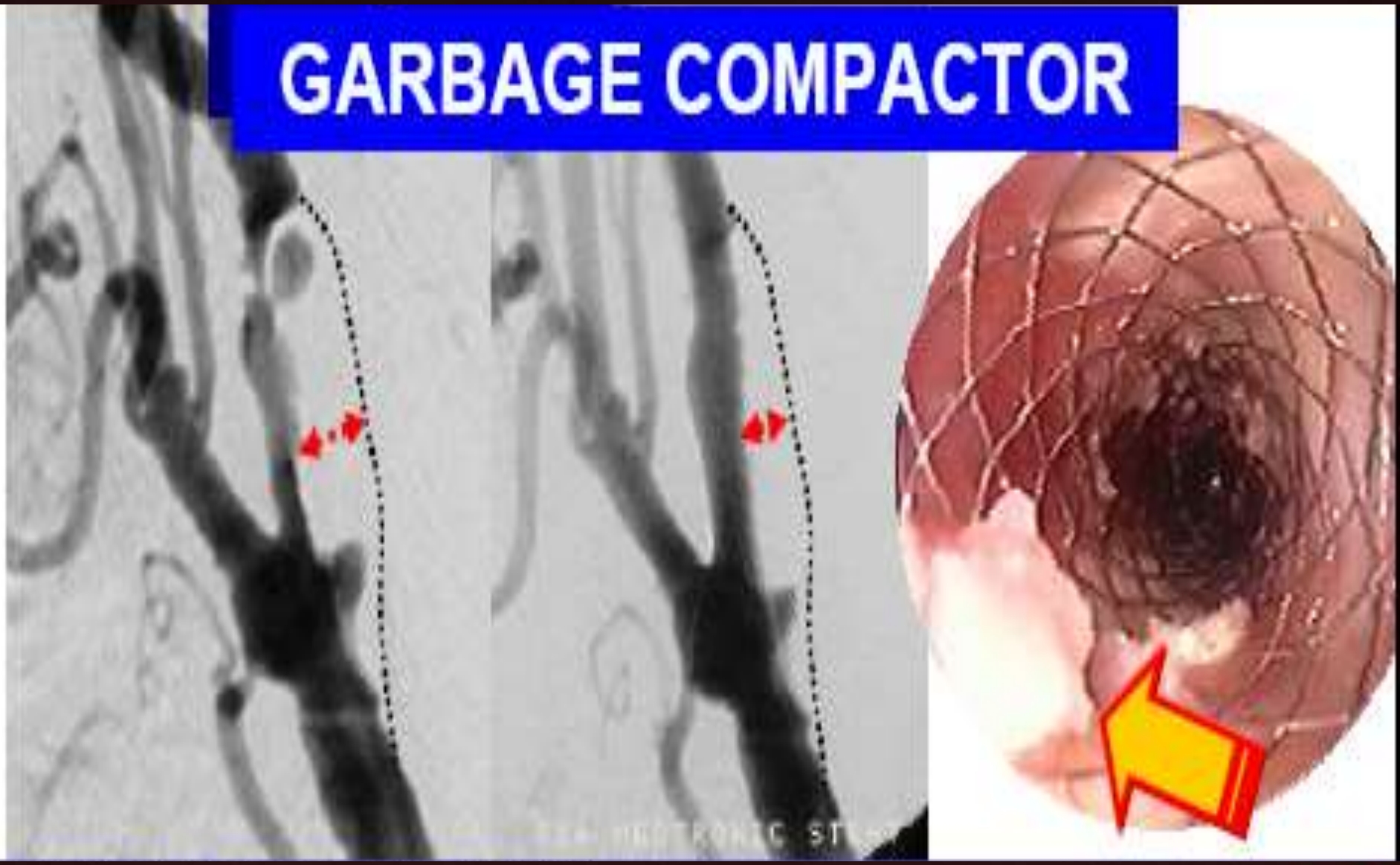
Equipoise and carotid therapy?

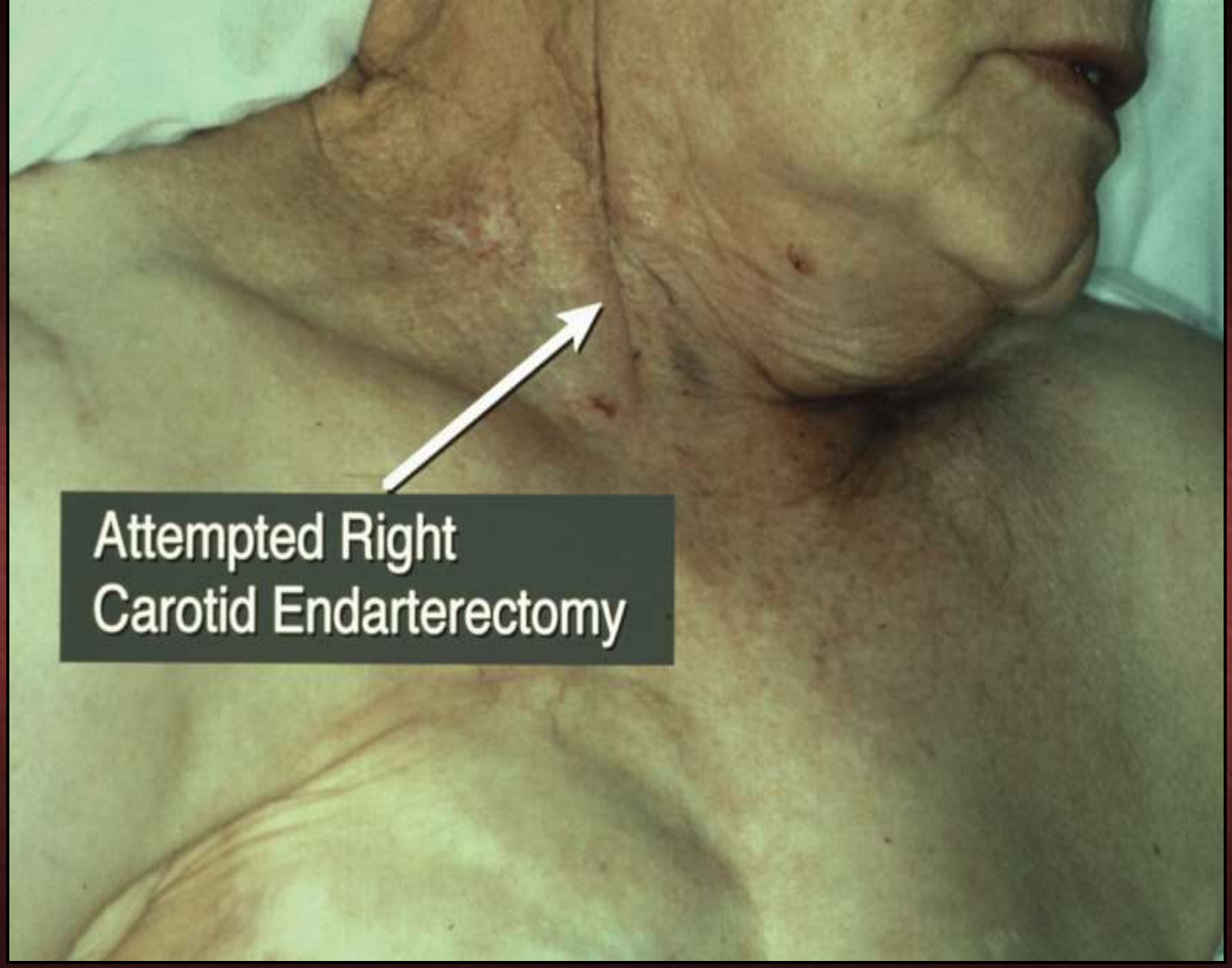
"The ethics of clinical research requires equipoise---a state of genuine uncertainty within the expert medical community regarding the comparative merits of each treatment arm in a trial."

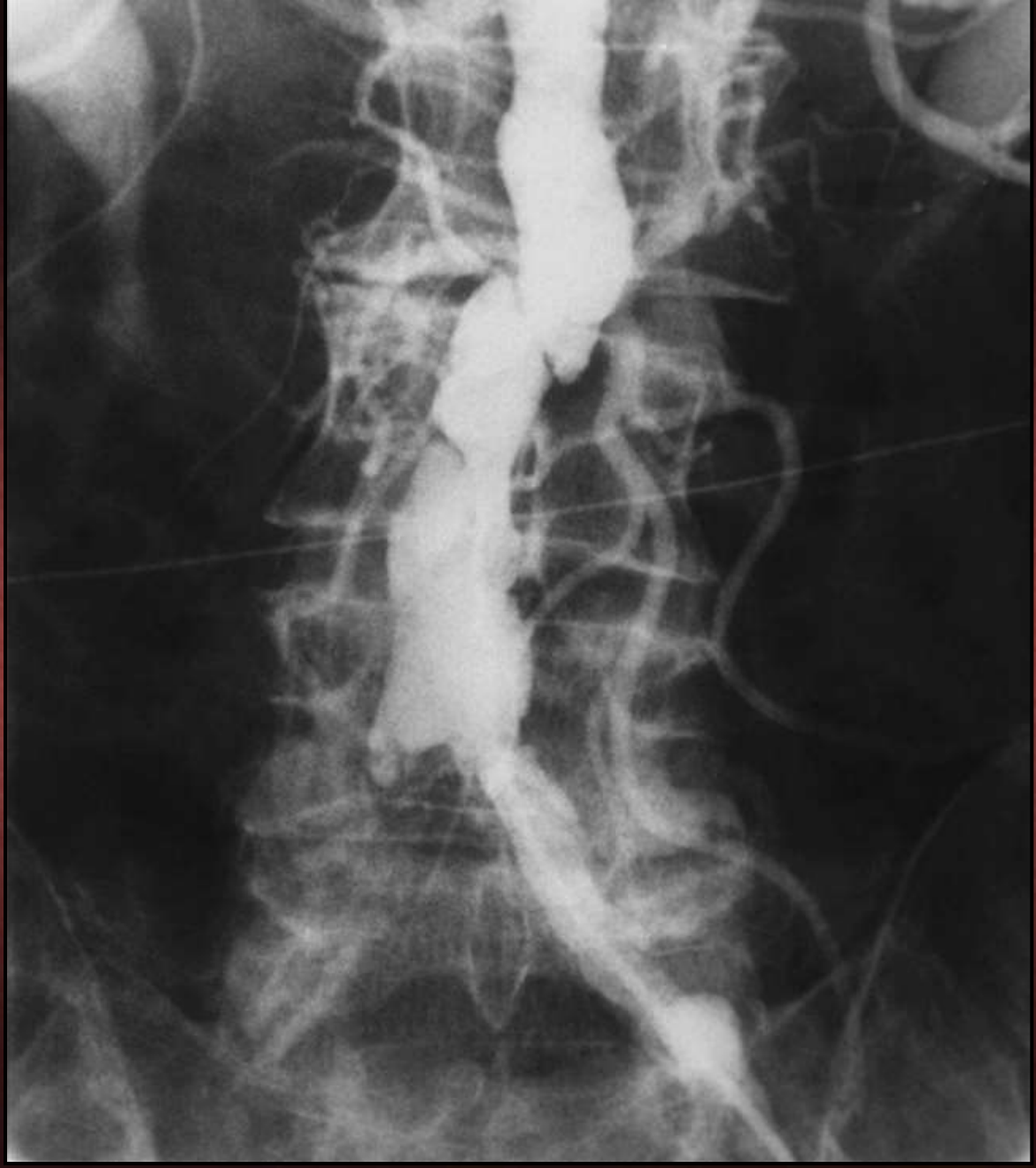
Equipoise and the ethics of clinical research.
Freedman B. N Engl J Med 1987 Jul 16;317(3):141-5

GARBAGE DISPOSAL

GARBAGE COMPACTOR




Attempted Right
Carotid Endarterectomy



D.D.H.
8-22-00

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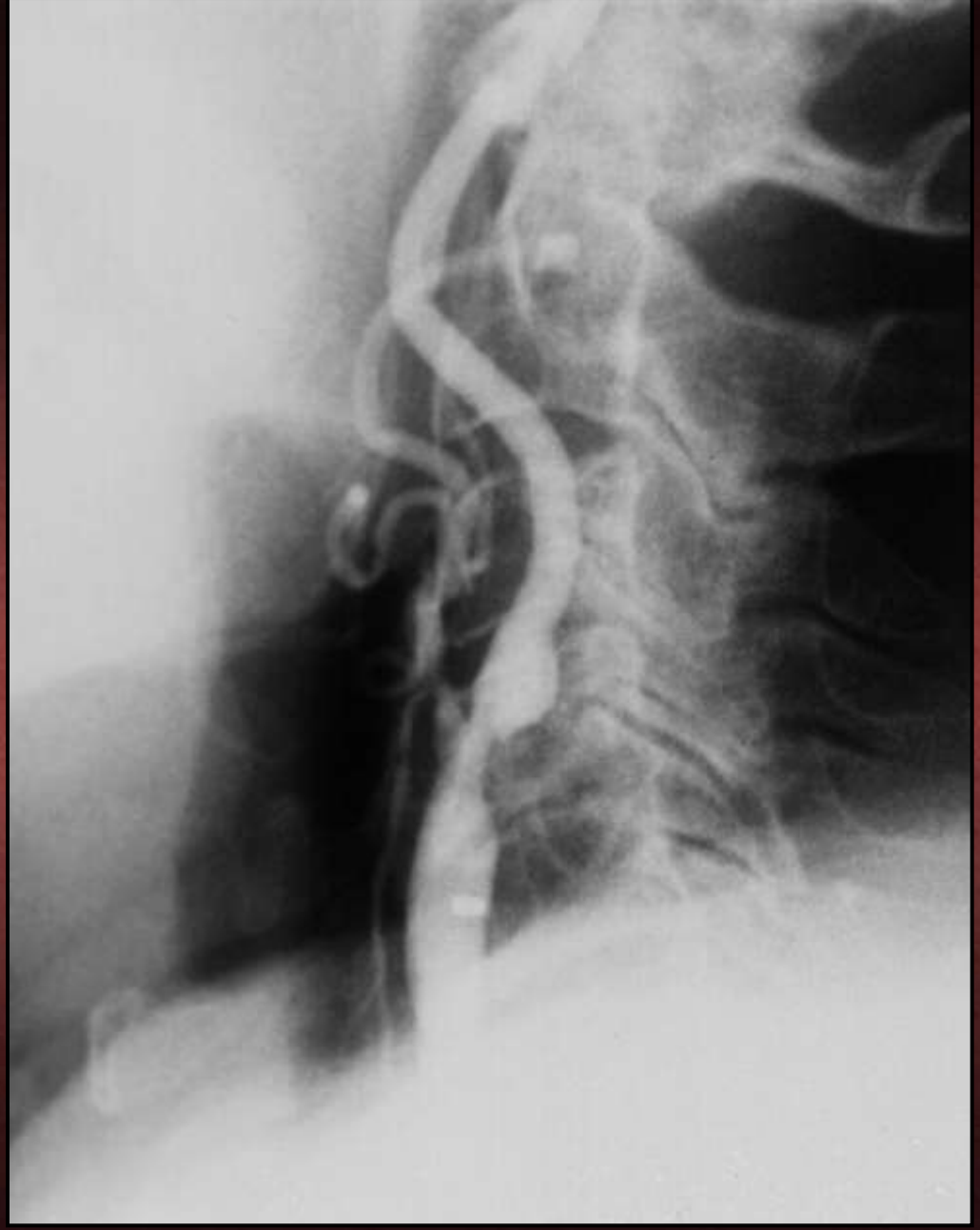

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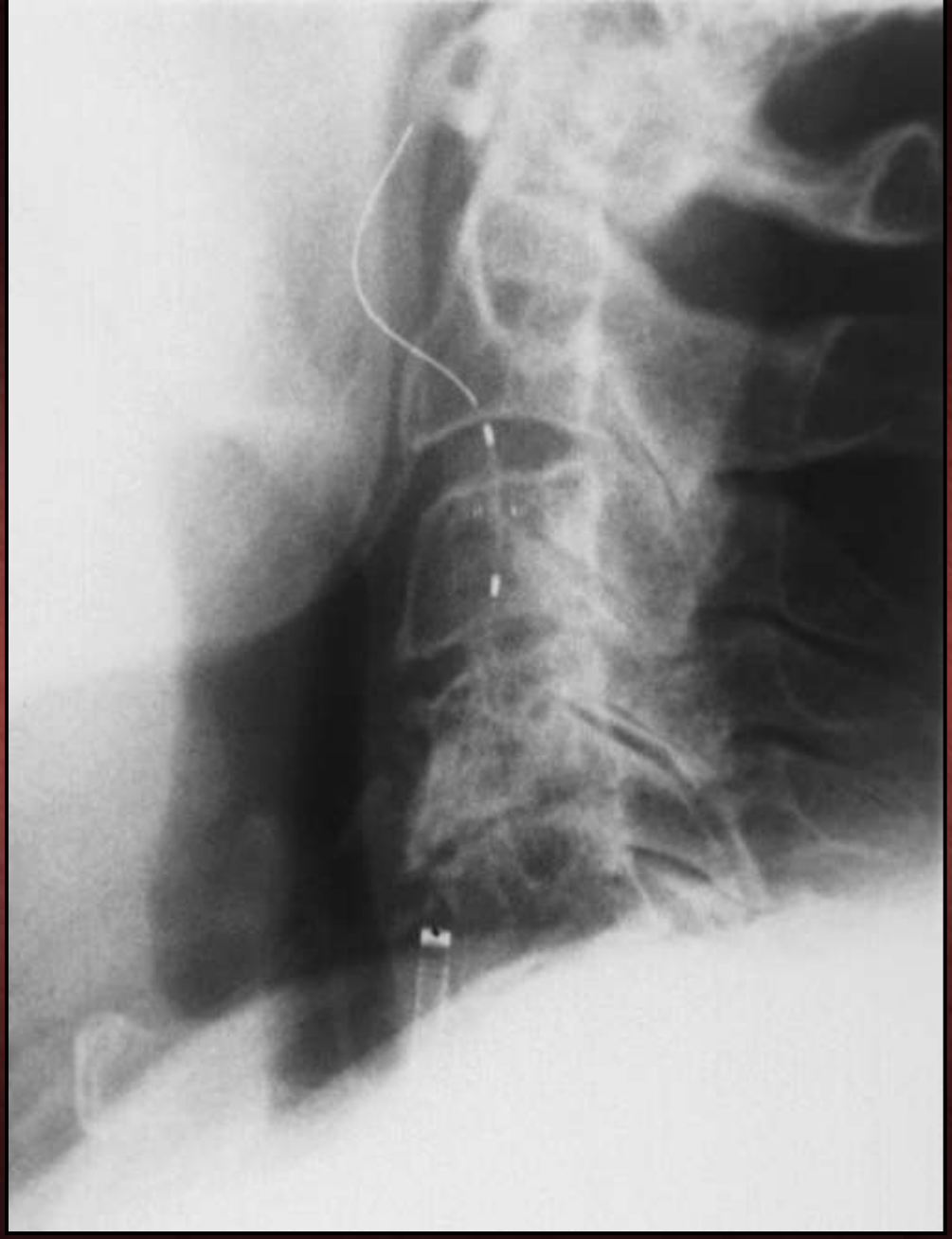

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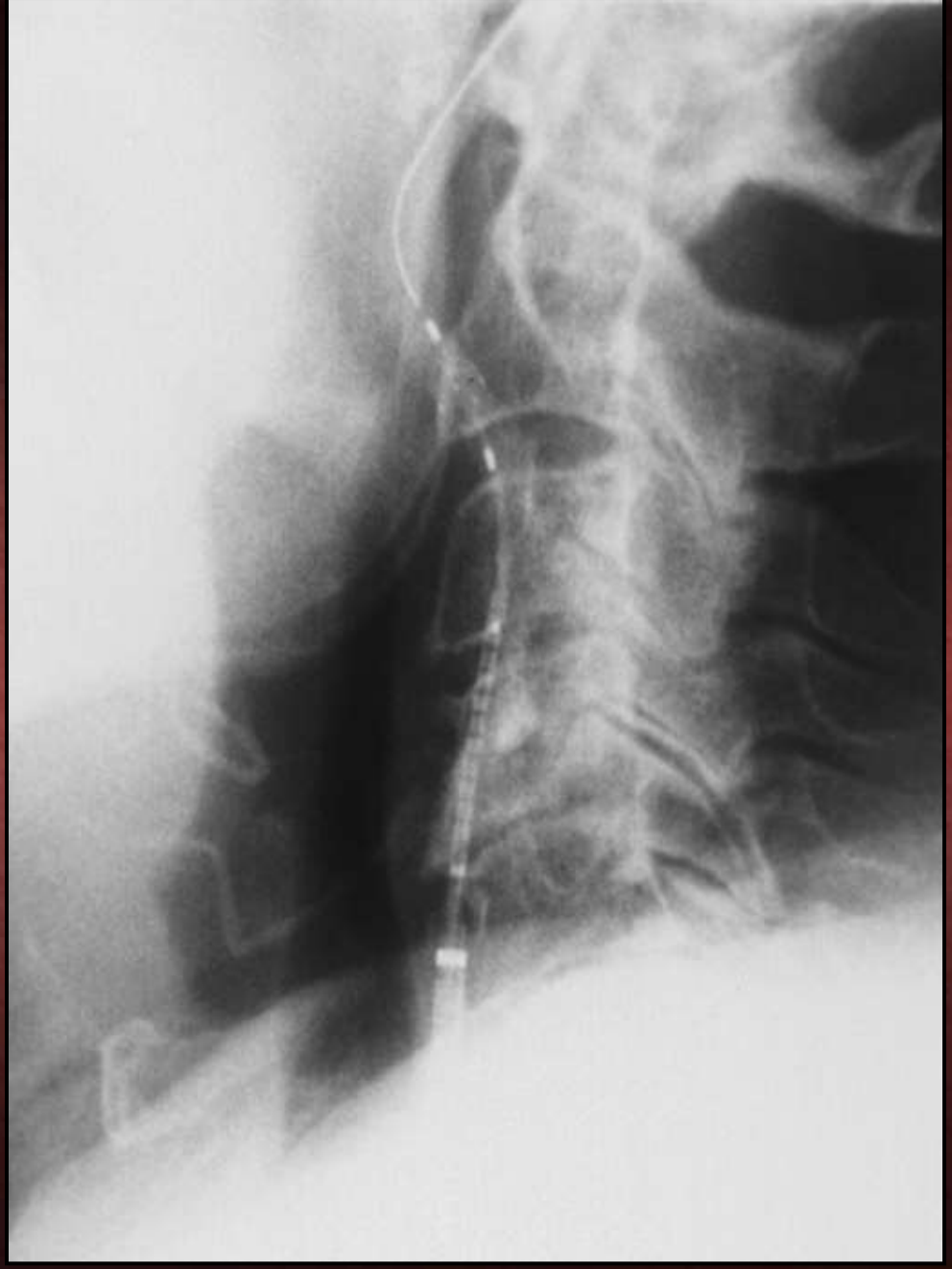

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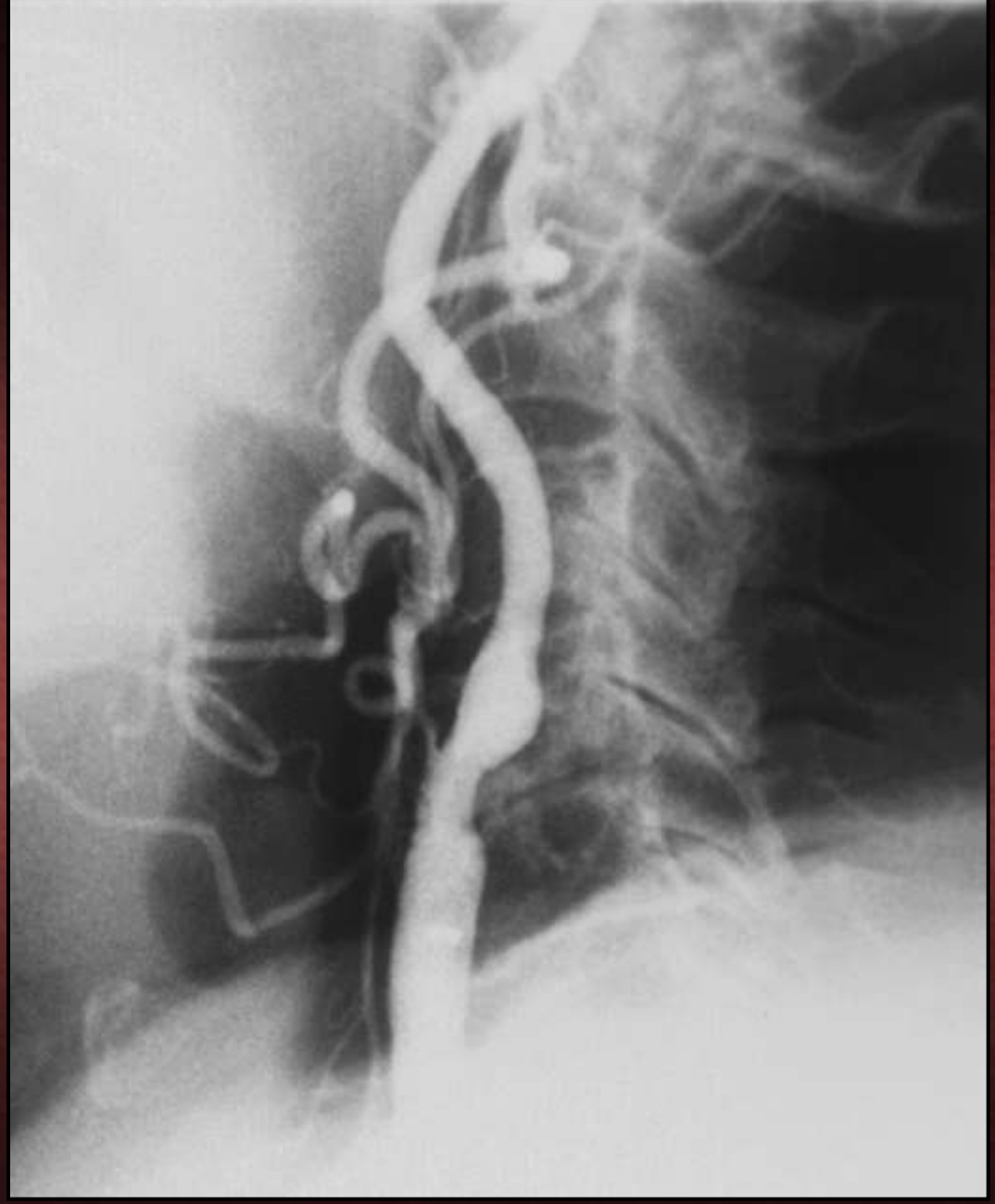

D.D.H.
8-22-00

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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

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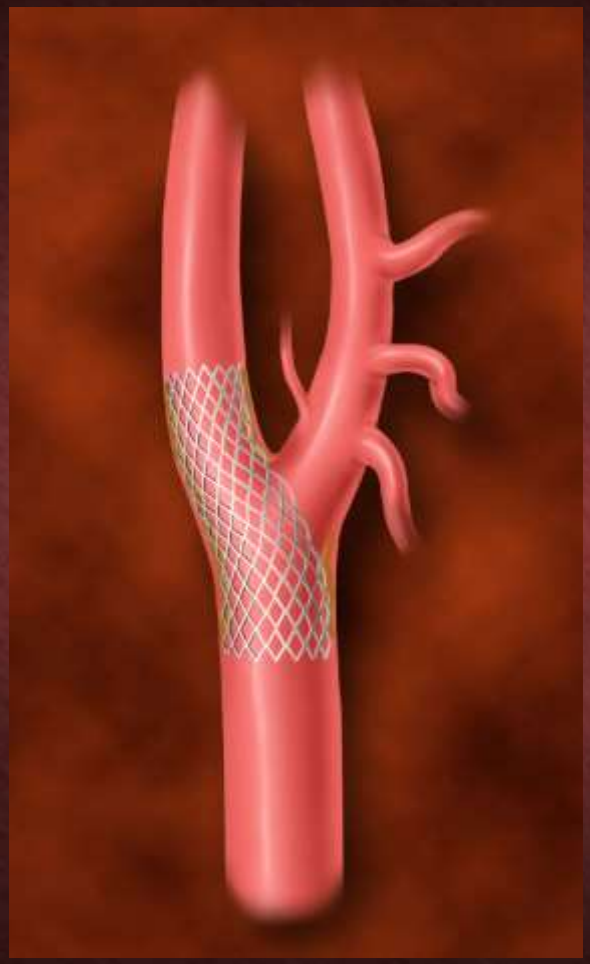
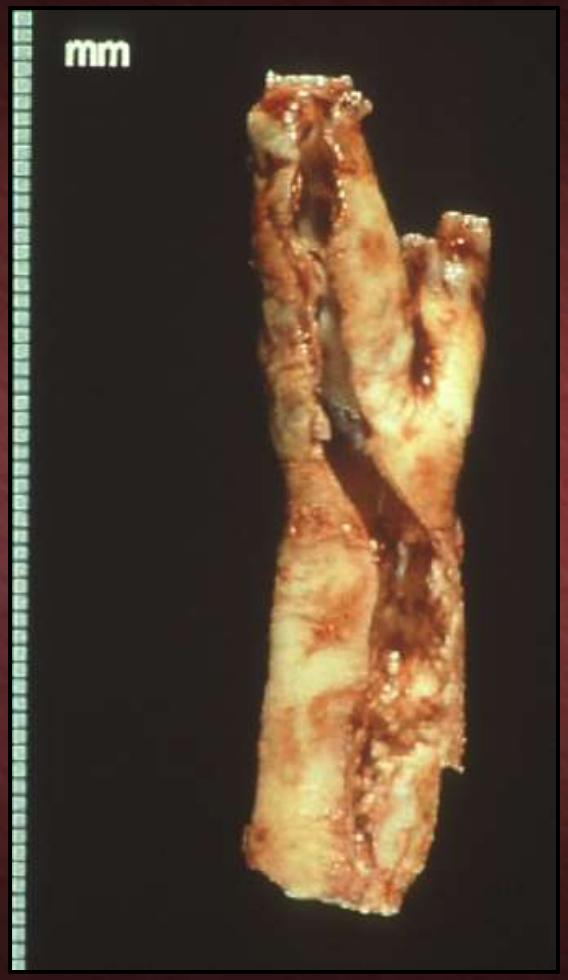
WHO WON?

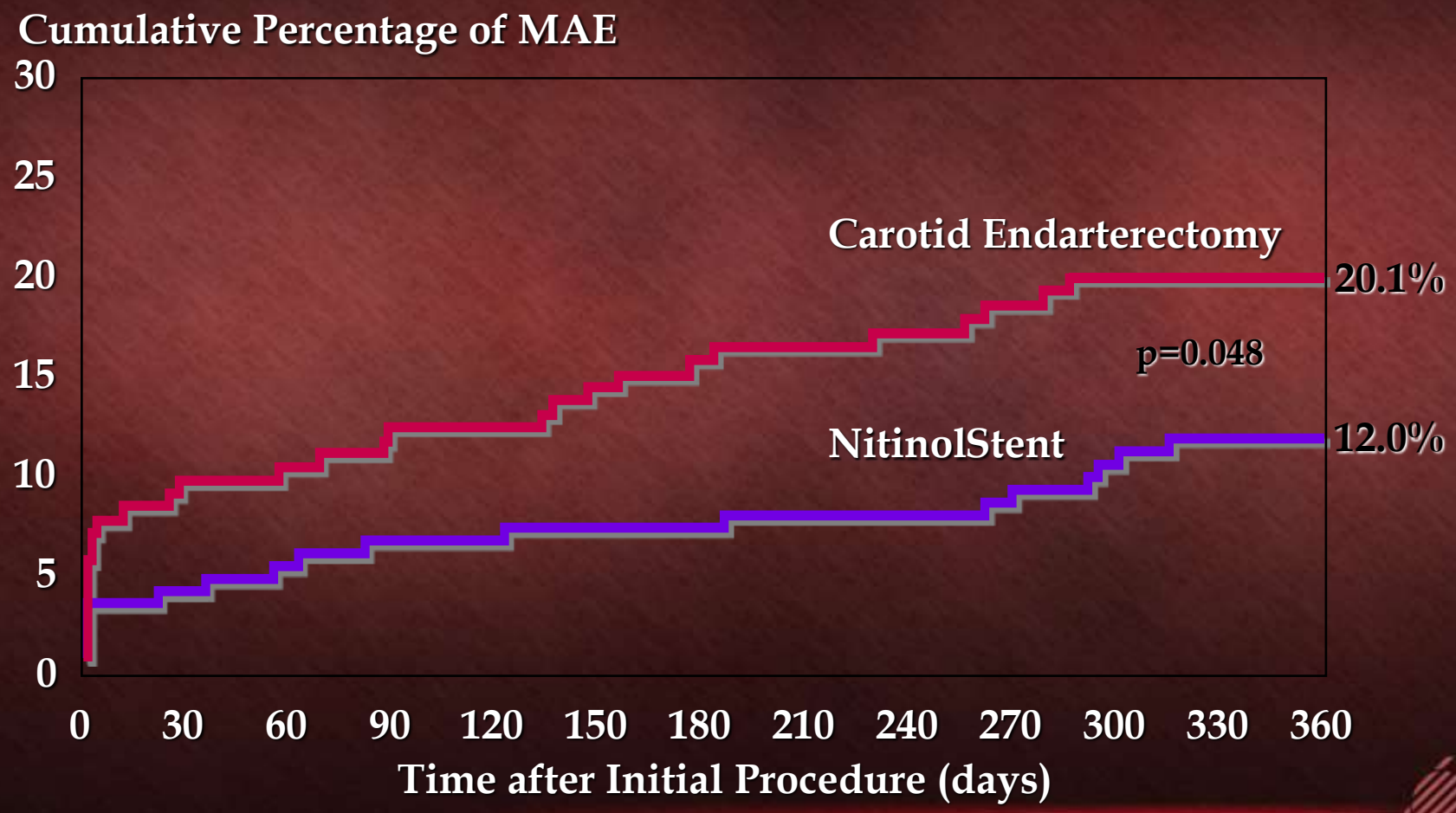


5.8%



12.6%

SAPPHIRE Trial: 1-Year Outcome - *sxatic and asxatic high surgical risk patients*



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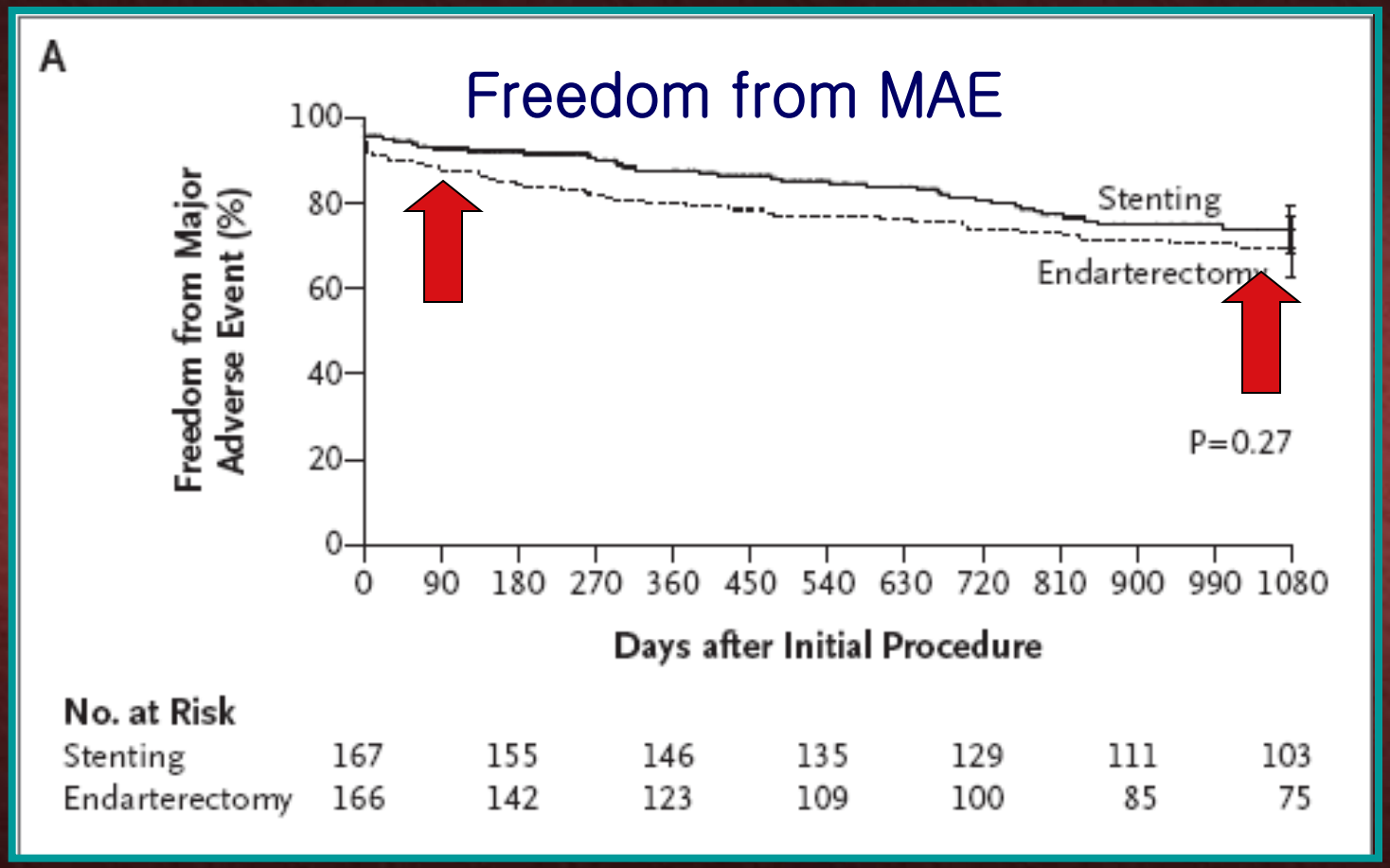
SAPPHIRE 3-Year Outcomes



N Engl J Med 2008;358:1572-9

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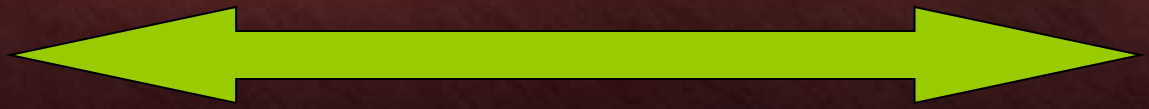
SAPPHIRE Trial

- First randomized study comparing Carotid Stenting With Emboli Protection versus CEA
- ONLY randomized trial of high-risk cohort
- Randomized patients defined by surgeons
- Provides adjudicated surgical complication rate for high risk patients, who were excluded from previous CEA trials, in hands of surgeons who have excellent track records ---->stroke/death higher than anticipated



CASE CLOSED

on Carotid Stenting

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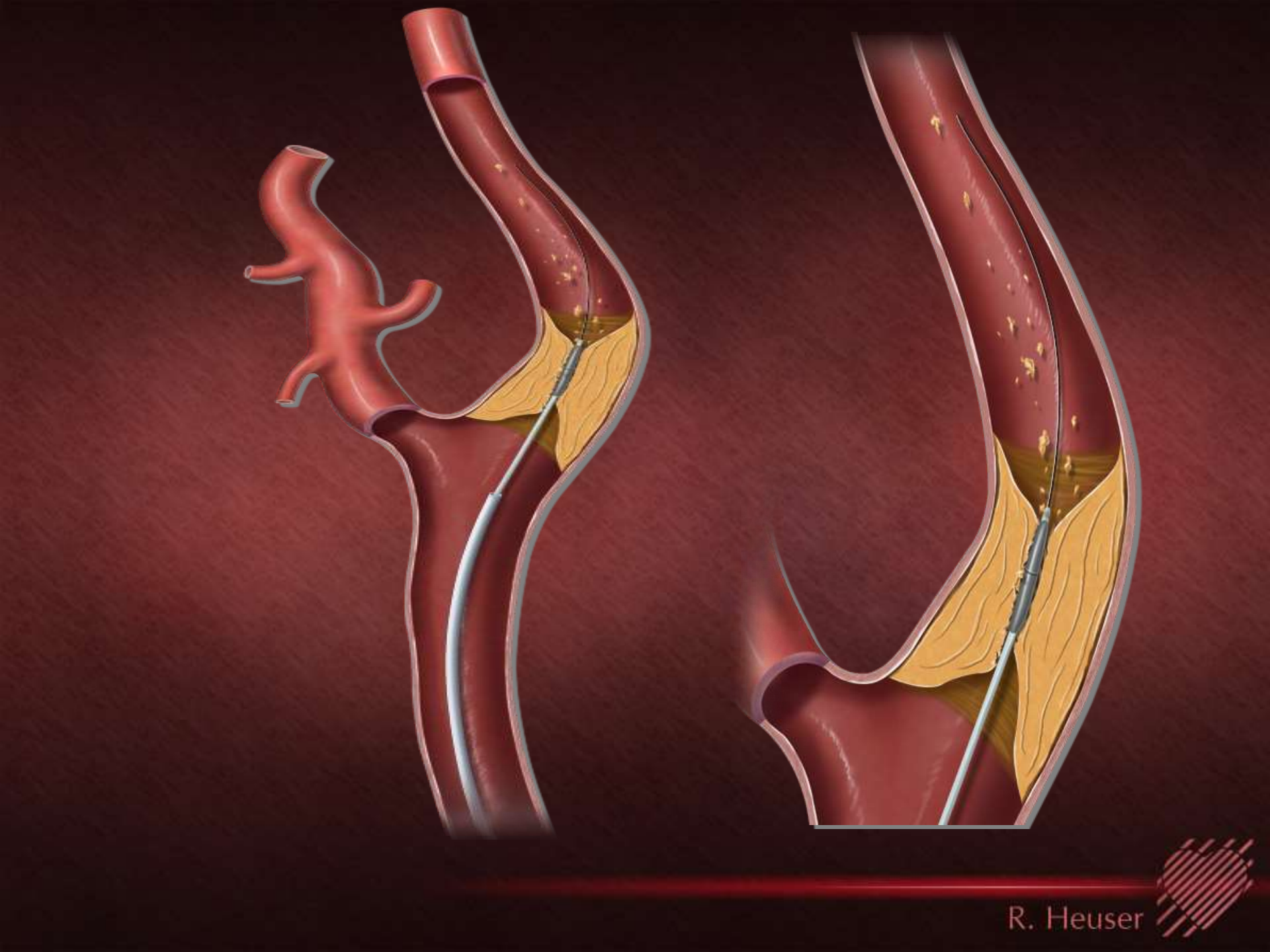
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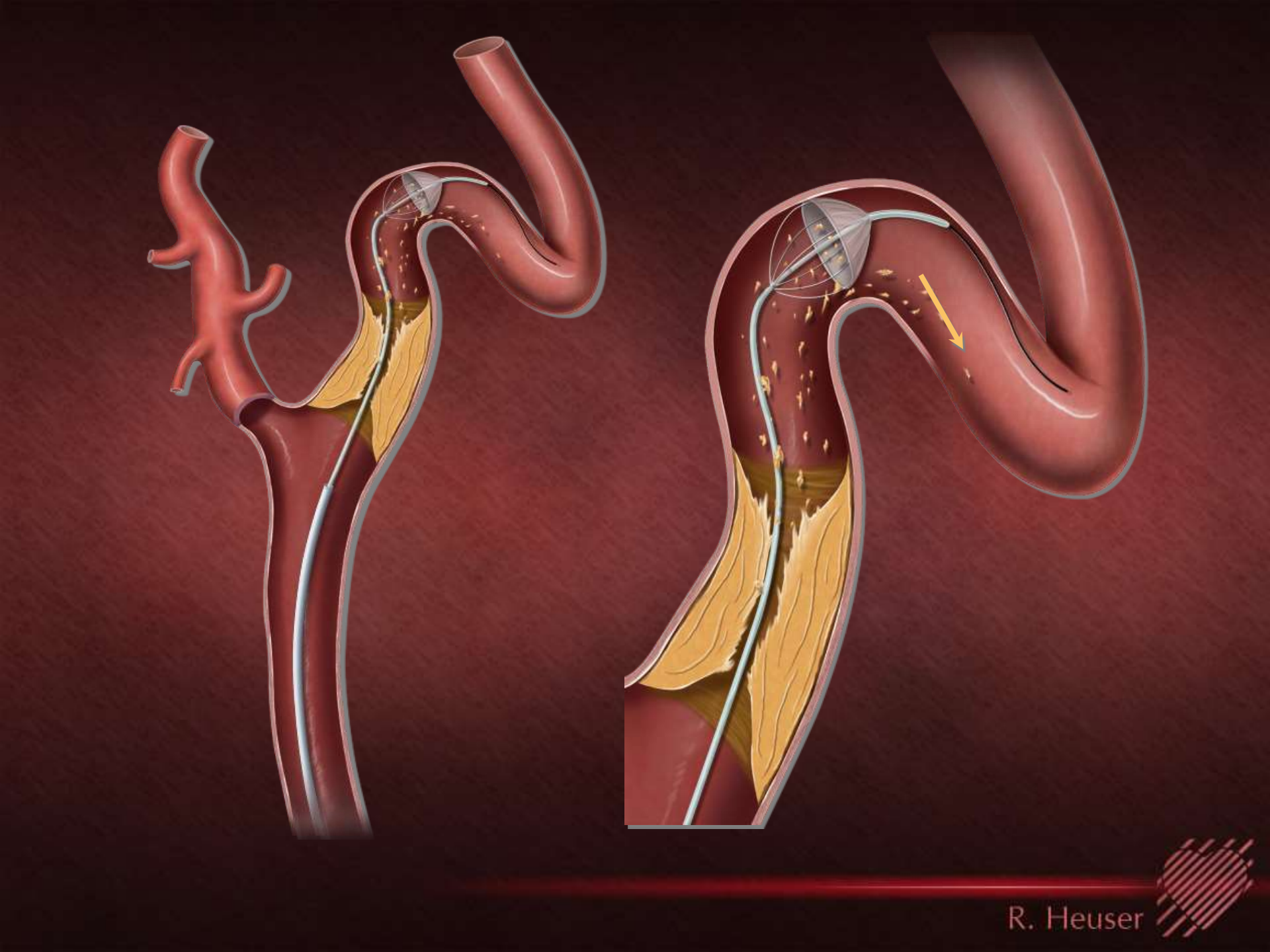
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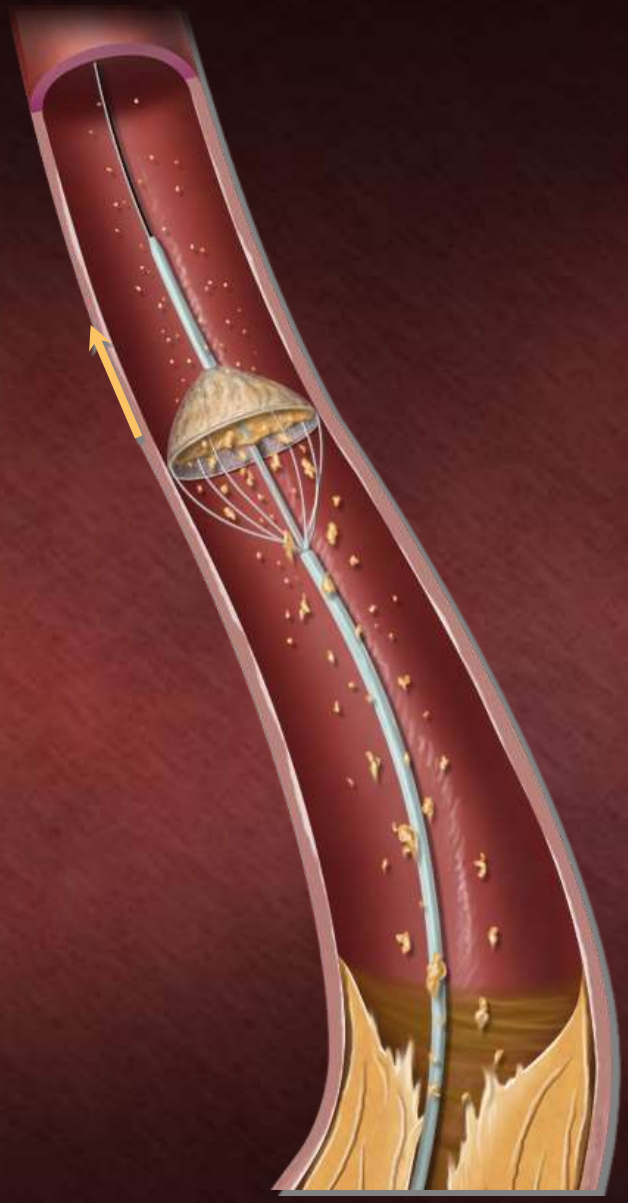

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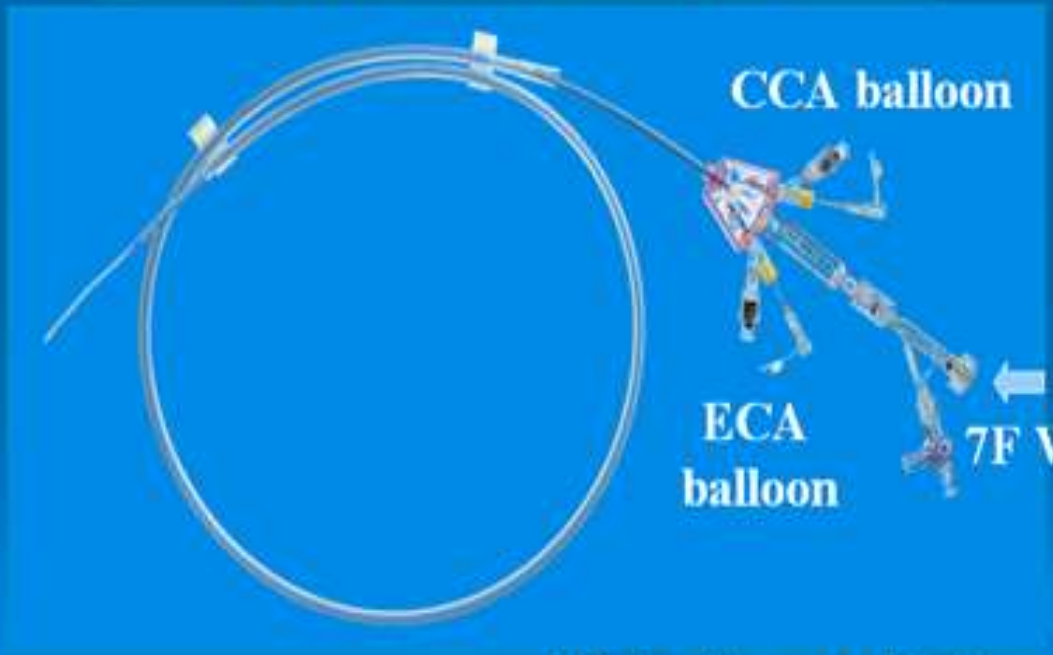
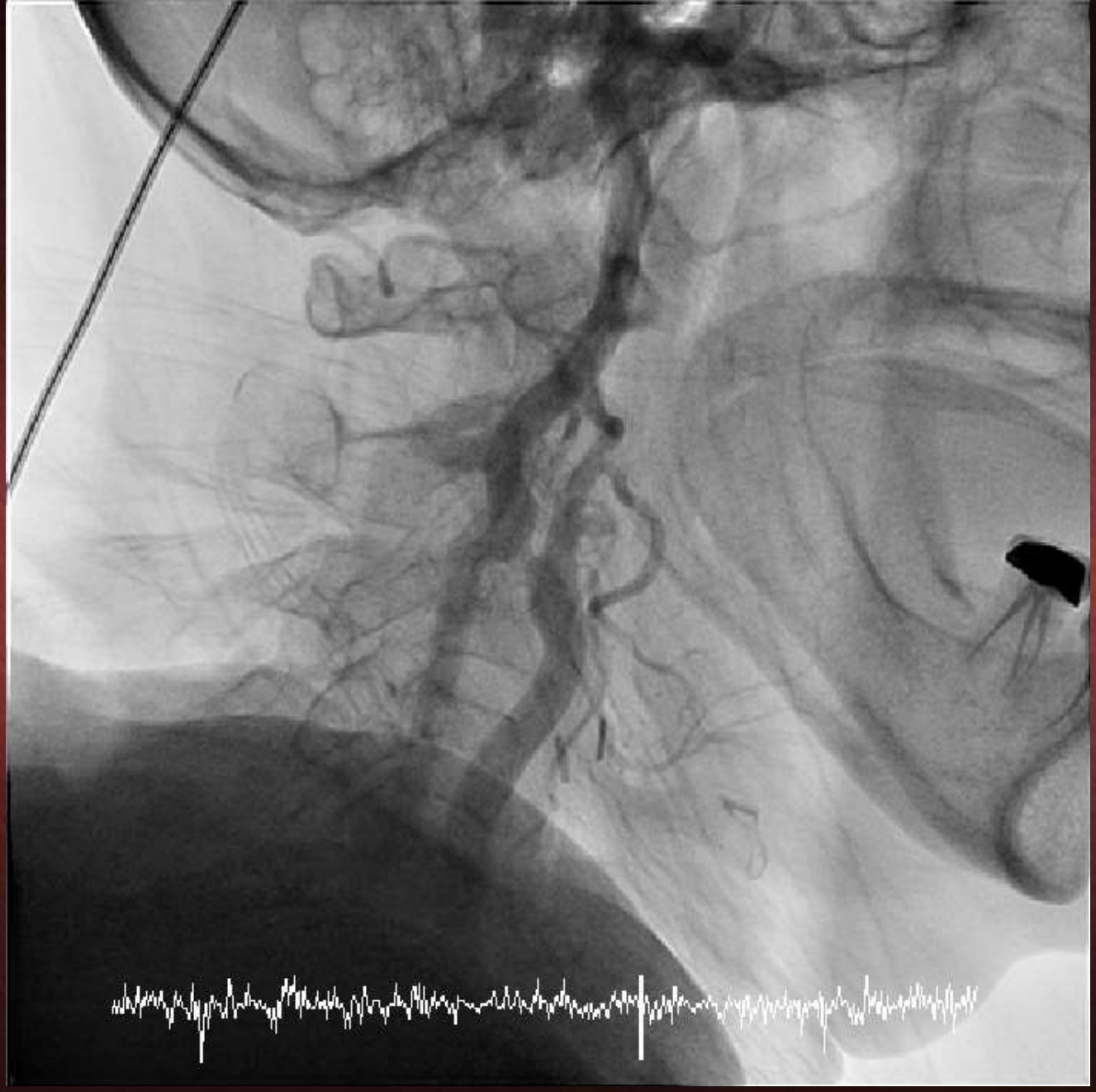
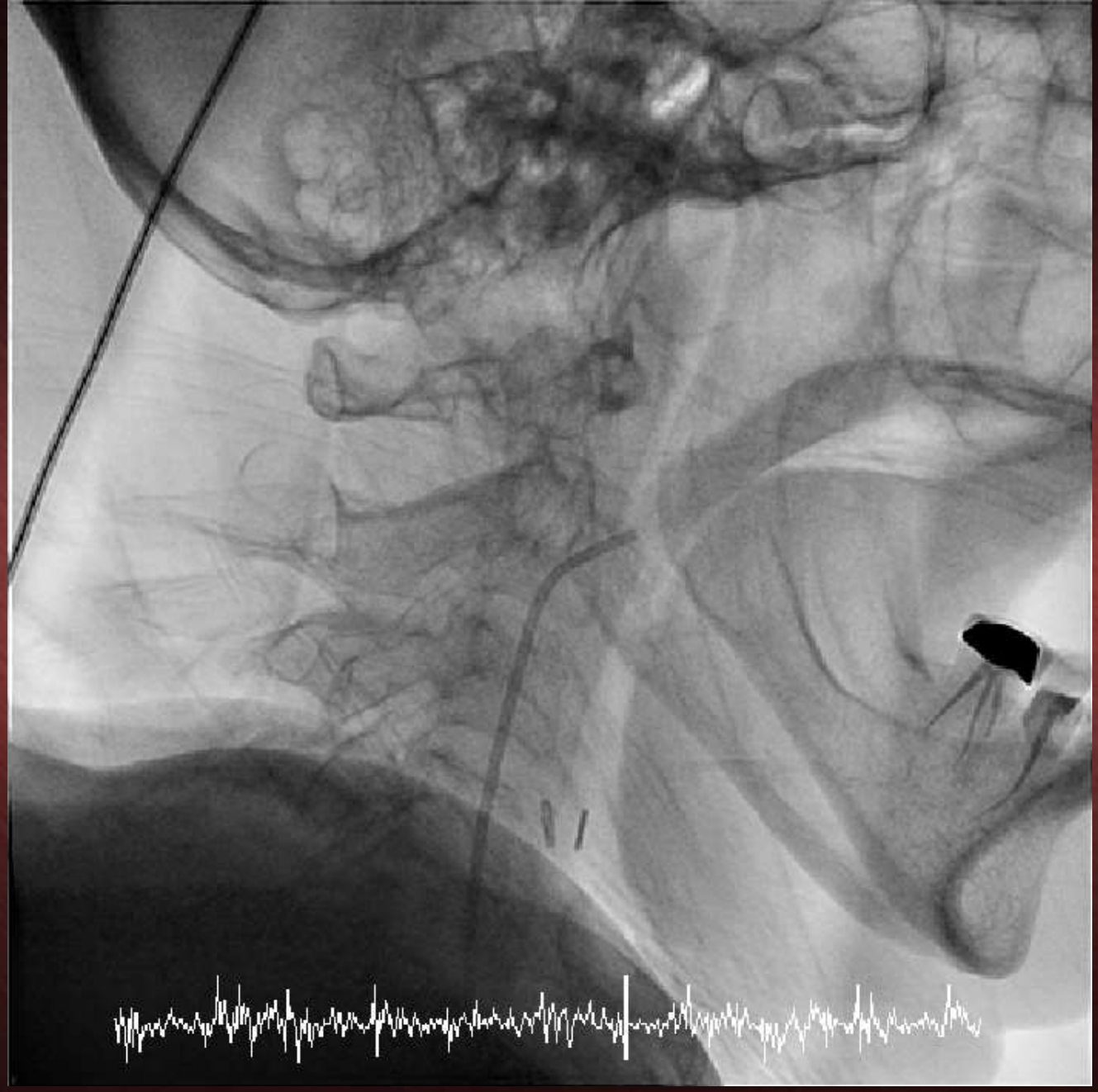
Single Device consisting of long 90 cm sheath and 2 occlusion balloons

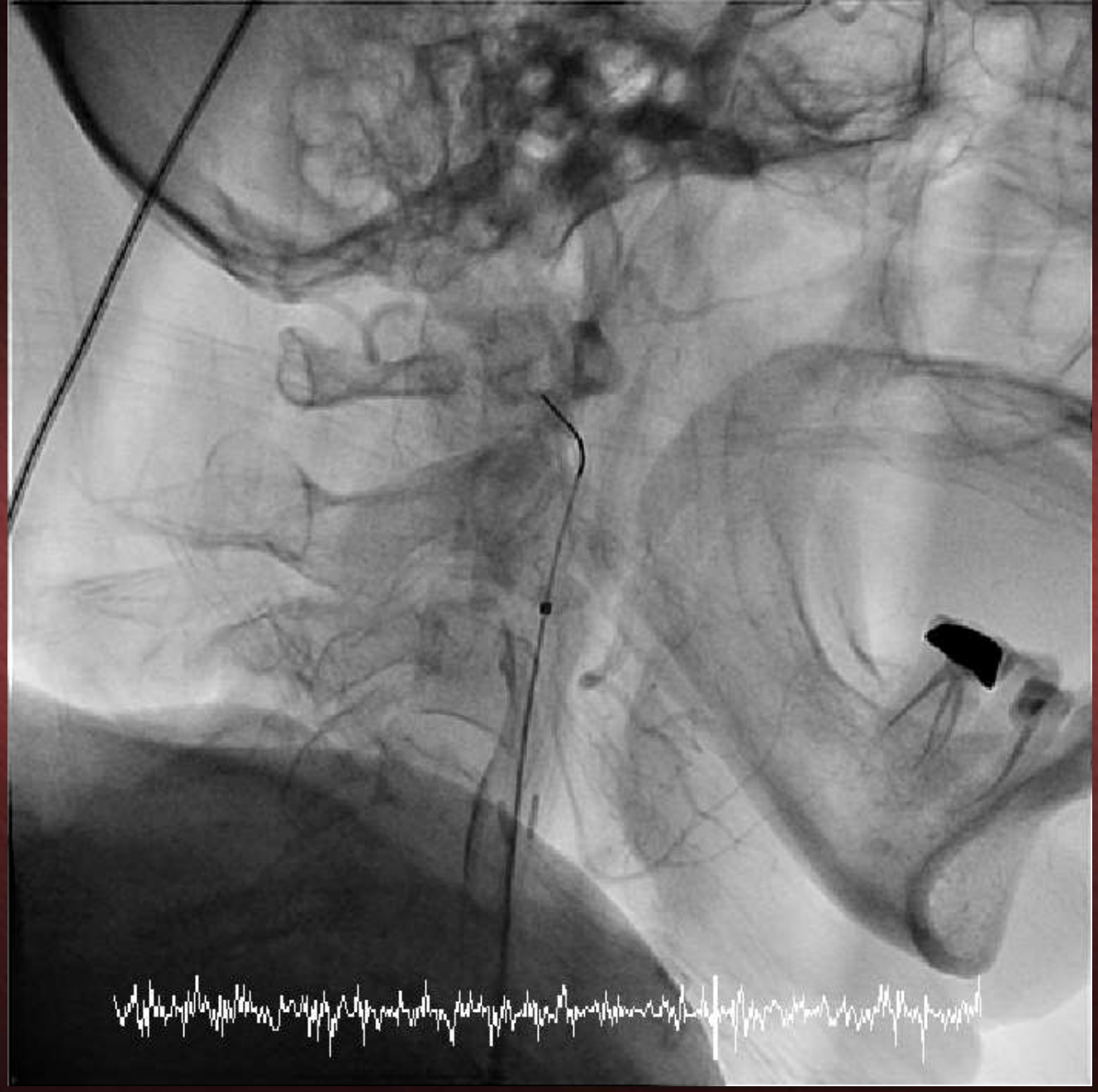


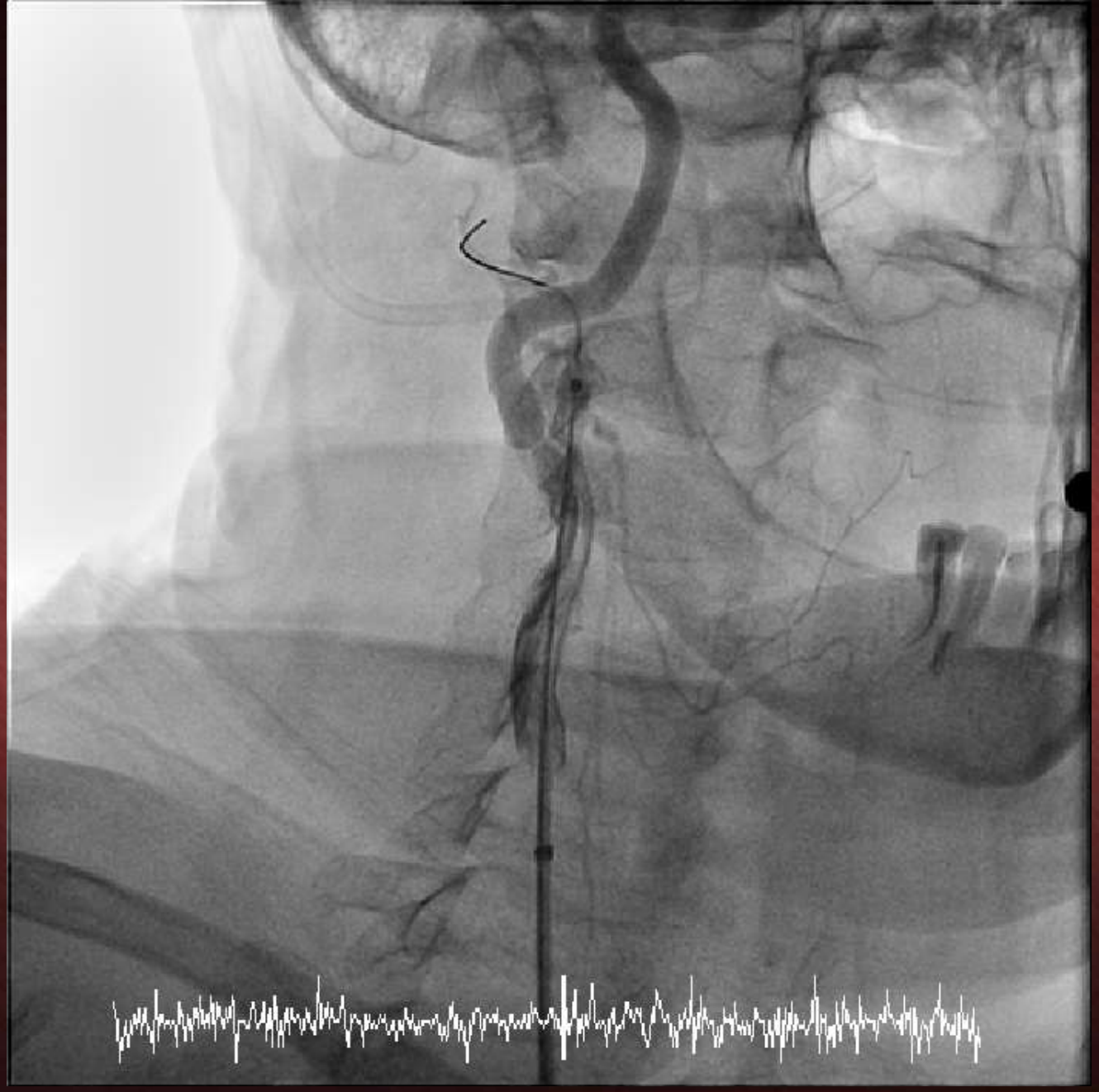
9F device available

RS is a 58 y/o patient with TIA's. She has had previous bi-lateral carotid endarterectomy and severe COPD









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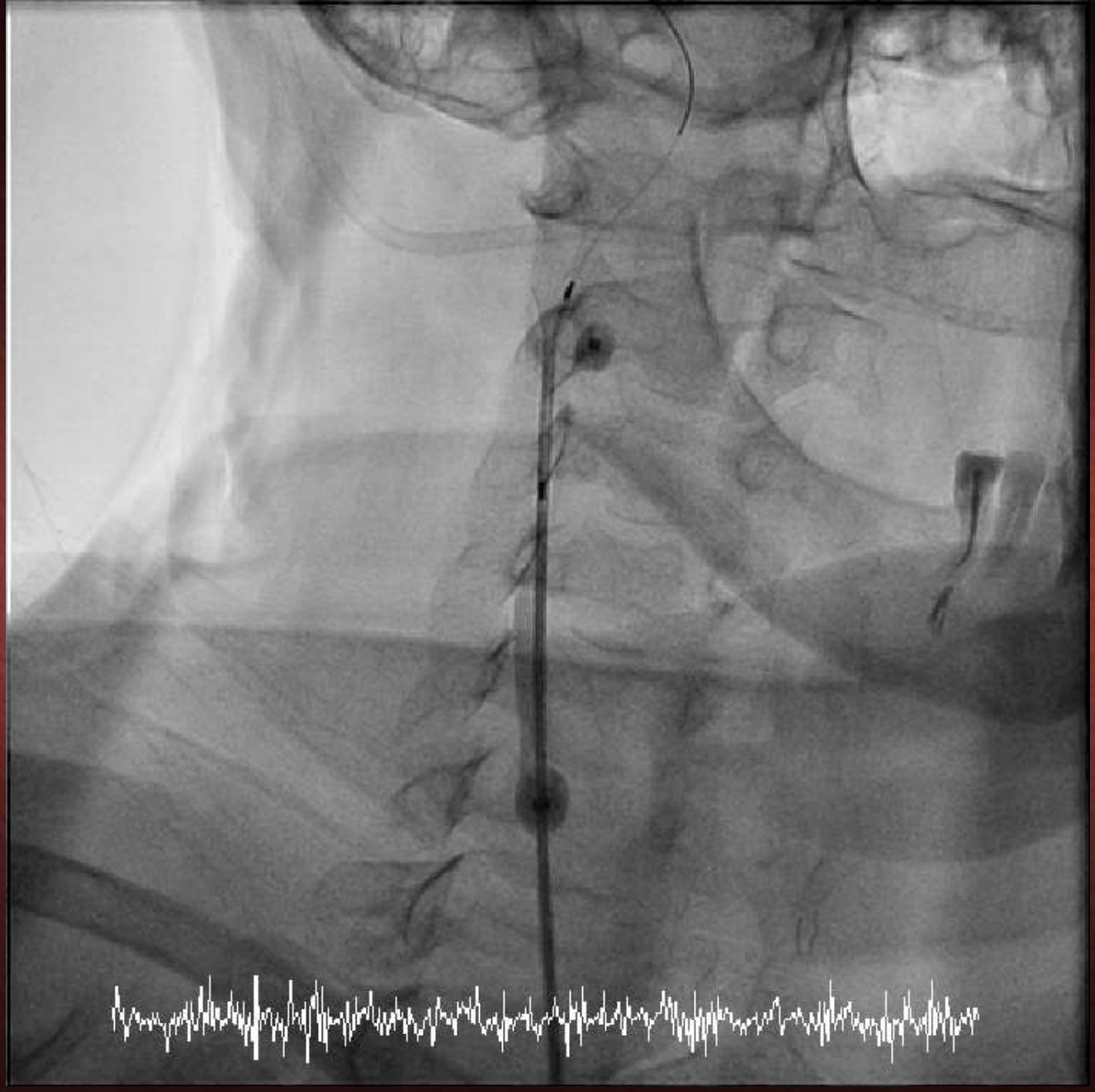

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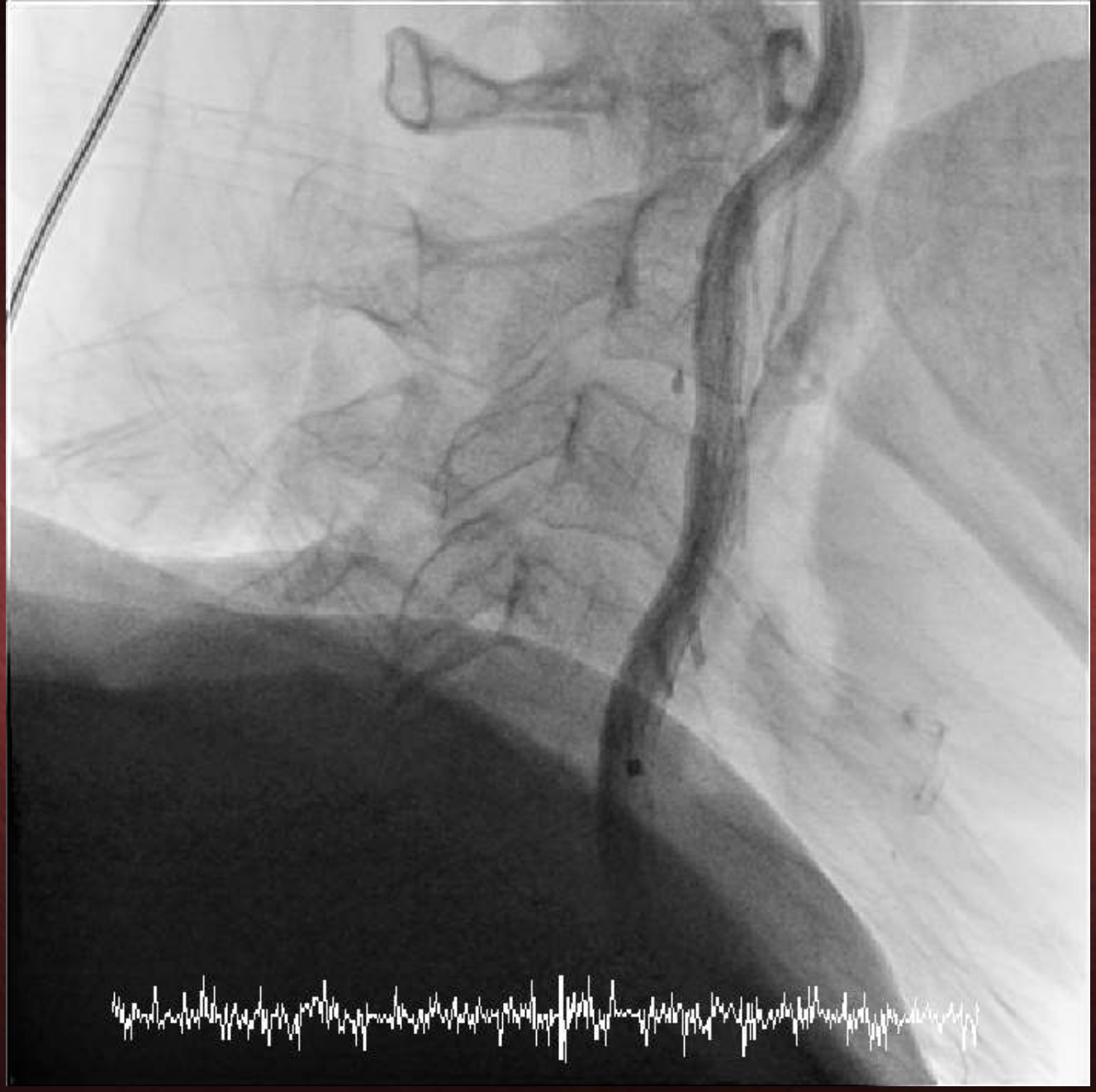

Proximal Endovascular Occlusion for Carotid Artery Stenting

Results From a Prospective Registry of 1,300 Patients

Eugenio Stabile, MD, PHD, Luigi Salemme, MD, Giovanni Sorropago, MD, Tullio Tesorio, MD, Wail Nammas, MD, Marianna Miranda, MD, Grigore Popusoi, MD, Angelo Cioppa, MD, Vittorio Ambrosini, MD, Linda Cota, MD, Giampaolo Pedicone, MD, Giovanni Della Pietra, MD, Angelo Ausiello, MD, Arturo Fontanelli, MD, Gianscarlo Biamino, MD, Paolo Rubino, MD
Mercogliano, Italy

Objectives This single-center registry presents the results of proximal endovascular occlusion (PEO) use in an unselected patient population.

Background In published multicenter registries, the use of PEO for carotid artery stenting (CAS) has been demonstrated to be safe and efficient in patient populations selected for anatomical and/or clinical conditions.

Methods From January 2006 to May 2009, 1,300 patients underwent CAS using PEO. Patients received an independent neurologic assessment before the procedure and at 6 h, 24 h, and 30 days after the procedure.

Results Procedural success was achieved in 99.7% of patients. In hospital, major adverse cardiac or cerebrovascular events included 5 deaths (0.38%), 6 major strokes (0.46%), 5 minor strokes (0.38%), and no acute myocardial infarction. At 30 days of follow-up, 2 additional patients died (0.15%), and 1 patient had a minor stroke (0.07%). The 30-day stroke and death incidence was 1.38% (n = 19). Symptomatic patients presented a higher 30-day stroke and death incidence when compared with asymptomatic patients (3.04% vs. 0.82%; $p < 0.05$). No significant difference in 30-day stroke and death rate was observed between patients at high (1.88%; n = 12) and average surgical risk (1.07; n = 7) (p = NS). Operator experience, symptomatic status, and hypertension were found to be independent predictors of adverse events.

Conclusions The use of PEO for CAS is safe and effective in an unselected patient population. Anatomical and/or clinical conditions of high surgical risk were not associated with an increased rate of adverse events. (J Am Coll Cardiol 2010;55:1661–7) © 2010 by the American College of Cardiology Foundation

>1000 Pts 30 Day Death/Stroke Sym 3.04% vs. Asym .82% P < .05%

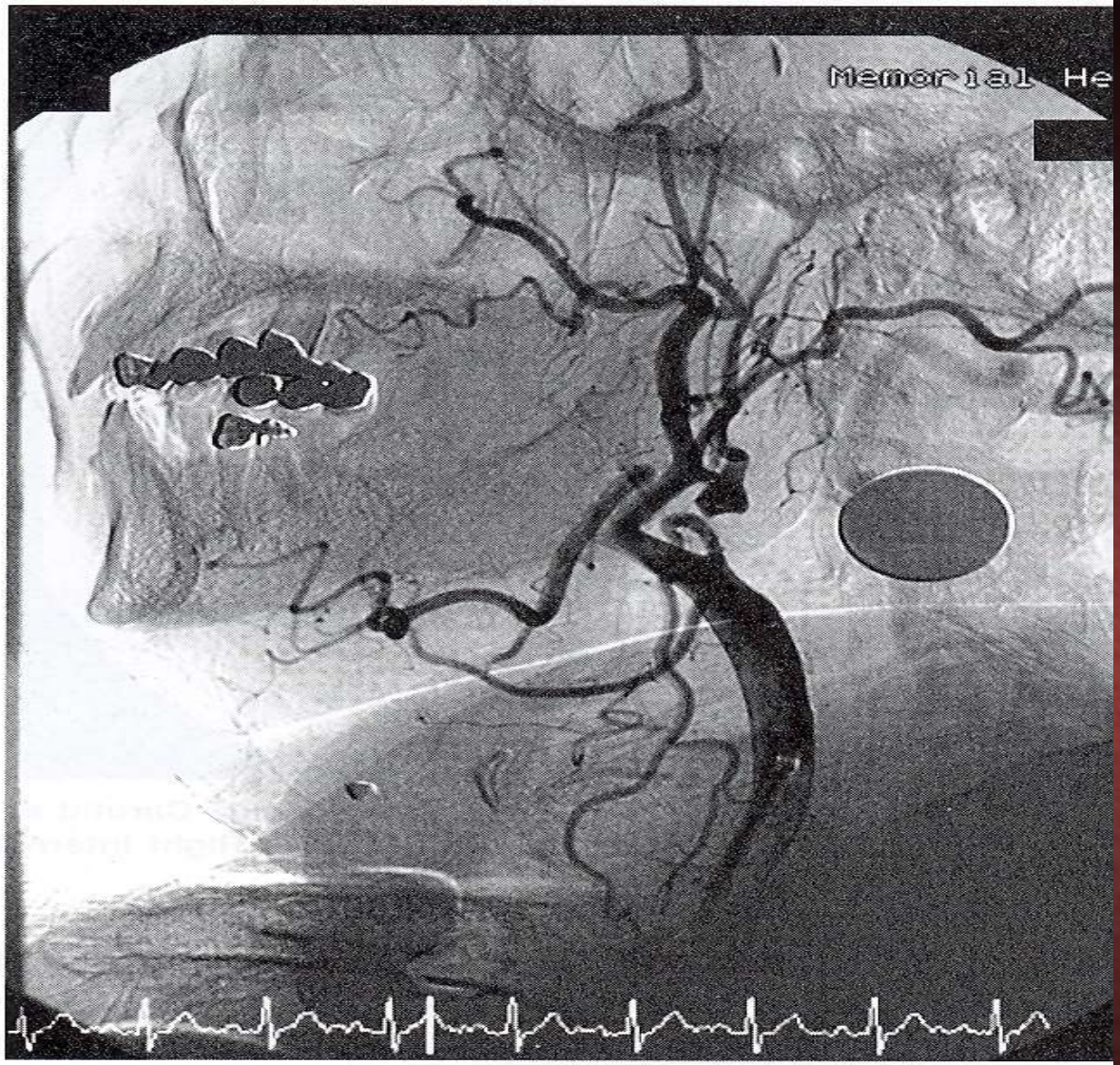

Fig. 1. Selective angiogram of the Right Common Carotid a
tery in the lateral view showing an angiographic string sig
(SS) at the ostium of the Right Internal Carotid artery.

Asymptomatic Carotid Stenosis Stenting v. Endarterectomy Trial (ACT I)

- Sources:
- L. Wechsler, Asymptomatic Carotid Stenosis Stenting v. Endarterectomy Trial (ACT I), ISC 2016.
- K. Rosenfield, Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis, published on February 17, 2016 at NEJM.org (DOI: 10.1056/NEJMoa1515706)

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ACT I Study Design

- Randomized non-inferiority trial of asymptomatic carotid stenosis CAS v. CEA 3:1
- Funded by Abbott Vascular
- 1453 patients enrolled from 2005 – 2013 at 62 sites in US (1089 CAS, 364 CEA)
- Original goal 1658 pts, study halted due to slow enrollment

ACT I Study Design

- Surgeons and interventionalists reviewed by SMC and IMC
- Lead-in enrollment prior to randomization
- Operations committee to review performance of sites
- All endpoints adjudicated by clinical events committee

Limitations

- Enrollment stopped early due to slow recruitment – power reduced from 80% - 75%
- Medical therapy based on then current guidelines
- No information on patients at participating sites not entered into trial
- Limited data on compliance with medical therapy
- Incomplete long term follow-up

Patient Selection

- Age < 80
- No symptoms for at least 180 days
- Asymptomatic status verified by neurologist prior to enrollment
- Standard medical and anatomic risk for surgery
- Stenosis ≥ 70% by ultrasound or angiography
- Stenosis assessed by ultrasound according to core lab standards

Endpoints

- Primary Endpoint
  - Stroke, MI, death within 30 days of procedure and ipsilateral stroke 31d – 1 year

- Secondary Endpoints
  - Device success within 30 d
  - Procedural success within 30 d
  - Composite morbidity measure (CN injury, vasc or wound injury, bleeding, surgical complications)
  - Freedom from clinically driven TLR 6, 12 mo
  - Freedom from ipsilateral stroke yr 2,3,4,5

Demographics

	CAS (N=1089)	CEA (N=364)
Age (mean)	67.7 ± 7.0	67.9 ± 6.9
Male	61.2%	56.9%
Caucasian	90.4%	89.8%
Hypertension	90.6%	89.6%
Hyperlipidemia	90.0%	87.9%
Diabetes	35.6%	32.4%
Smoking	73.7%	71.2%
CAD	53.4%	51.1%
Hx of stroke	6.7%	4.7%
Stenosis (mean)	73.7% ± 8.8	73.9% ± 10.2
Ulcerated	16.2%	14.5%

Primary Endpoint: ITT

– Stroke, MI, death within 30 days of procedure and ipsilateral stroke 31d – 1 year

	CAS (N=1089)	CEA (N=364)	Diff	Upper Limit 95% CI	p Value NI
Primary Endpoint	3.9% ± 0.9%	3.4% ± 0.98%	0.4%	2.27 %	0.01

Proving Non-inferiority of CAS vs. CEA

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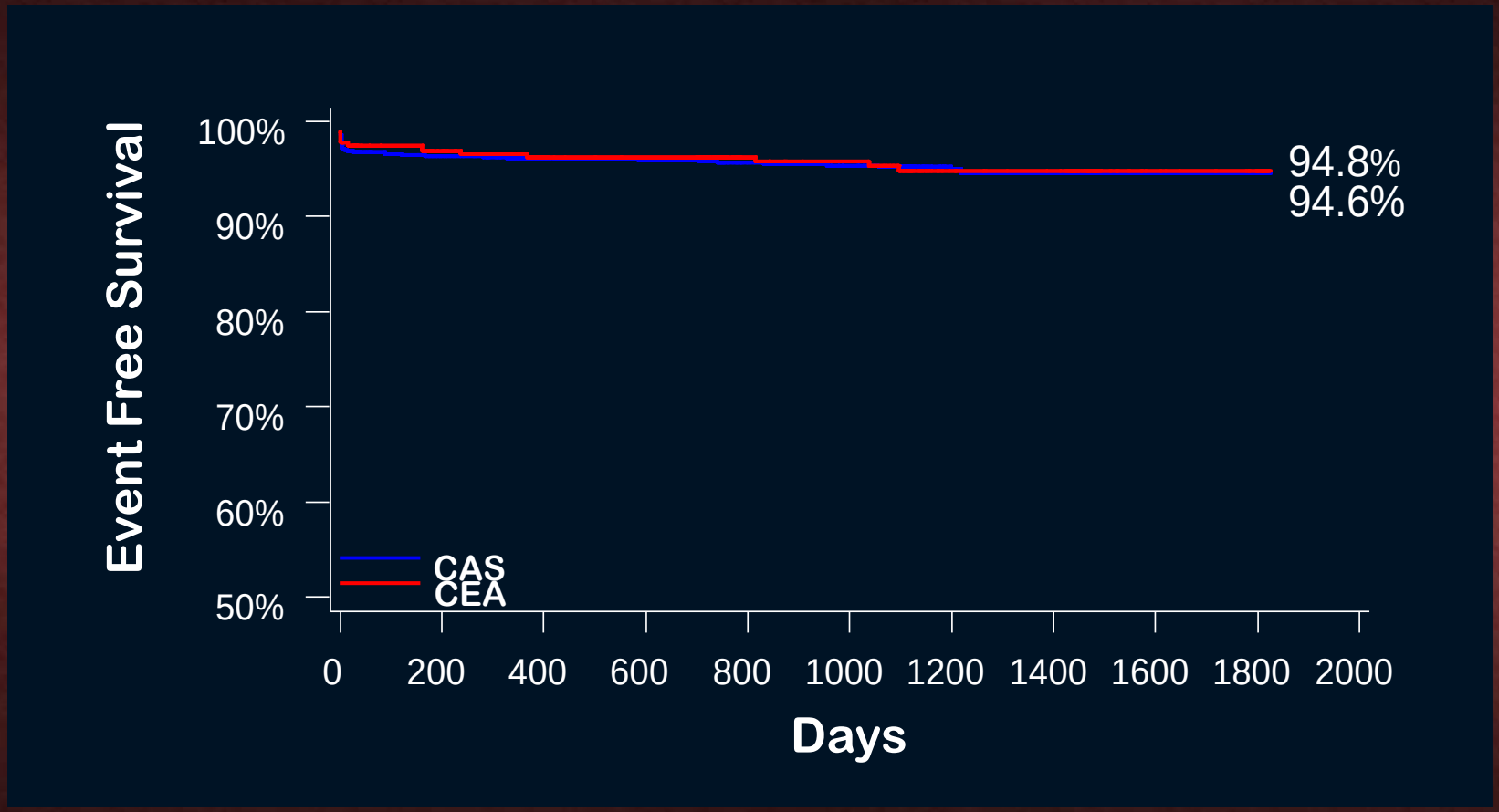
30 Day Outcomes

	CAS	CEA	p
Stroke, MI, Death	3.3%	2.6%	0.60
Stroke, Death	2.9%	1.7%	0.33
Major stroke, Death	0.6%	0.6%	1.00
Major stroke	0.5%	0.3%	1.00
Minor stroke	2.4%	1.1%	0.20
Composite morbidity *	2.8%	4.7%	0.13

* Composite morbidity – cranial n. injury, peripheral n. injury, vascular injury, noncerebral bleeding, endarterectomy or puncture site bleeding

Freedom from Death, Stroke and MI within 30 Days and Ipsilateral Stroke 31 Days to 5 Years



Days	0	(0, 30]	(30, 365]	(365, 730]	(730, 1095]	(1095, 1460]	(1460, 1825]
CAS Number at Risk	1089	1067	1016	862	729	544	364
CEA Number at Risk	364	354	325	285	246	182	112

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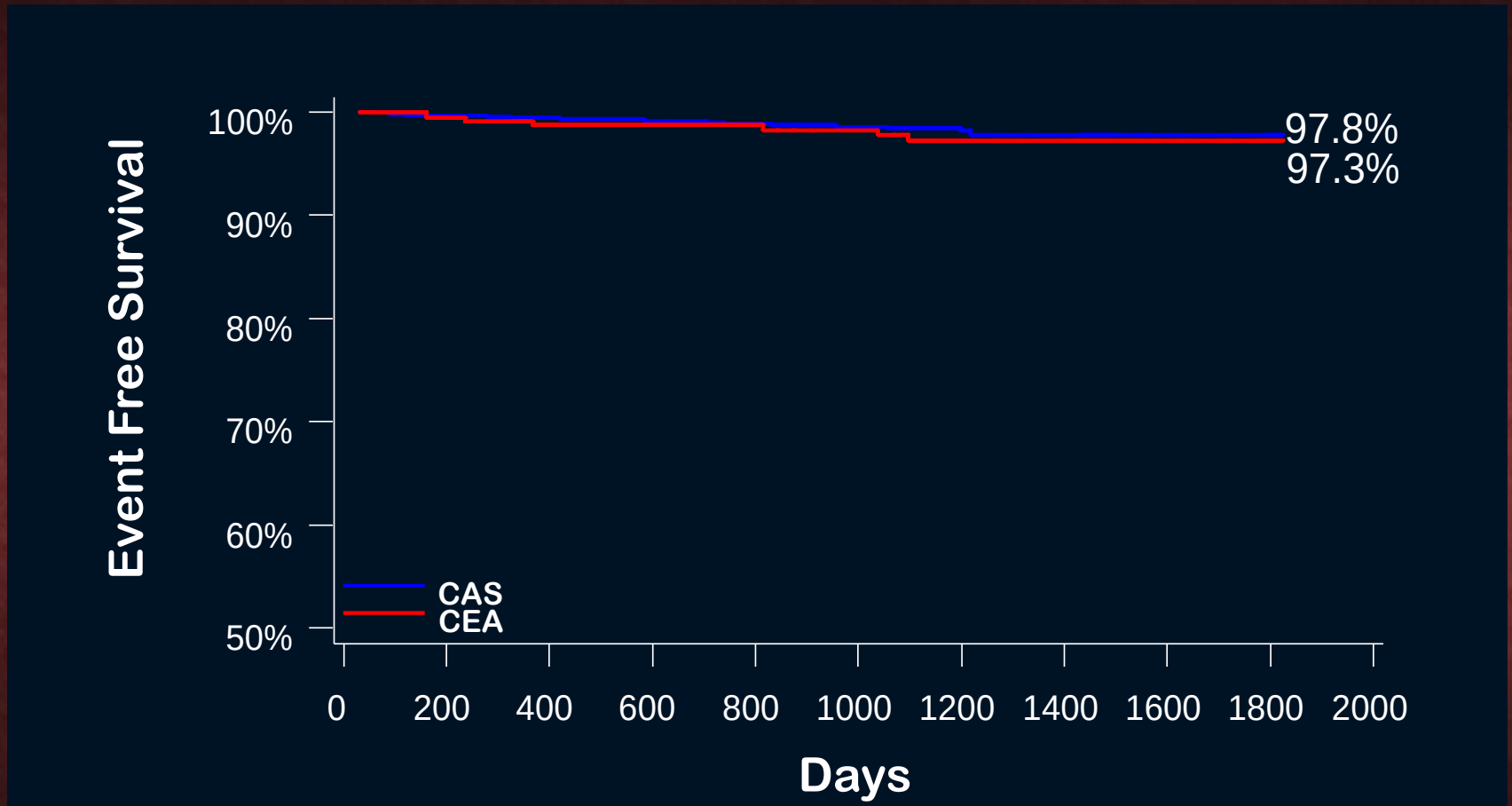
Freedom from Ipsilateral Stroke from 31 Days to 5 Years



Days	31	(31, 365]	(365, 730]	(730, 1095]	(1095, 1460]	(1460, 1825]
CAS Number at Risk	1049	1045	887	751	561	375
CEA Number at Risk	333	333	291	251	185	115

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Five Year Outcomes

	CAS	CEA	p[1]
31 d – 5 yr freedom from ipsilateral stroke	97.8%	97.3%	0.51
5 yr freedom from stroke	93.1%	94.7%	0.44
5 yr freedom from clinically driven revascularization	98.4%	96.7%	0.05
5 yr survival	87.1%	89.4%	0.21

[1] Log-rank

ACT I v. CREST (Asymptomatic)

	CAS	CEA	p
ACT I – Primary Endpoint	3.8%	3.4%	0.01[1]
CREST – Primary Endpoint	5.6%	4.9%	0.56[2]
ACT I – 30 d Stroke, MI, Death	3.3%	2.6%	0.60
CREST – 30 d Stroke, MI, Death	3.5%	3.6%	0.96
ACT I – 30 d Stroke, Death	2.9%	1.7%	0.33
CREST – 30 d Stroke, Death	2.5%	1.4%	0.15

[1] 1-sided non-inferiority test
[2] 2-sided superiority test

CREST – 1181 Asx pts: 594 CAS, 587 CEA
ACT I – 1453 Asx pts: 1089 CAS, 364 CEA

Summary

- For asymptomatic, non-octogenarian, standard surgical and anatomic risk patients with significant carotid stenosis:
  - CAS is non-inferior to CEA for 30 day DSMI and 1 year ipsilateral stroke.
  - CAS and CEA have similar five year rates of stroke and survival.

Long-term Results of Stenting vs Endarterectomy for Carotid Artery Stenosis (CREST)

- Source:
- T. Brott, Long-term Results of Stenting vs Endarterectomy for Carotid-Artery Stenosis, ISC 2016.
- T. Brott, Long –term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis, published on February 18, 2016 at NEJM.org (DOI: 10.1056/NEJMoa1505215)

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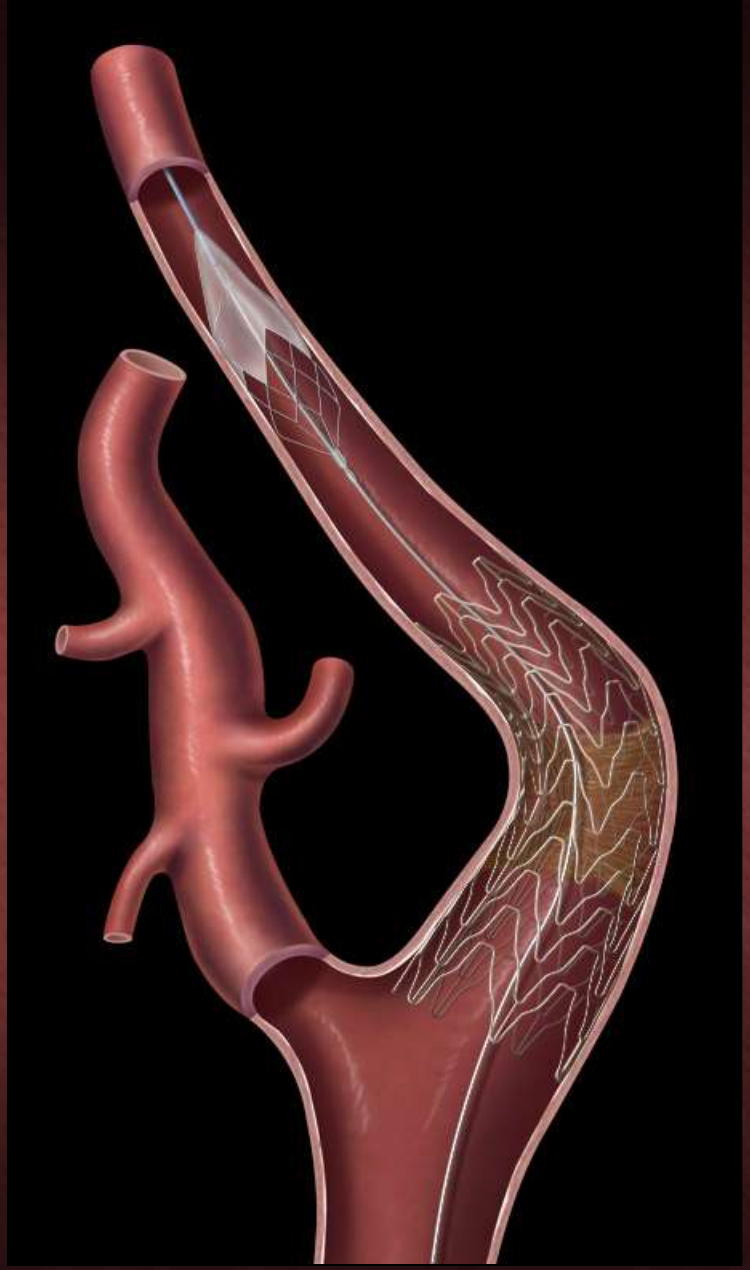

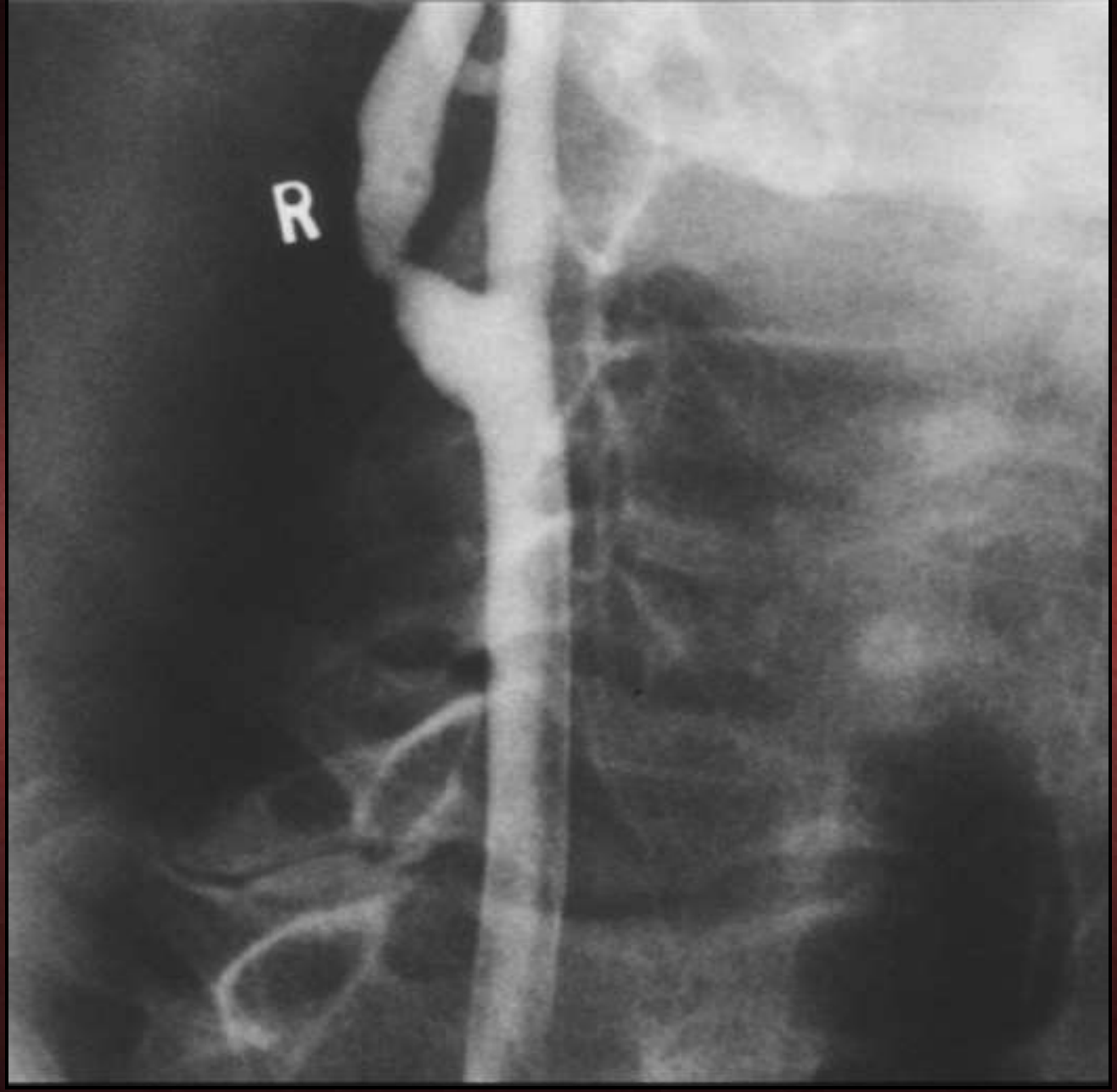
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Background

- CREST randomized 2502 patients with ≥ 70% carotid stenosis to stenting or endarterectomy.
- After 2.5 years of follow-up, no difference in stroke, MI, or death at 30 days or subsequent ipsilateral stroke was reported.
- Life-expectancy for Medicare-age (65 and older) women is 20 years and 10 years of men.
- CREST was extended to 10 years.

Primary Long-term Endpoint

- Durability: Ipsilateral stroke after 36 days post-procedure, up to 10 years.

*30 days for the procedure for patients who received their treatment within 30 days from randomization (i.e., per protocol treatment), and 36 days for patients treated beyond 30 days.

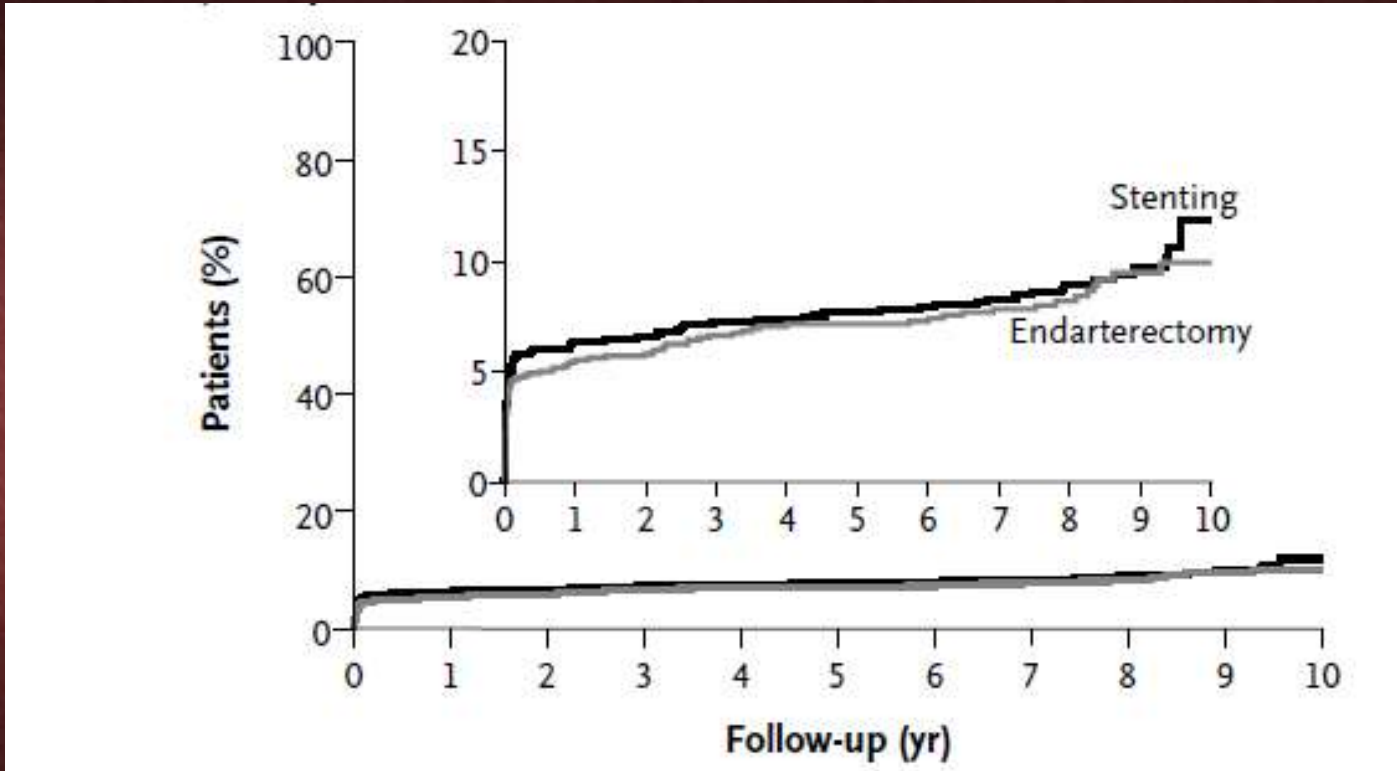
Study Population

- Follow-up includes all patients.
- Long-term population:
  - 1607 patients consented;
  - 195 declined to participate;
  - 700 consent not attempted (withdrew, died, completed initial study or met primary composite outcome).

Primary Composite Endpoint (Periprocedural Period plus 10-Yr Follow-up)

Primary Composite End point	# Events	Rate (95% CI)	Hazard Ratio (95% CI)	P value
Stenting	108	11.8% (9.1-14.8)	1.10 (0.83-1.44)	0.51
Surgery	97	9.9% (7.9-12.2)		

Primary Composite Endpoint



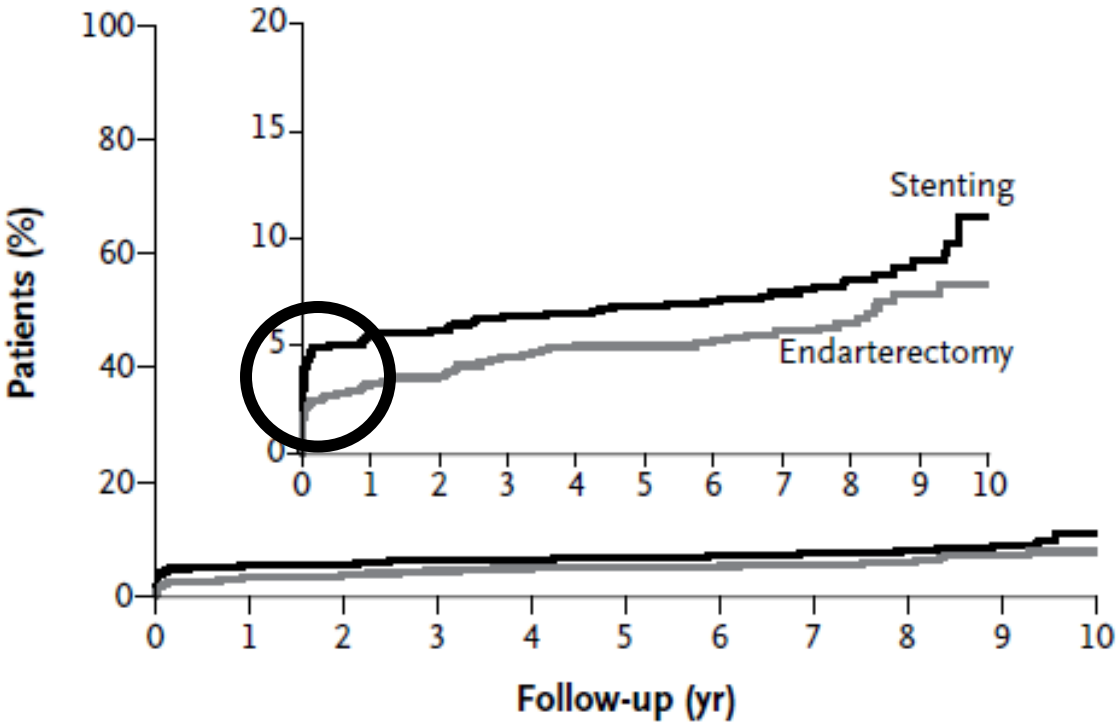
No. at Risk

Endarterectomy	1240	1104	1036	949	833	736	695	620	438	243	66
Stenting	1262	1103	1041	972	884	774	738	676	477	264	68

Stroke or Periprocedural Death (Periprocedural Period plus 10-Yr Follow-up)

Primary Composite End point	# Events	Rate (95% CI)	Hazard Ratio (95% CI)	P value
Stenting	98	11.0% (8.5-13.9)	1.37 (1.01-1.86	0.04
Surgery	71	7.9% (5.9-10.0)		

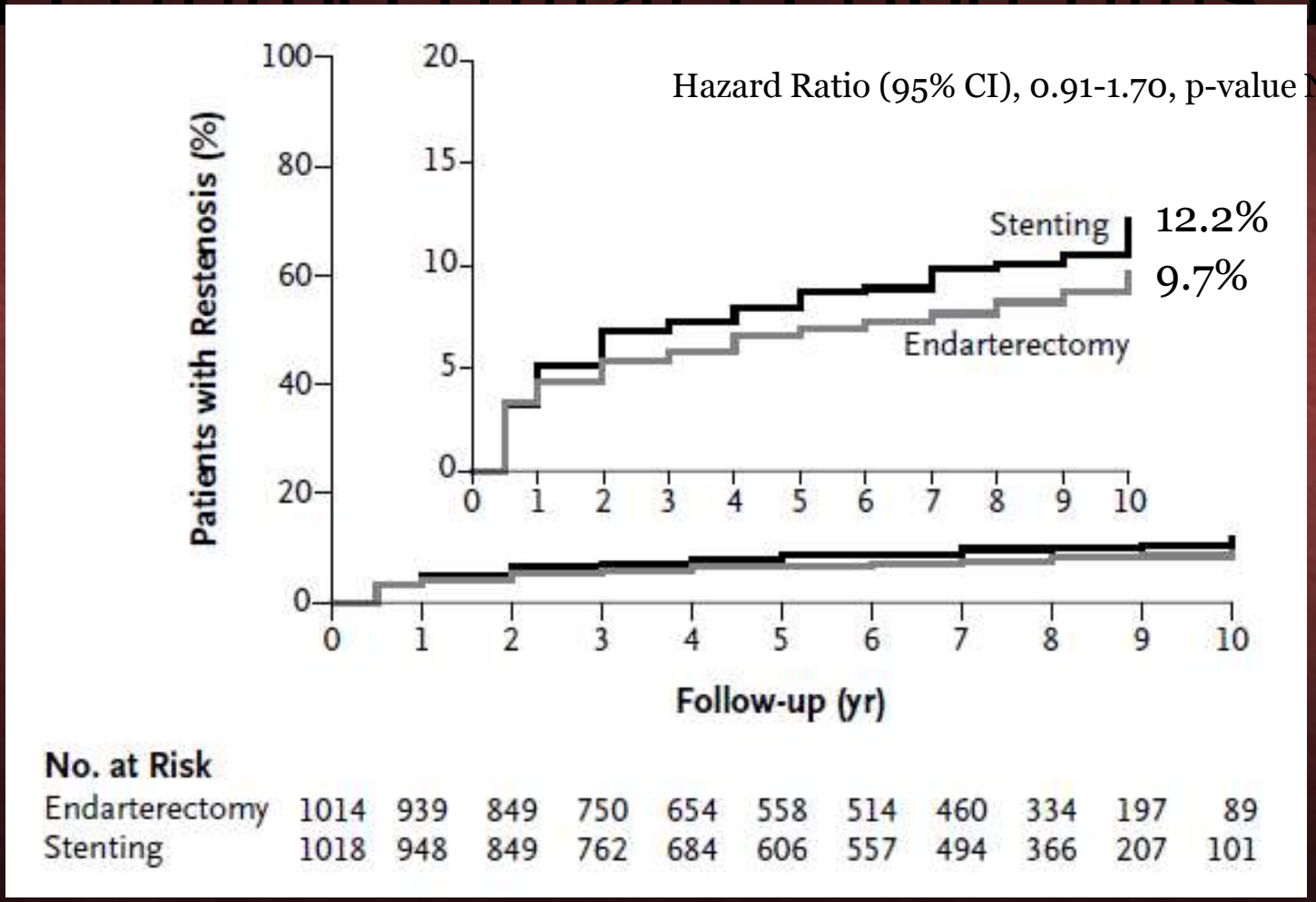
Stroke or Periprocedural Death (Periprocedural Period plus 10-Yr Follow-up)



No. at Risk

Endarterectomy	1240	1127	1056	967	848	744	703	624	442	245	67
Stenting	1262	1111	1049	979	889	777	741	679	479	265	68

Rate of Restenosis (Periprocedural Period plus 10-



Conclusions

- Post-procedural rates of stroke for stenting or surgery are similar, and they are very low
- Symptomatic status is not a predictor of post-procedural outcomes
- CREST long-term composite results are similar for stenting and surgery over a time horizon appropriate for elderly patients with severe carotid artery disease

ACT-I 5-Year Results

- In summary, the ACT-I results demonstrated (asymptomatic, non-octogenarian, standard anatomic risk patients with significant carotid stenosis):
  - CAS is non-inferior to CEA for 30-day DSMI and 1-year ipsilateral stroke
  - CAS and CEA have similar 5-year rates of stroke and survival

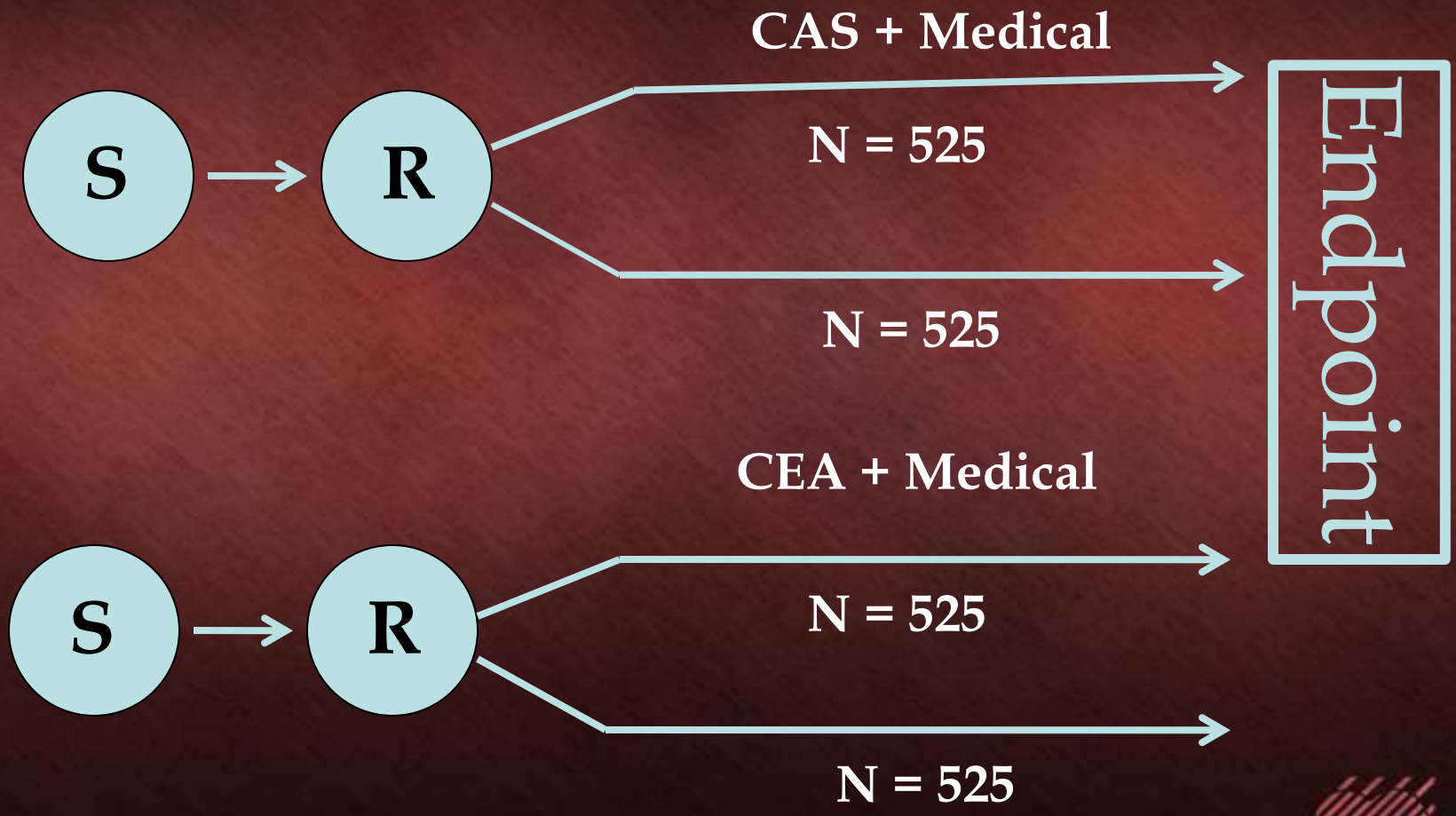
ACT- I 5-Year Results

Secondary endpoints –

- CAS had a higher freedom from TLR than CEA (98.4% vs 96.7%, p=0.05)

Therapy for Carotid Stenosis
The Future

CREST – 2
Parallel Study Design
(N = 1,050 in each trial)



Endpoints = stroke & death in first 30 days and ipsilateral stroke thereafter up to 4

Let the battles begin

R. Heuser

Summary: CEA vs. CAS

- Widely divergent and strongly held opinions regarding the role and efficacy of CAS
- Well-conducted trials show CAS performed by experienced operators utilizing proper technique in appropriately selected pts is a safe and effective procedure and is FDA approved
- If any procedure is done…it must be combined with optimal medical therapy.