Carotid Artery Stenting for Symptomatic Patients

How to Maximize Benefit and Reduce Risk

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Conflict of Interest

- No conflict to report in relation to this presentation

Clinical Trials vs. Clinical Practice

I. Physicians make decisions in an environment of inescapable uncertainty despite all the available "evidence" –Or lack thereof.

II. Our individual bias colors our interpretation of the "evidence" as well as our clinical decisions

III. Operator experience and technique are *never* adequately accounted for in multi-center clinical trials

Options for Management of Carotid Artery Stenosis

Stand alone medical management

Medical management + Carotid revascularization

CAS vs. CEA

- High Surgical Risk Patients: Symptomatic & Asymptomatic
- Standard Surgical Risk Patients: Symptomatic & Asymptomatic

Maximizing benefit and reducing risk of CAS

- Role of patient
- Role of operator
- Role of devices

Stand Alone Medical Therapy

I. Medical therapy should be the cornerstone of any therapeutic modality in patients with carotid occlusive disease to reduce the *global risk of stroke*.

II. Stand alone medical therapy is inferior to CEA (and speculatively to CAS) *assuming that procedural safety thresholds are met:*

   A. *Death/stroke <3% for asymptomatic patients*

   B. *Death/stroke <6% for symptomatic patients*

III. The argument that “contemporary” medical therapy changes the balance of risk/benefit ratio of carotid revascularization in most patients is speculative and yet to be proven!

CEA vs. CAS

High-Surgical Risk Patients: Symptomatic & Asymptomatic

The SAPPHIRE Trial: 3-Year Outcome

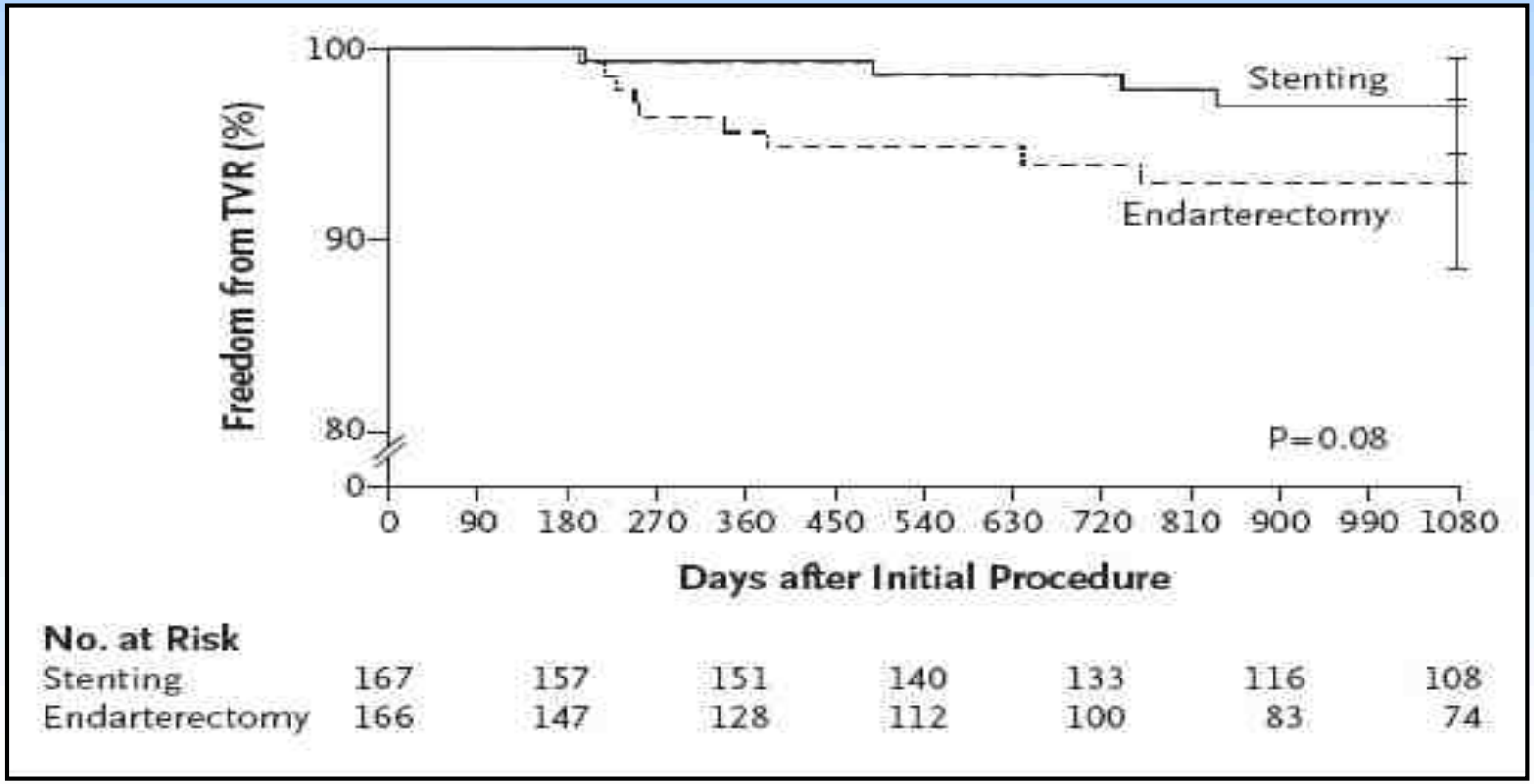
Event	Stenting (N=167)	Endarterectomy (N=167)	P Value
	no. (%) [% as estimated by Kaplan–Meier method]		
Death	31 (18.6) [20.0]	35 (21.0) [24.2]	0.68
Cardiac cause	15 (9.0) [9.8]	15 (9.0) [10.9]	0.99
Neurologic cause	3 (1.8) [2.2]	4 (2.4) [2.9]	0.99
Other cause	13 (7.8) [9.4]	16 (9.6) [12.4]	0.70
Stroke	15 (9.0) [10.1]	15 (9.0) [10.7]	0.99
Major ipsilateral	2 (1.2) [1.3]	5 (3.0) [3.3]	0.45
Major nonipsilateral	1 (0.6) [0.6]	5 (3.0) [4.1]	0.21
Minor ipsilateral	9 (5.4) [6.1]	4 (2.4) [3.0]	0.26
Minor nonipsilateral	4 (2.4) [2.7]	4 (2.4) [2.8]	0.99
Myocardial infarction	9 (5.4) [6.1]	14 (8.4) [9.4]	0.39
Q-wave	0	2 (1.2) [1.2]	0.50
Non–Q-wave	9 (5.4) [6.1]	12 (7.2) [8.2]	0.65
Target-vessel revascularization	4 (2.4) [3.0]	9 (5.4) [7.1]	0.26

Gurm HS, et al. N Engl J Med 2008;358:1572-9.

CEA vs. CAS

High-Surgical Risk Patients: Symptomatic & Asymptomatic

The SAPPHIRE Trial: 3-Year Outcome



Gurm HS, et al. N Engl J Med 2008;358:1572-9.

CEA vs. CAS

High-Surgical Risk Patients: Symptomatic & Asymptomatic

I. CAS is at least as safe and effective as CEA in high surgical risk patients

II. Nonetheless, this term describes a diverse group of patients (symptom status, co morbidities) and clinical decisions need to be made on a case by case basis

III. Medical therapy alone should be strongly considered in asymptomatic patients who are high risk of CEA and CAS

CEA vs. CAS

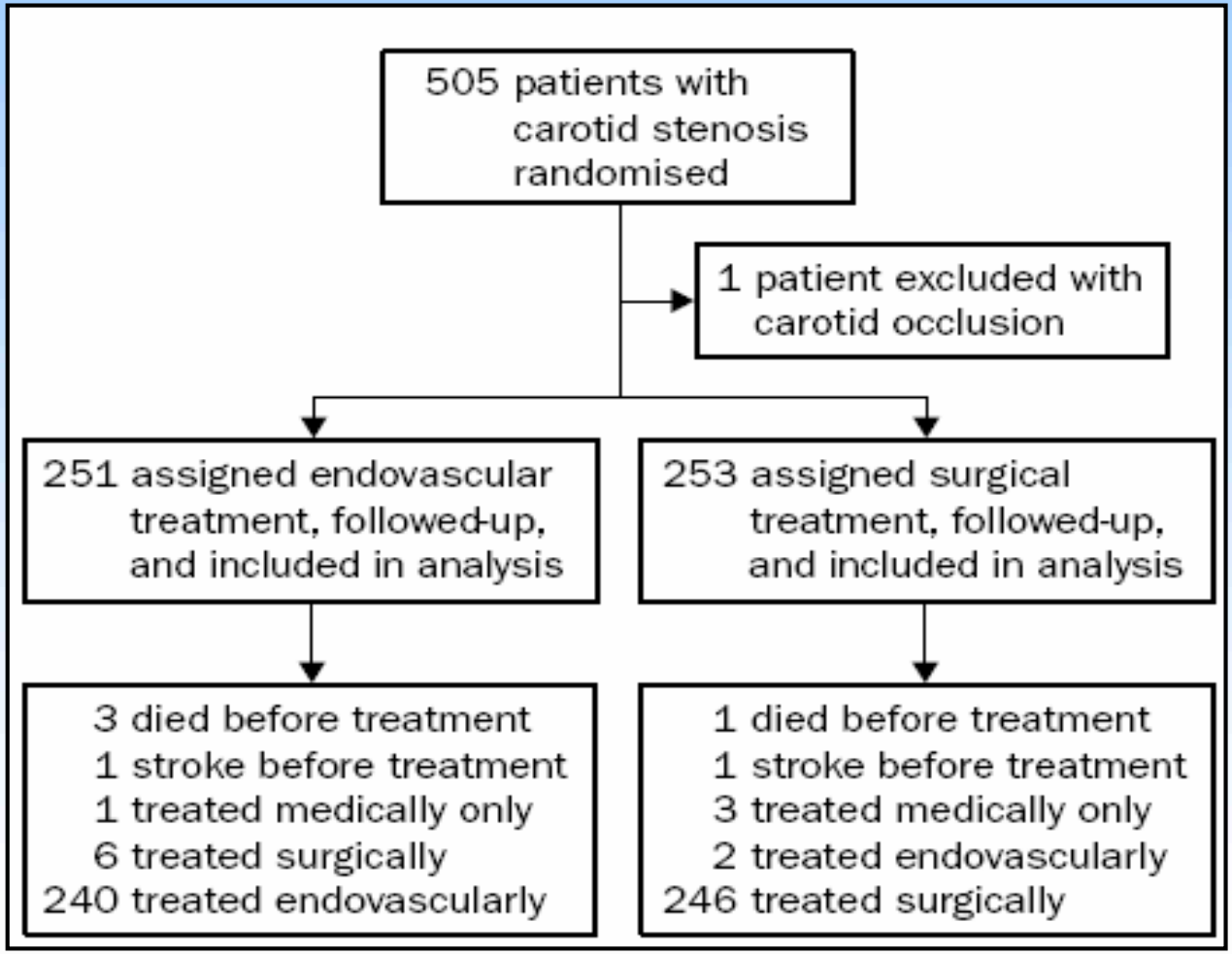
Standard Surgical Risk Patients

Symptomatic Patients

- The RCTs
  - CAVATAS
  - EVA 3-S
  - SPACE
  - ICSS
  - CREST

Standard Surgical Risk Patients
Symptomatic Patients: The CAVATAS trial

- Mostly Carotid angioplasty
- No distal protection



The CAVATAS Investigators. Lancet 2001; 357: 1729–37

Standard Surgical Risk Patients
Symptomatic Patients: The CAVATAS trial

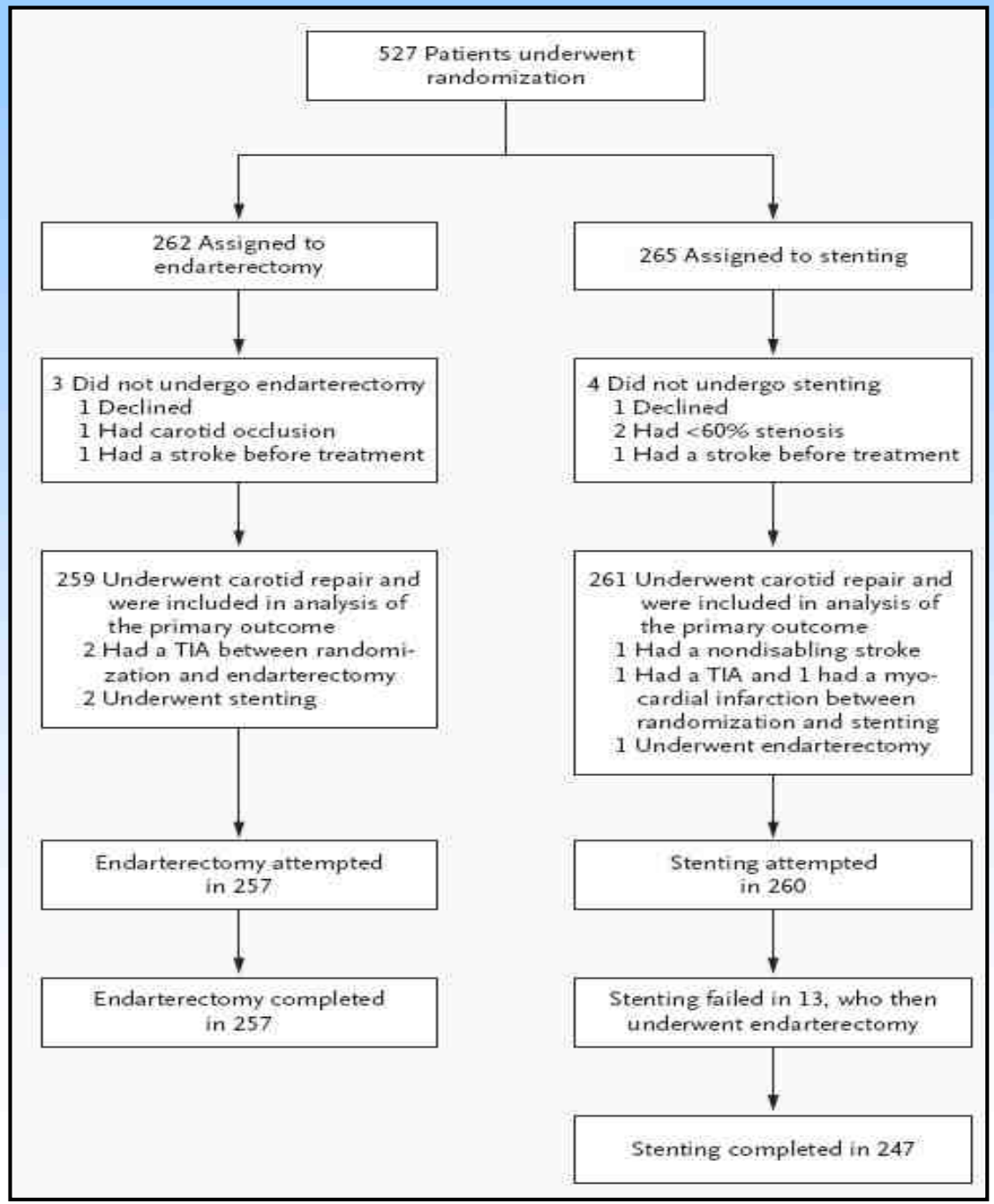
	Endovascular group (n=251)	Surgical group (n=253)	p
Major outcome events			
Death	7 (3%)	4 (2%)	NS
Disabling stroke	9 (4%)	11 (4%)	NS
Non-disabling stroke	9 (4%)	10 (4%)	NS
Death or disabling stroke	16 (6%)	15 (6%)	NS
Death or any stroke	25 (10%)	25 (10%)	NS
Other outcome events			
Cranial nerve palsy	0	22 (9%)	<0·0001
Peripheral nerve palsy	0	2 (1%)	NS
Haematoma (requiring surgery or extending hospital stay)	3 (1%)	17 (7%)	<0·0015
Myocardial infarction (non-fatal)	0	3 (1%)	NS
Pulmonary embolus	0	2* (1%)	NS

The CAVATAS Investigators. Lancet 2001; 357: 1729–37

Standard Surgical Risk Patients Symptomatic Patients: The EVA 3S trial

CAS Arm:

- 39% treated by physicians in-training
- 1.8 patients per center per year
- No pre-dilatation: 83%
- No distal protection: 8%
- No pre-procedure dual antiplatelet therapy 17%



Mas JL et al. N Engl J Med 2006;355:1660-71.

Standard Surgical Risk Patients

Symptomatic Patients:

The EVA 3S trial

Outcome Event	Endarterectomy (N=259)	Stenting (N=261)	Unadjusted Relative Risk (95% CI)	P Value
	no. of patients (%)			
Nonfatal stroke	7 (2.7)†	23 (8.8)‡	3.3 (1.4–7.5)	0.004
Symptoms lasting 7 days or more	6 (2.3)	20 (7.7)		
Nondisabling	6 (2.3)	16 (6.1)		
Disabling§	1 (0.4)	7 (2.7)		
Death	3 (1.2)	2 (0.8)	0.7 (0.1–3.9)	0.68
Fatal stroke	2 (0.8)†	1 (0.4)‡		
Other cause	1 (0.4)¶	1 (0.4)‖		
Any stroke or death	10 (3.9)	25 (9.6)	2.5 (1.2–5.1)	0.01
Any disabling stroke or death	4 (1.5)	9 (3.4)	2.2 (0.7–7.2)	0.26

Mas JL et al. N Engl J Med 2006;355:1660-71.

Standard Surgical Risk Patients

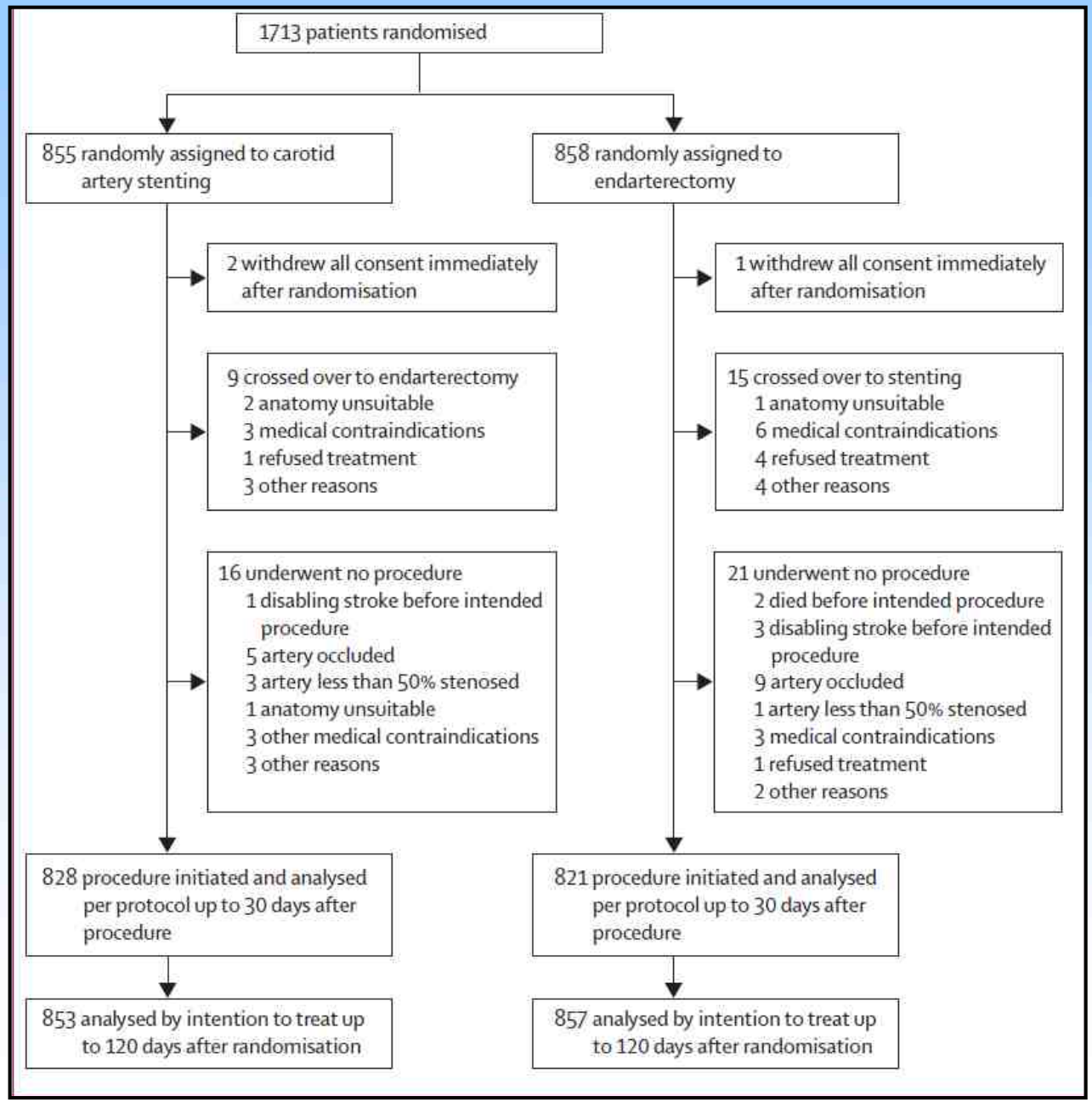
Symptomatic Patients:

The EVA 3S trial

- The EVA 3S investigators concluded that CEA is safer and more effective that CAS, but they also concluded that:
  - Operator experience with CAS does not matter!
  - Cerebral protection with CAS is not important!
  - Dual antiplatelet therapy prior to and after CAS is not important!

Does that make sense?

Standard Surgical Risk Patients Symptomatic Patients: The ICSS trial



International Carotid Stenting Study investigators. Lancet **2010; 375: 985–97**

Standard Surgical Risk Patients

Symptomatic Patients:

The ICSS trial

	Stenting group (n=828)	Endarterectomy group (n=821)	p value*
Time from randomisation to treatment (days)	9 (5–17)	11 (5–24)	<0·0001
≤14	578 (70%)	469 (57%)	..
>14	250 (30%)	352 (43%)	..
Time from most recent event to treatment (days)	35 (15–82)	40 (18–87)	0·013
≤14	205 (25%)	151 (18%)	..
>14	623 (75%)	668 (81%)	..

Data are number (%) or median (IQR) in the per-protocol analysis. Three patients in the endarterectomy group were randomised more than 12 months after onset of symptoms. The date of the most recent event was unknown in two patients (endarterectomy group). *Mann-Whitney *U* test.

Table 2: **Time from randomisation and from most recent ipsilateral event to allocated treatment**

Standard Surgical Risk Patients

Symptomatic Patients:

The ICSS trial

	Stenting group (n=853)	Endarterectomy group (n=857)	Hazard ratio (95% CI)	Risk difference, % (95% CI)	p value*
Stroke, death or procedural myocardial infarction	72 (8·5%)	44 (5·2%)	1·69 (1·16 to 2·45)	3·3% (0·9 to 5·7)	0·006
Any stroke	65 (7·7%)	35 (4·1%)	1·92 (1·27 to 2·89)	3·5% (1·3 to 5·8)	0·002
Any stroke or death	72 (8·5%)	40 (4·7%)	1·86 (1·26 to 2·74)	3·8% (1·4 to 6·1)	0·001
Any stroke or procedural death	68 (8·0%)	36 (4·2%)	1·95 (1·30 to 2·92)	3·8% (1·5 to 6·0)	0·001
Disabling stroke or death	34 (4·0%)	27 (3·2%)	1·28 (0·77 to 2·11)	0·8% (–0·9 to 2·6)	0·34
All-cause death	19 (2·3%)	7 (0·8%)	2·76 (1·16 to 6·56)	1·4% (0·3 to 2·6)	0·017

Data are number of first events (Kaplan-Meier estimate at 120 days). Risk differences are calculated from Kaplan-Meier estimates at 120 days. *Log-rank test.

Table 3: Outcome measures within 120 days of randomisation (intention-to-treat population)

	ITT analysis (events up to 120 days after randomisation)		Per-protocol analysis (events between 0 days and 30 days after treatment)	
	Stenting group (n=853)	Endarterectomy group (n=857)	Stenting group (n=828)	Endarterectomy group (n=821)
Any stroke	65*	35	58*	27
Ipsilateral stroke	58	30	52	25
Ischaemic stroke	63	28	56	21
Haemorrhagic stroke	3	5	2	5
Uncertain cause	0	2	0	1
Non-disabling stroke	39	14	36	11
Lasting fewer than 7 days	9†	5‡	8†	5‡
Lasting more than 7 days	31	9	29	6
Disabling stroke	17§	20	14	14
Fatal stroke	9	2	8	3
Procedural myocardial infarction	3	4	3	5
Non-fatal myocardial infarction	0	4	0	5¶
Fatal myocardial infarction	3	0	3	0
Death unrelated to stroke or myocardial infarction	7	5	1	1
Cranial nerve palsy	1‖	45	1‖	45
Disabling cranial nerve palsy	1‖	1	1‖	1
Haematoma	31	50	30	50
Severe haematoma**	9	28	8	28

Standard Surgical Risk Patients

Symptomatic Patients: The ICSS trial

What is the primary endpoint?

- The 3-year rate of fatal or disabling stroke in any territory

The ICSS trial
Operator Qualifications

- Surgeon: 50 CEA
- Interventionalist: 50 stenting procedures (can be coronary or peripheral, with at least ten cases in the carotid artery).
  - Centers that did not fulfill these criteria joined as supervised centers and their trial procedures had to be proctored by an outside surgeon or interventionist until the proctor was satisfied that the centre was proficient in undertaking the procedure.

The ICSS trial

Impact of Operator Qualifications on Outcome

During the trial, two sites were suspended. All the patients allocated to CAS (n=11, five with disabling stroke or death) or CEA during the same time period (n=9, one with fatal stroke) at these centers were included in the analyses.

In the CAS arm, 64 pts (8%) had their procedure aborted before the insertion of a stent:

- 38 due to difficulty gaining access to the stenosis
- 15 due to the finding of an occluded artery
- 7 due to a stenosis <50%
- 1 due to a fatal stroke
- 1 due to fatal myocardial infarction
- 2 due to other medical complications

In the CEA arm, only 2 pts (0.2%) had their procedure aborted due to allergy to anasthesia (1) or general distress (1).

The ICSS trial

Use of Embolic Protection Devices

- Embolic protection devices (EPDs)
  - The protocol recommended that EPDs should be used *whenever the local investigator thought that one could be used safely*, but this was not mandatory.
  - EPDs were not used in 28%
  - No proximal EPDs were used

Standard Surgical Risk Patients

Symptomatic Patients:

The ICSS trial

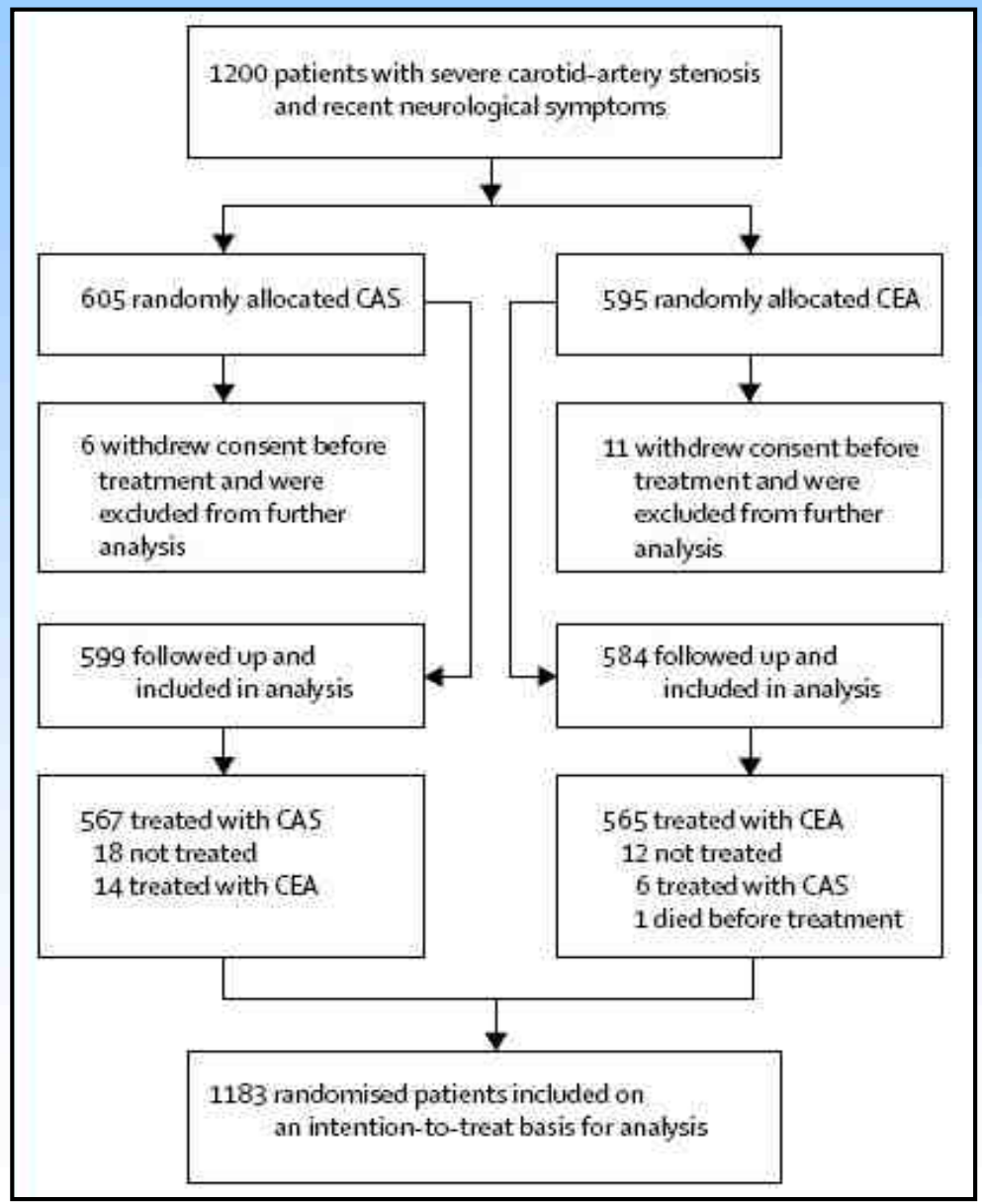
- The ICSS investigators concluded that CEA is safer and more effective that CAS (*not based on the primary endpoint*), but they also concluded that:
  - Operator experience with CAS does not matter!
  - Cerebral protection with CAS is not important!

Standard Surgical Risk Patients

Symptomatic Patients: The SPACE trial

-Trial stopped prematurely due to lack of funding

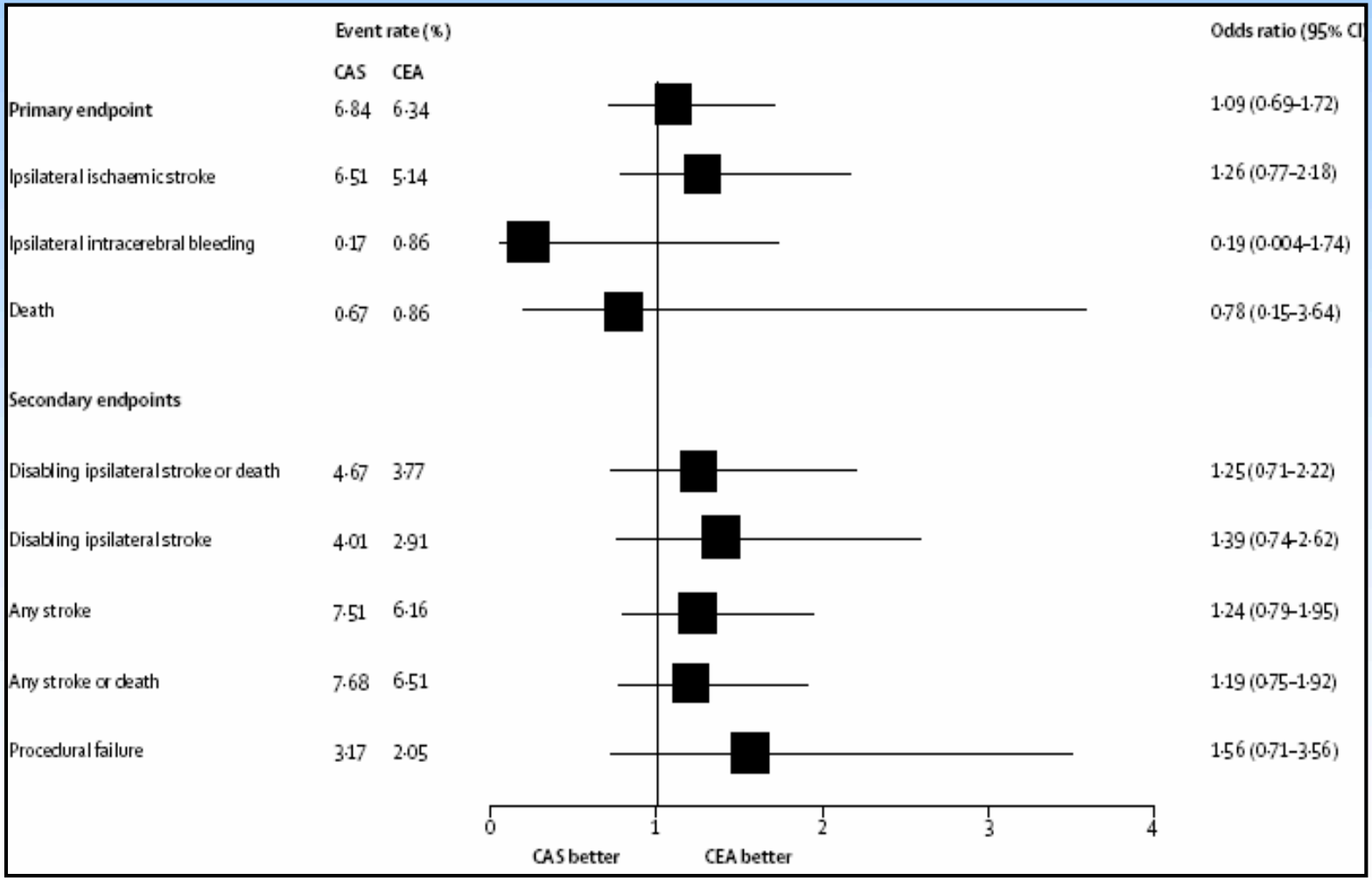
- EPD use 29%



The SPACE Collaborative Group. Lancet. 2006;368:1239-1247.

Standard Surgical Risk Patients

Symptomatic Patients: The SPACE trial



The SPACE Collaborative Group. Lancet. 2006;368:1239-1247.

Standard Surgical Risk Patients

Symptomatic Patients: The SPACE trial

	Number (%)		Absolute difference*	Odds-ratio
	CAS	CEA	CAS–CEA (90% CI)	CAS/CEA (95% CI)
Age ≤75 years	29/490 (5·92%)	26/438 (5·94%)	-0·02 (-2·65 to 2·56)	1·00 (0·58 to 1·72)
Age >75 years	12/109 (11·01%)	11/146 (7·53%)	3·48 (-2·82 to 10·1)†	1·52 (0·59 to 3·97)†
Male	28/431 (6·50%)	27/418 (6·46%)	0·04 (-2·80 to 2·86)	1·01 (0·58 to 1·74)
Female	13/168 (7·74%)	10/166 (6·02%)	1·71 (-3·03 to 6·53)†	1·31 (0·51 to 3·44)†

The CREST trial

- Prospective, multicenter, randomized, controlled trial with blinded endpoint adjudication
- Comparing CEA and CAS in 2502 patients with symptomatic and asymptomatic stenosis
- 108 US and 9 Canadian sites
- Team included neurologist, interventionalist, surgeon, and research coordinator at each institution

The CREST trial

Primary Endpoint

- Peri-procedural
  - A composite of: any clinical stroke, myocardial infarction, death
- Post-procedure
  - Ipsilateral stroke up to 4 years

The CREST trial

Major Eligibility Criteria

- Symptomatic
  - ≥50% by angiography
  - ≥70% by ultrasound or
  - >70% by MRA/CTA if ultrasound is 50-69%
- Asymptomatic
  - ≥60% by angiography
  - ≥70% by ultrasound or
  - >80% by MRA/CTA if ultrasound is 50-69%

The CREST trial

Primary Endpoint

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

The CREST trial

Interaction with Primary Endpoint

- No effect detected for symptomatic status and sex
- Interaction suggested for age

The CREST trial

Primary Endpoint

	CAS vs. CEA	Hazard Ratio	95% CI	P value
All Stroke	4.1% vs. 2.3%	HR=1.79	1.14-2.82	0.01
Major Stroke	0.9% vs. 0.7%	HR=1.35	0.54-3.36	0.52
MI	1.1% vs. 2.3%	HR=0.50	0.26-0.94	0.03
Cranial nerve palsey	0.3% vs. 4.8%	HR=0.07	0.02-0.18	<0.0001

CAS in Symptomatic Patients

What did we learn from clinical trials?

- EVA 3-S and ICSS
  - Inexperienced operators should not perform CAS in symptomatic patients with or without EPDs
- SPACE and CREST
  - CAS is a reasonable alternative to CEA in symptomatic patients when performed by reasonably experienced hands

Patient and Anatomic Selection Criteria

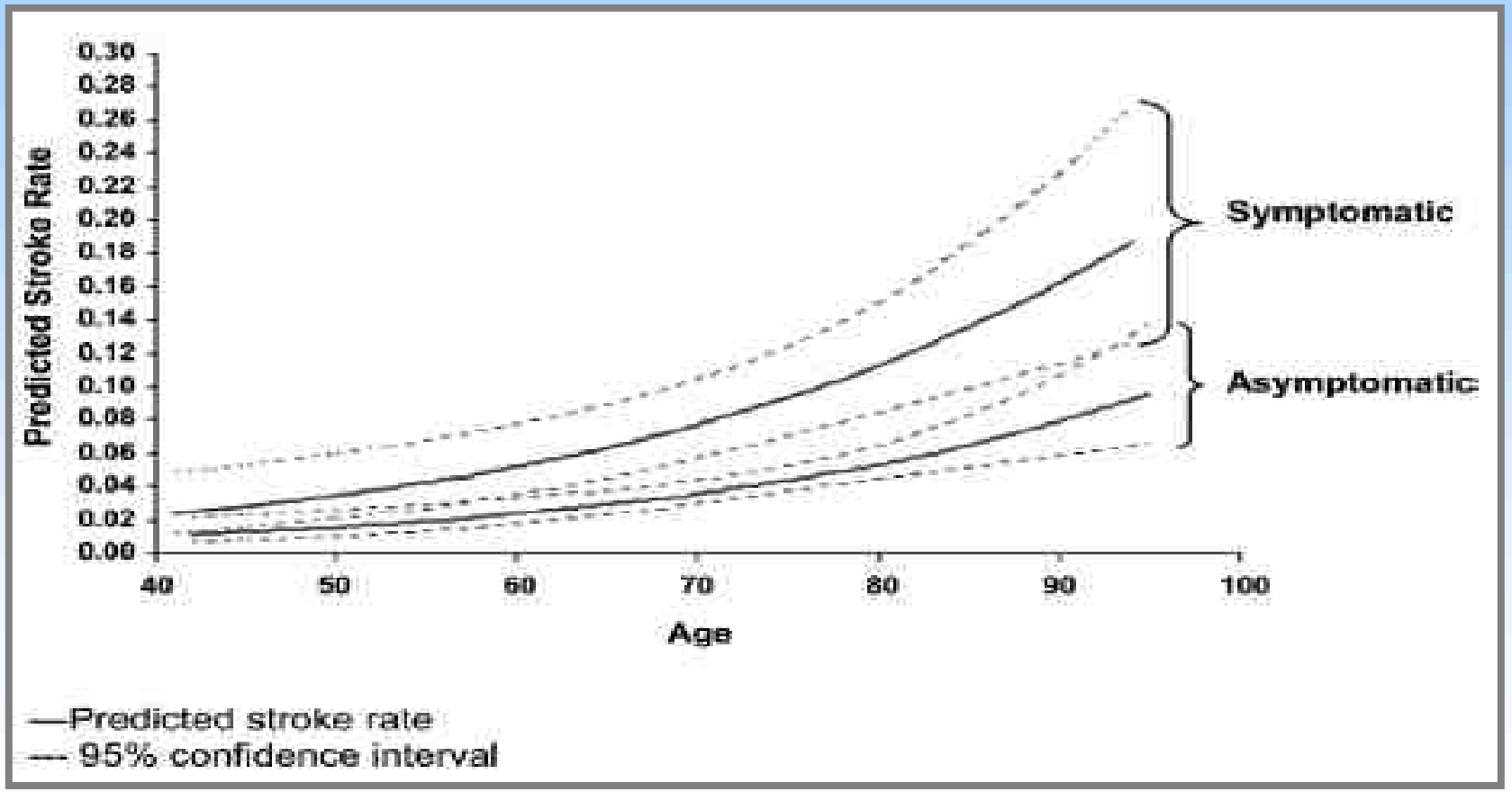
to Maximize Success and Avoid Complications

Who is at High Risk for CAS?

- Patient risk profiling for CAS is a crucial step to optimize success. However, patient selection should be done in the context of the following:
  - Patient-based risk
    - Clinical (age, symptom status, renal insufficiency)
    - Anatomic complexity
  - Operator-based risk
    - Experience
  - Access to devices
    - Stent design and embolic protection method

Who is at High Risk for CAS?

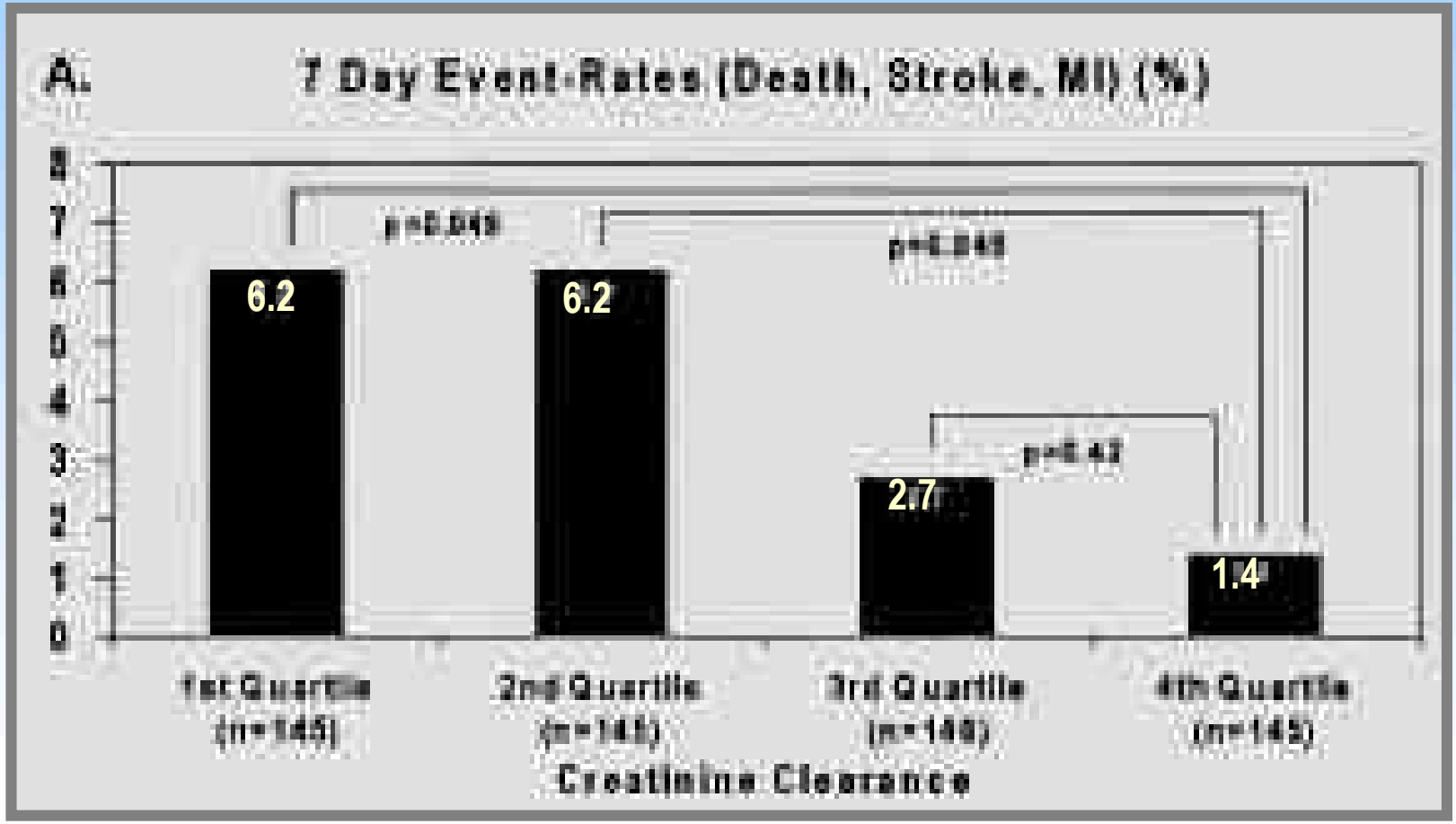
Impact of Age and Symptom Status



Gray W. for the The CAPTURE Registry Investigators. CCI. 2007;70:1025–1033

Who is at High Risk for CAS?

Impact of CRI



Saw J, Yadav J et al. Am J Cardiol 2004;94:1093–1096)

Who is at High Risk for CAS?

Impact of CRI

- Measures to reduce morbidity in these patients:
  - Pre-procedure MRA to define anatomy and the potential working views, thereby reducing intra procedural iodinated contrast volume
  - Pre-procedure intravenous hydration and renal protective pharmacotherapy
  - Dilution of iodinated contrast with saline

Who is at High Risk for CAS?

Impact of Clinical Risk Factors

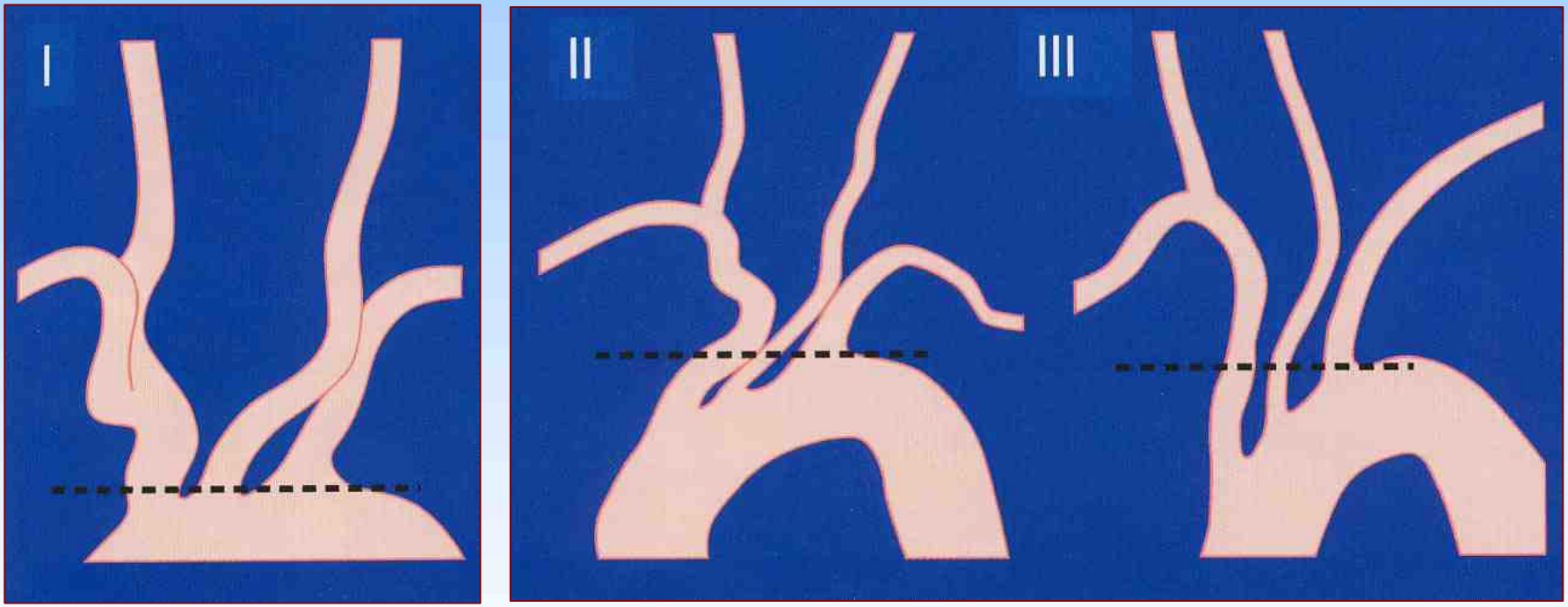
- The clinical indicators of increased procedural risk with CAS (age, symptoms, and renal insufficiency) are also indicators of increased risk of stroke / death with medical therapy and CEA.
- Therefore, none of these risk factors should be used *alone* as a reason to deny patients access to CAS
- The weight of clinical risk factors should be judged in the context of:
  - Concomitant anatomic complexity
  - Operator experience

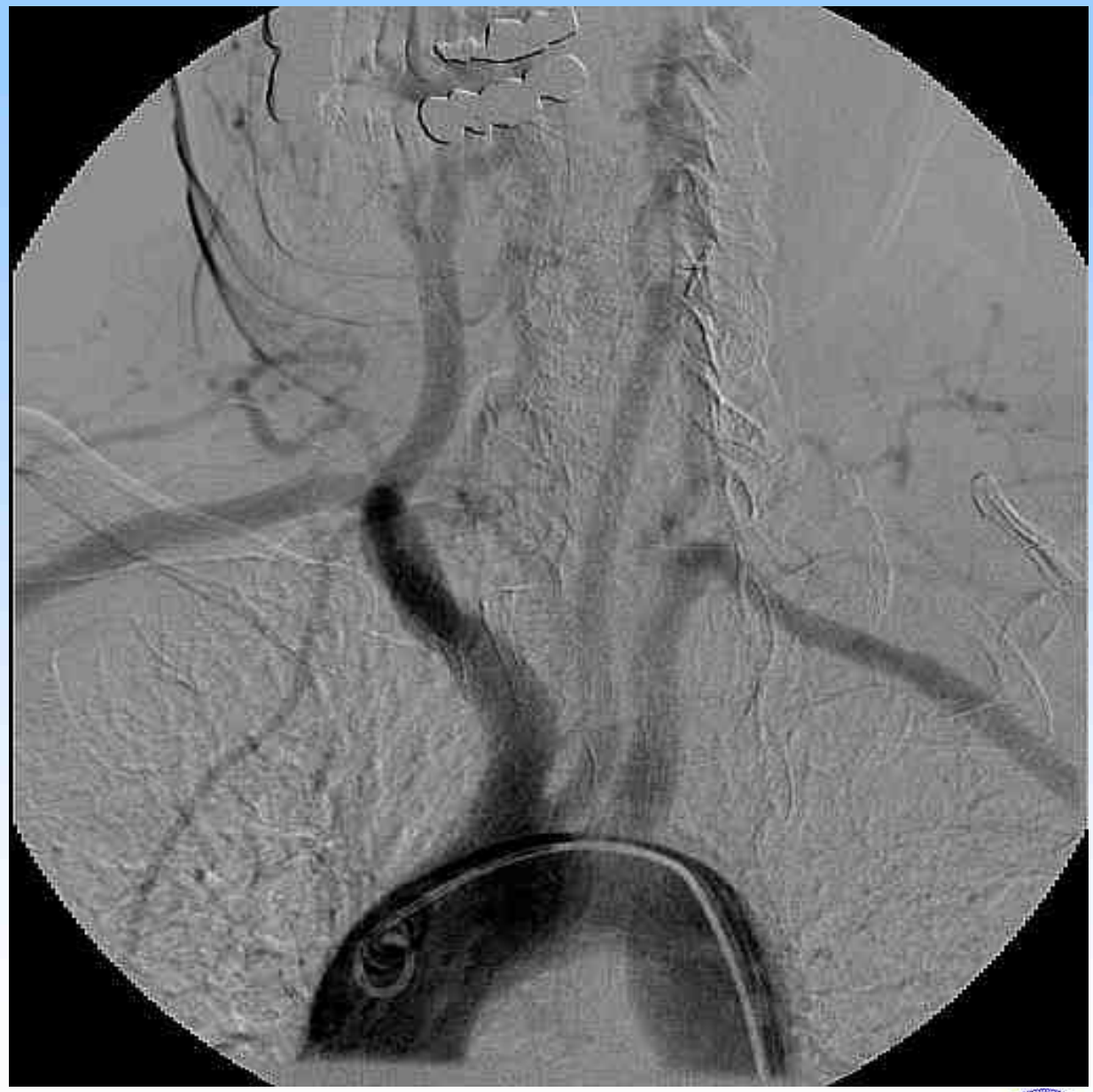
Anatomic-Based Risk

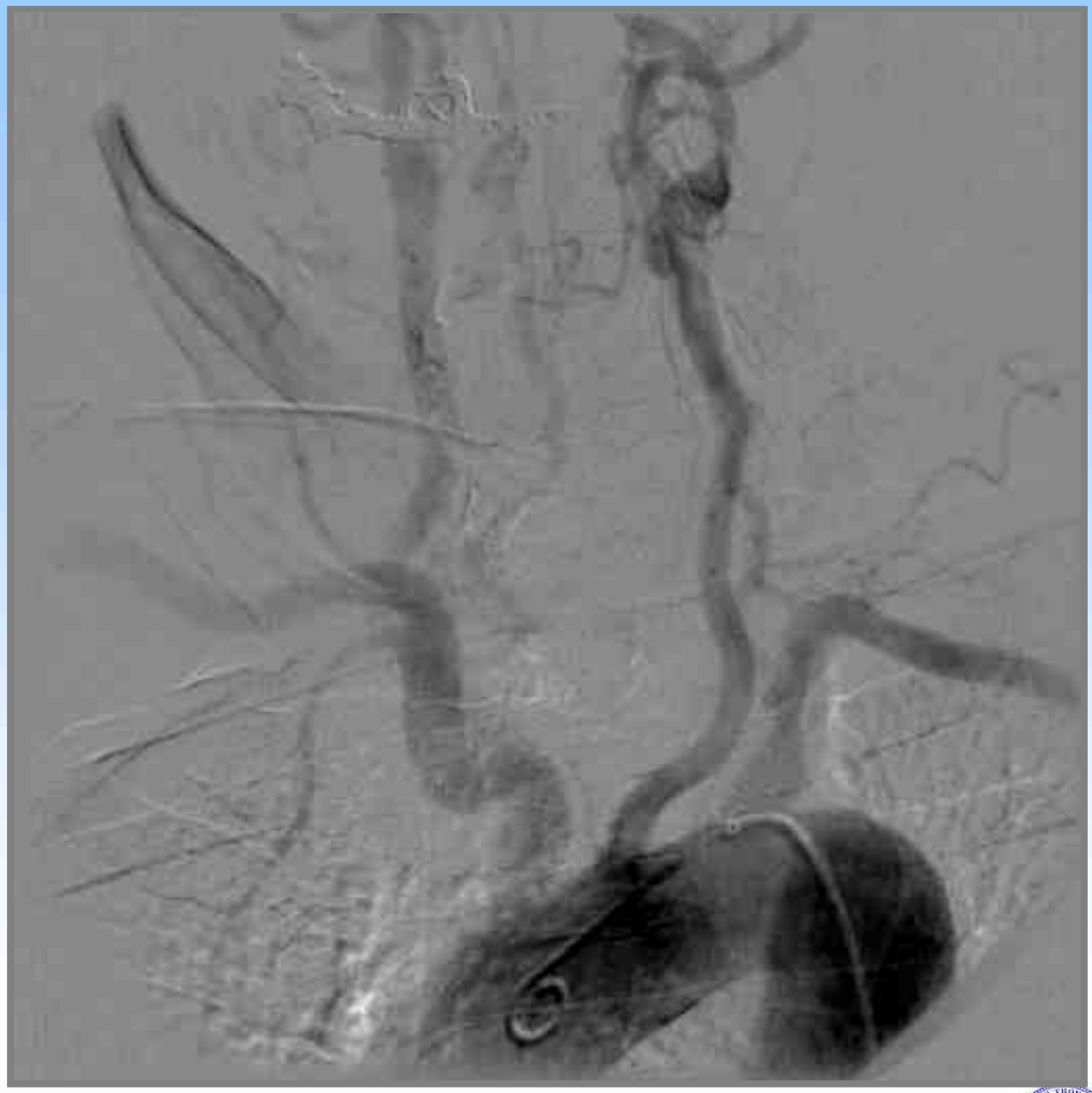
- Difficult access to the common carotid artery:
  - Type III aortic arch +/- atherosclerotic disease
  - Common carotid artery disease
  - Common carotid artery tortousity
  - Arm access
- Lesion site complexity:
  - Severe proximal or distal kinks
  - Heavy calcifications, particularly when combined with tortuous origin of ICA
  - Thrombus
  - “String” sign

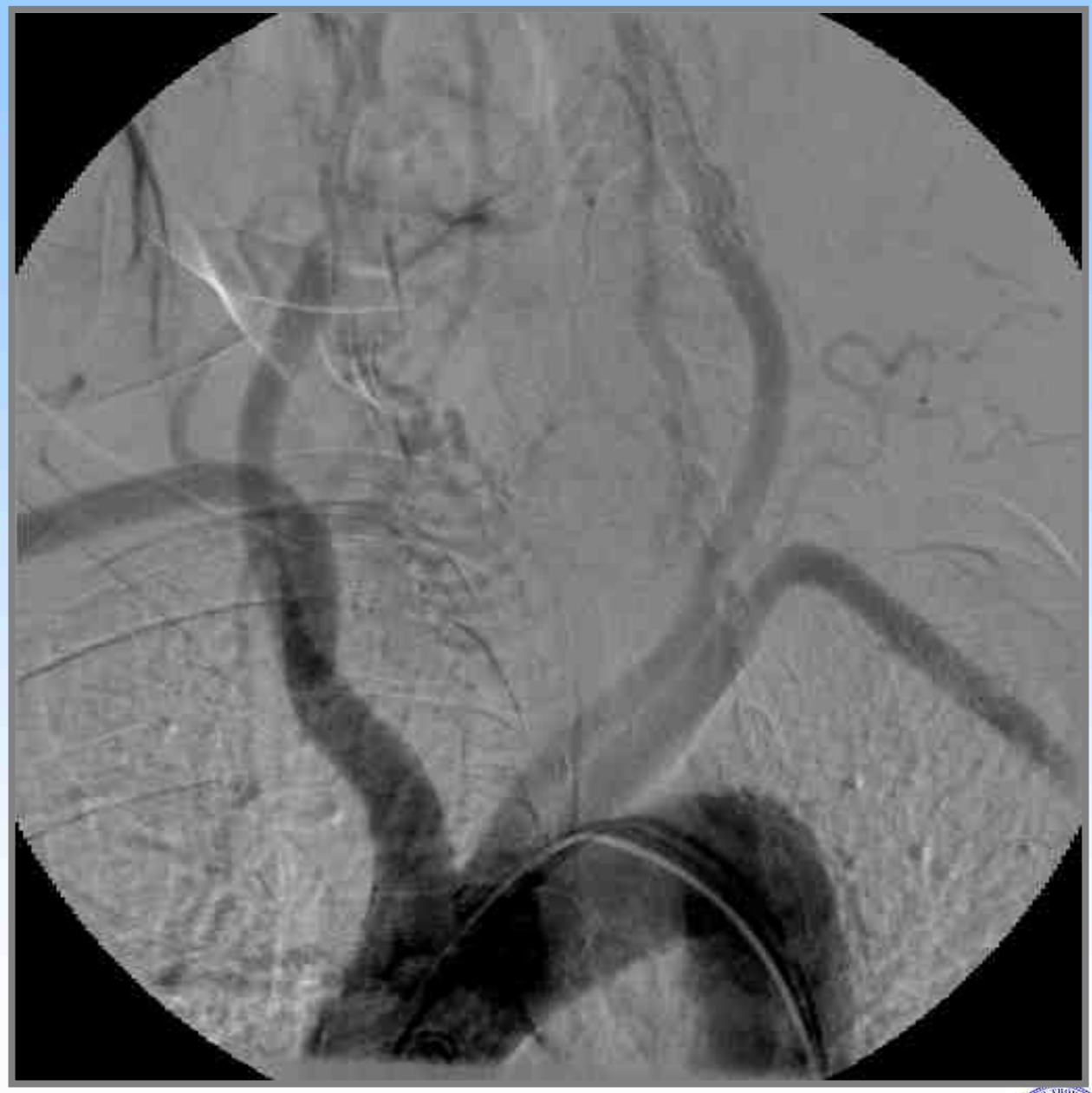
Who is at High Risk for CAS?

Aortic Arch Complexity



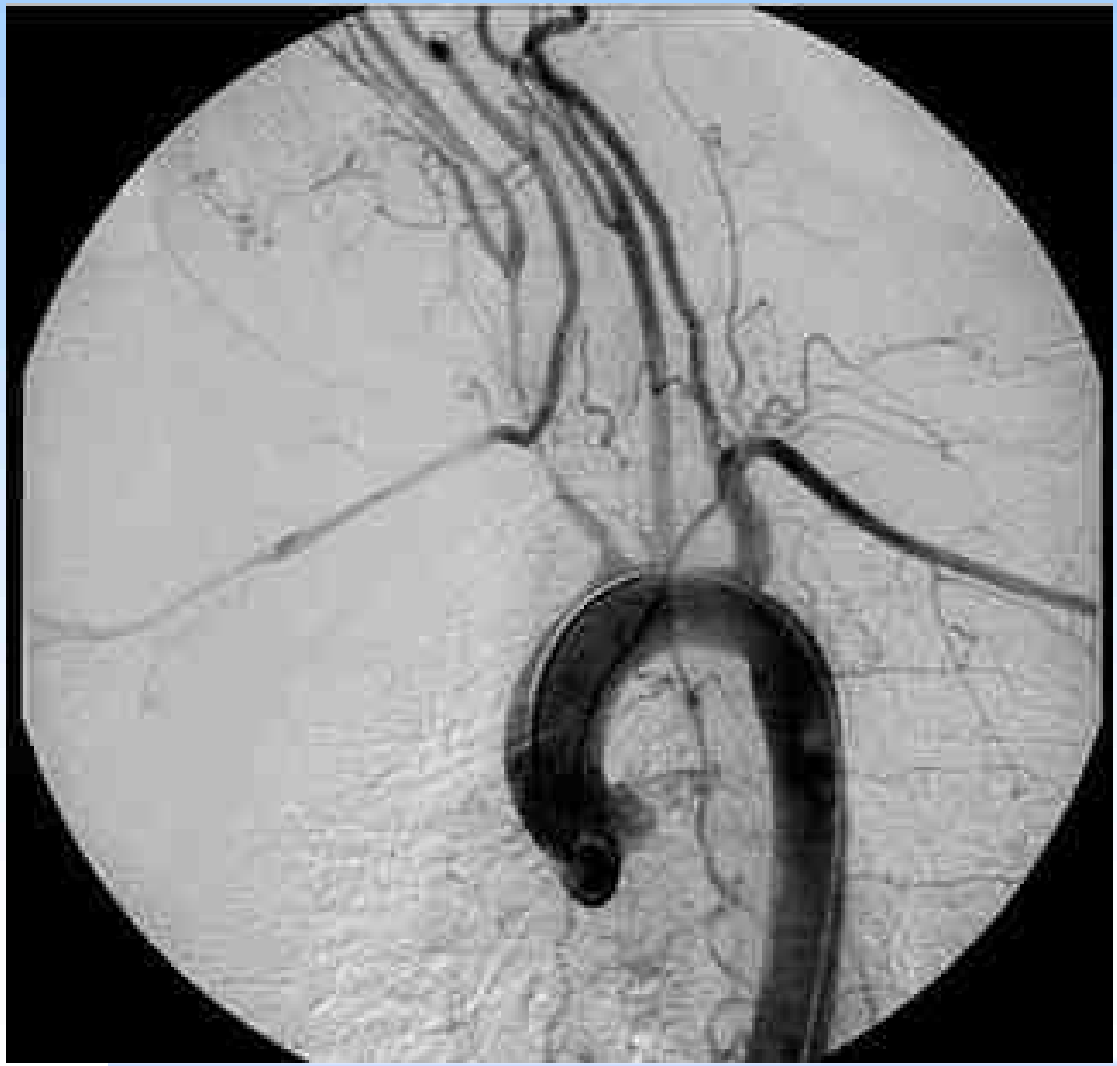






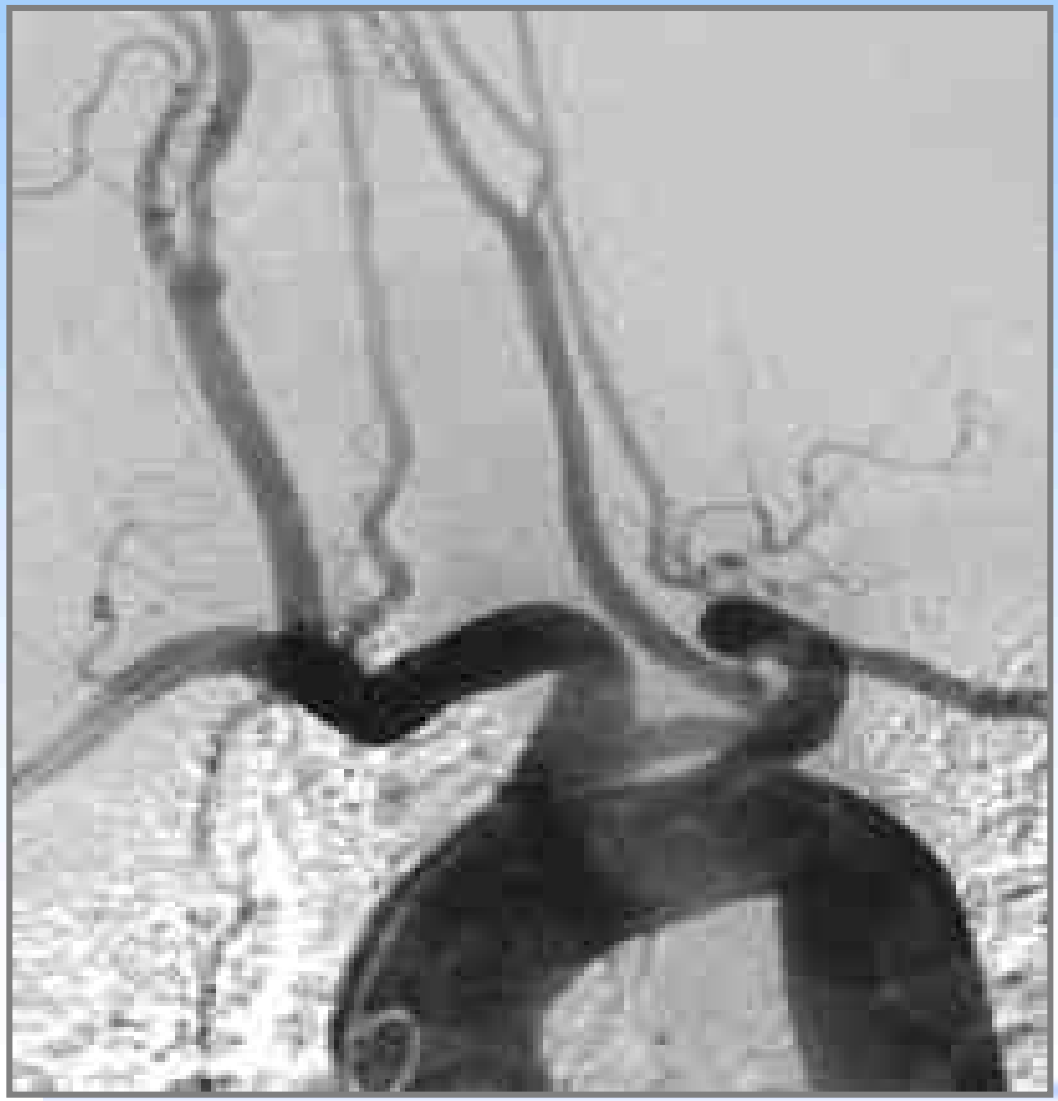
Who is at High Risk for CAS?

Common Carotid Artery Disease



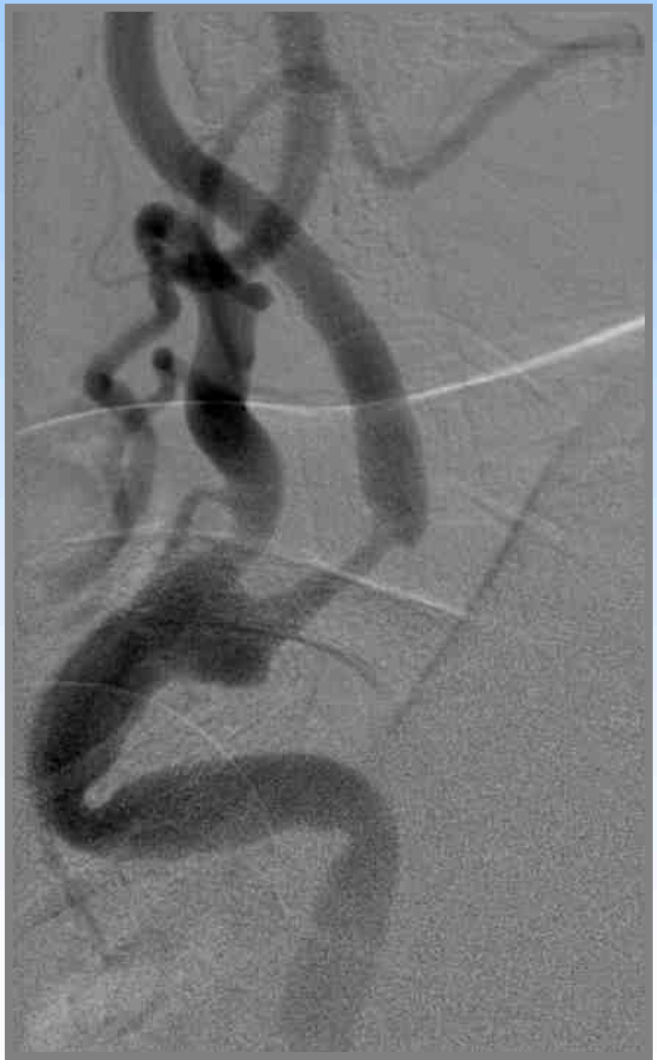
Who is at High Risk for CAS?

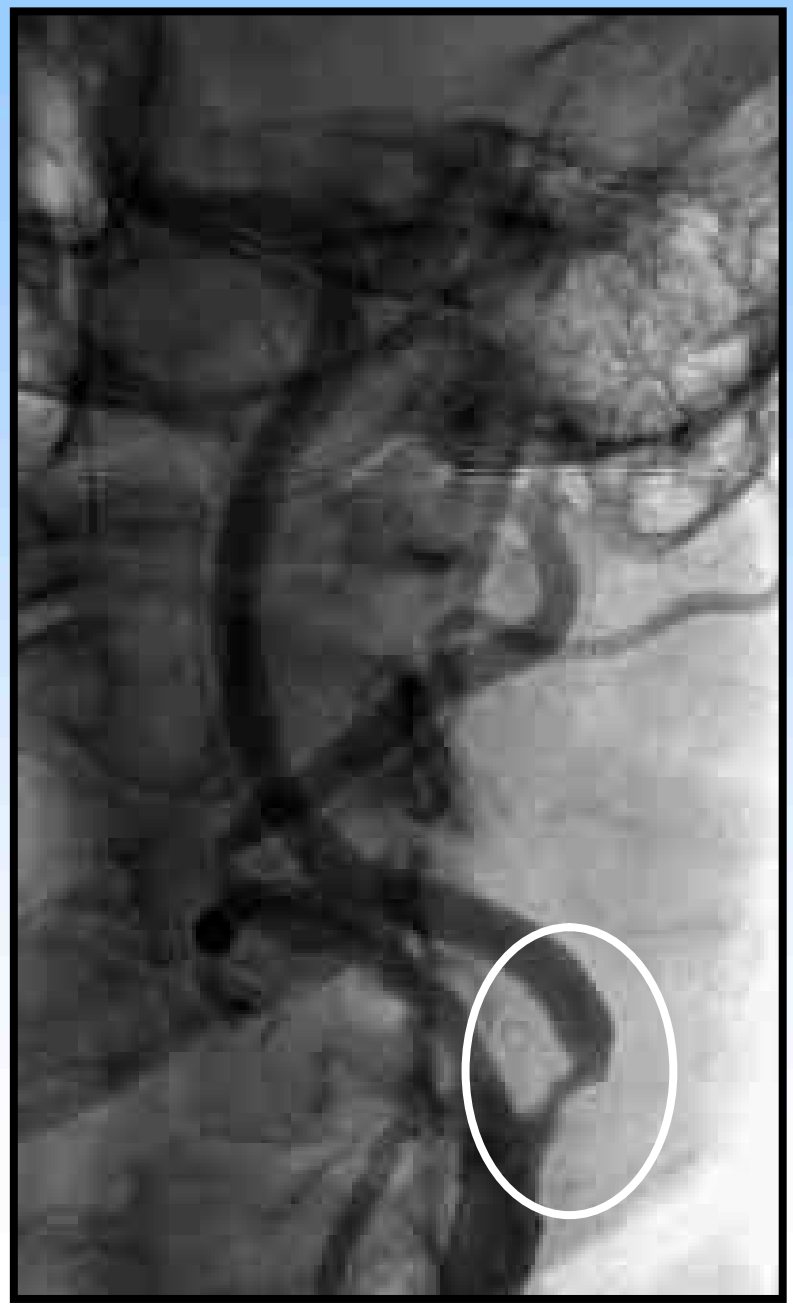
Common Carotid Artery Tortuosity

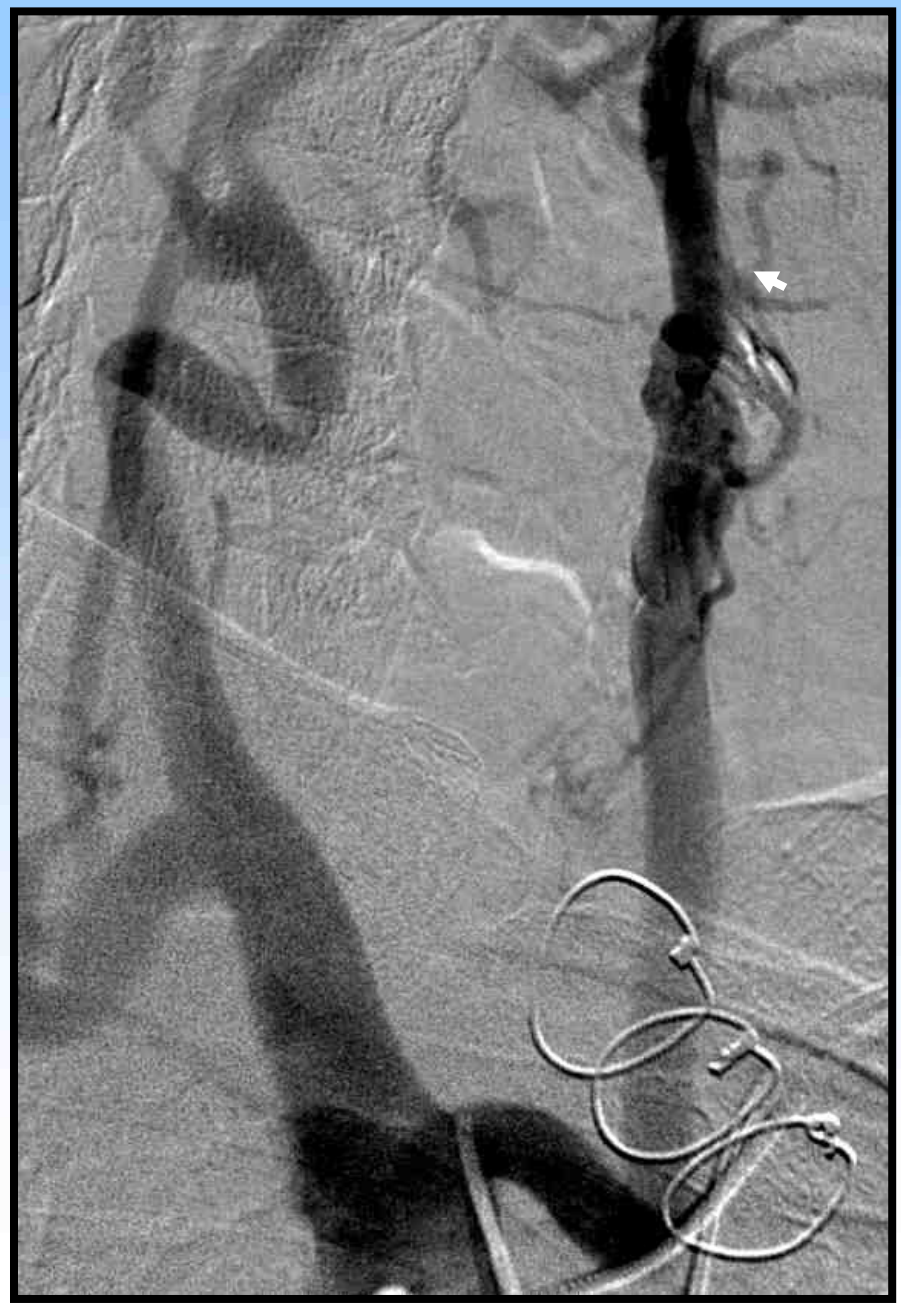


Who is at High Risk for CAS?

Common Carotid Artery Tortuosity

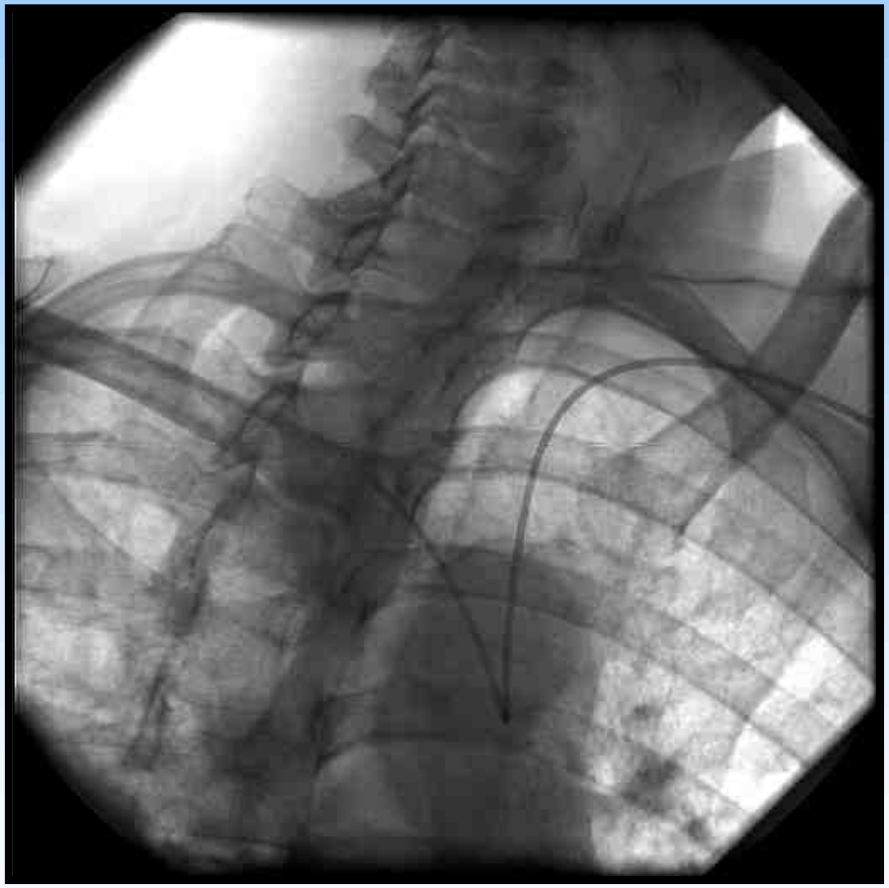


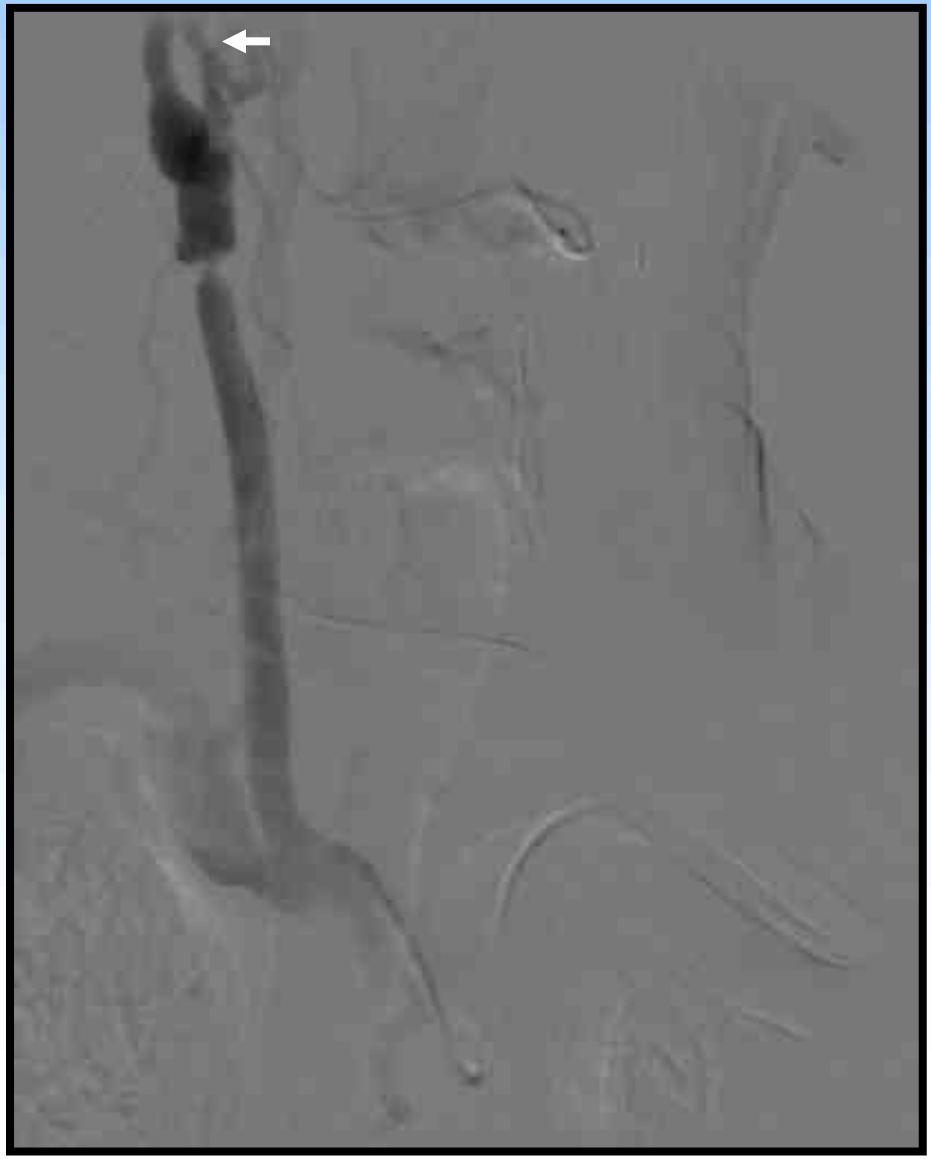




Who is at High Risk for CAS?

Non Femoral Artery Access





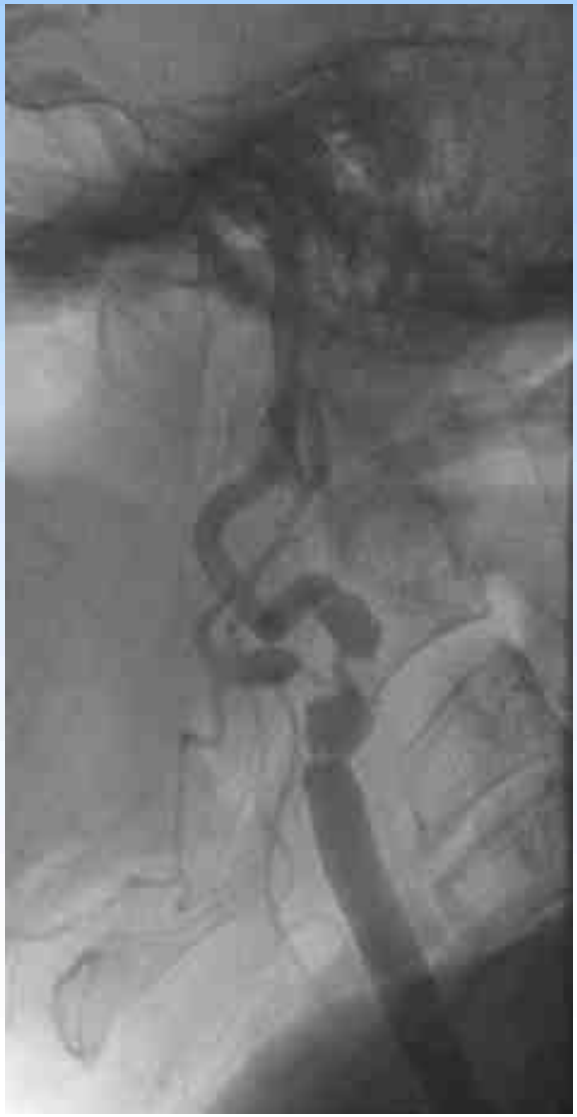
- 74 yr. old asymptomatic patient.
- 90% RICA stenosis after CEA
- Aortic occlusion

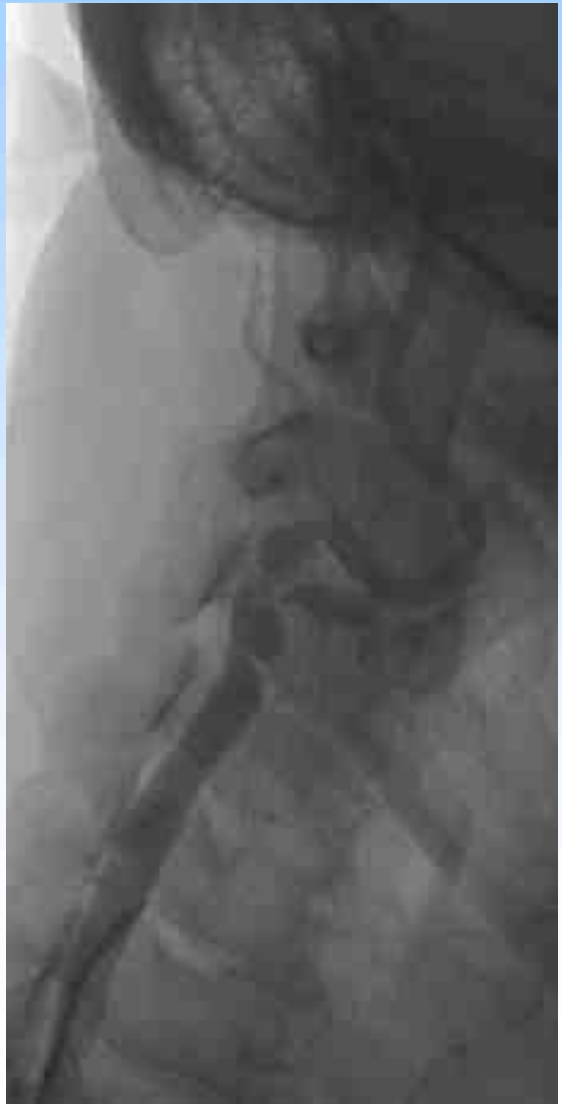
Who is at High Risk for CAS?

ICA kinks / CCA disease / ECA disease

-81 yr. old male with unstable angina and l-sided TIA:

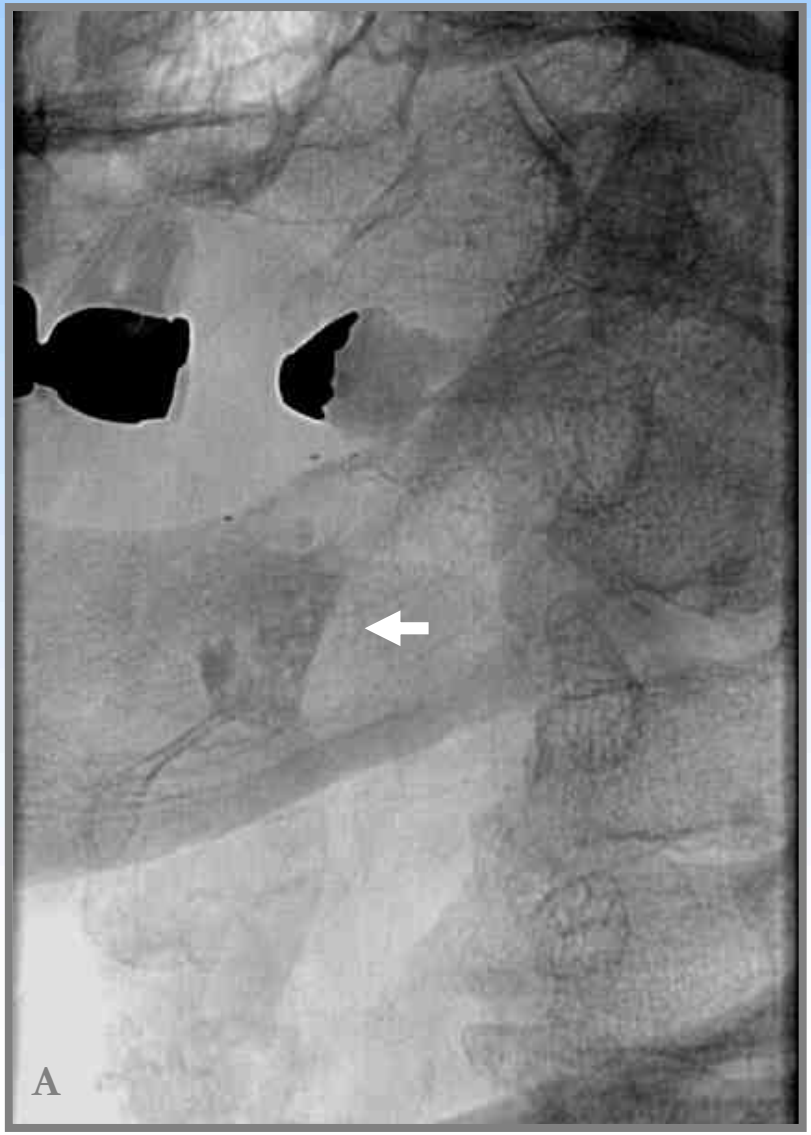
- 3 vessel CAD
- 80% RICA stenosis with involvement of the CCA and ECA
- Severe ICA tortousity

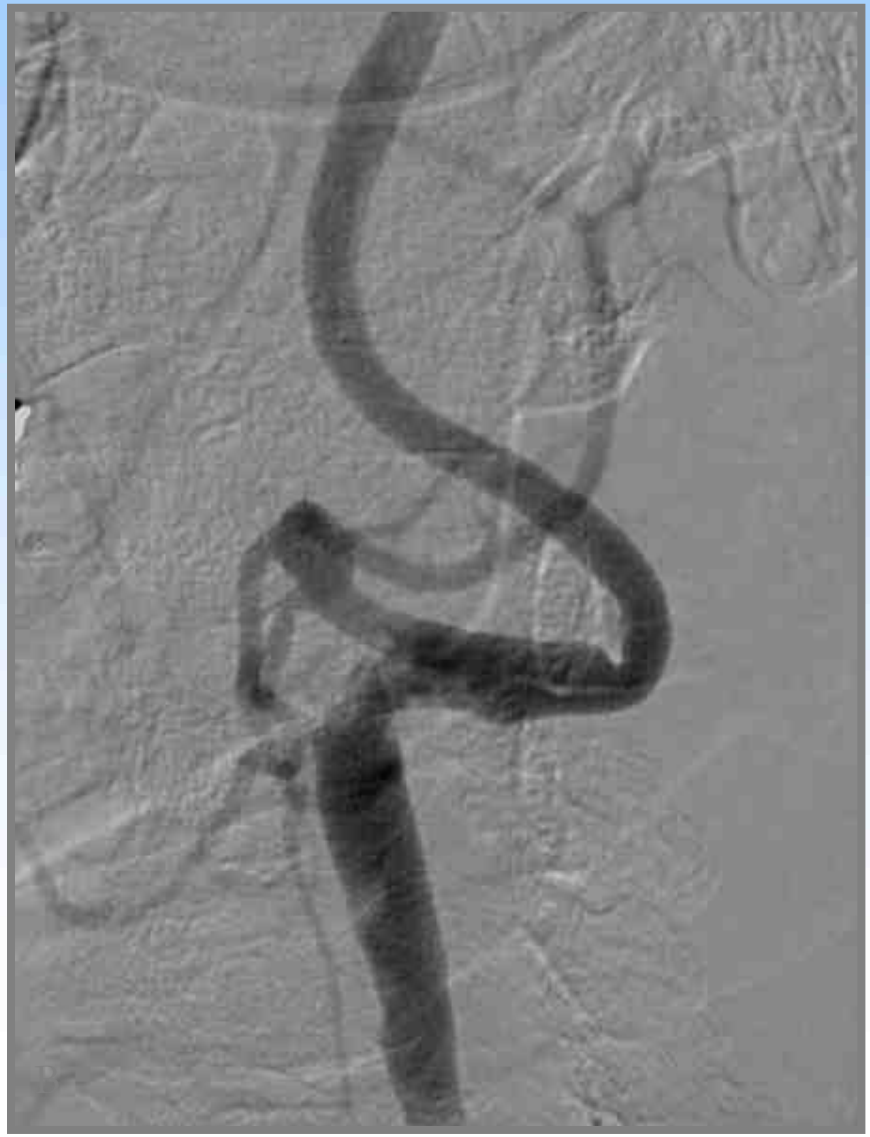


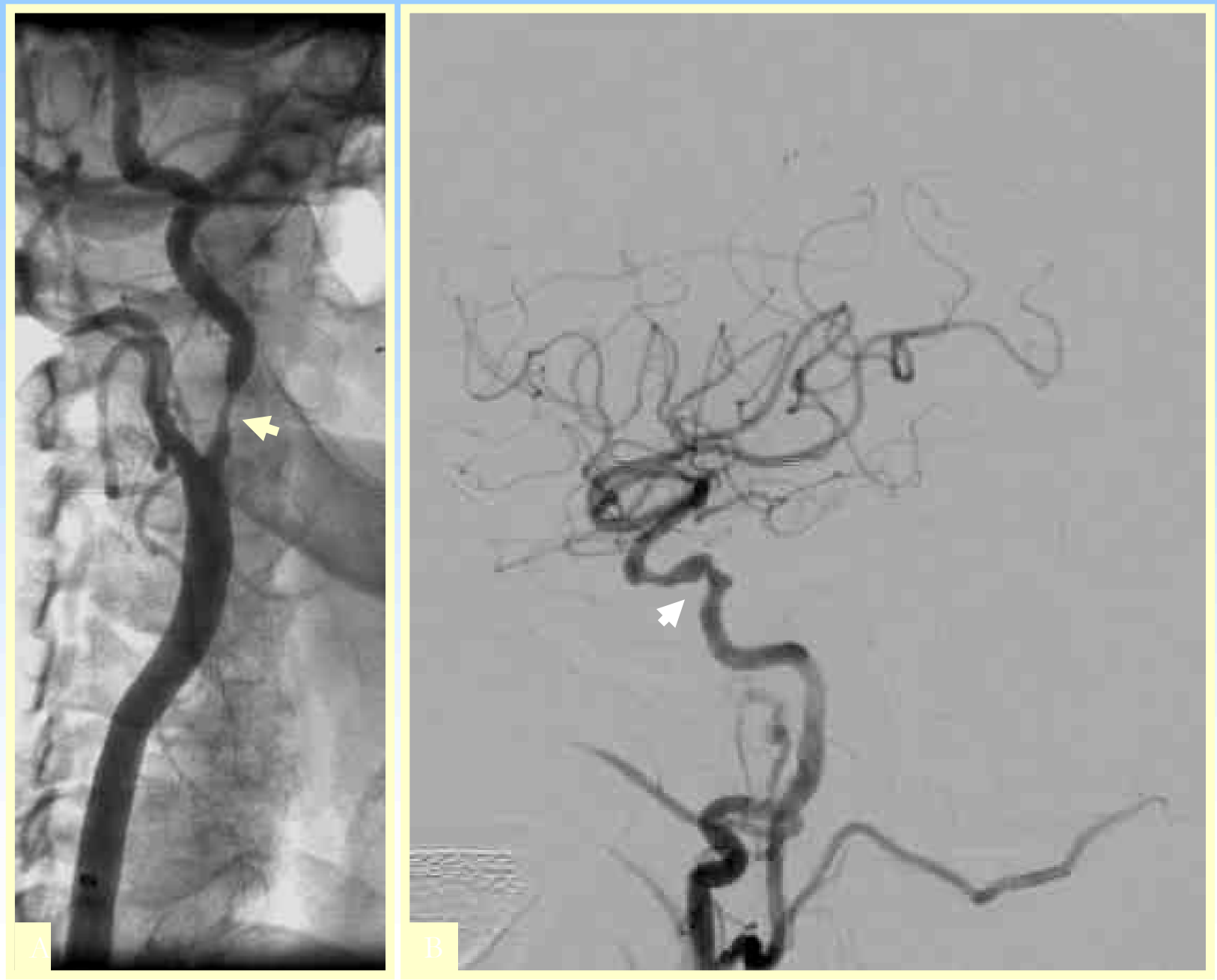


Who is at High Risk for CAS?

ICA Calcification / Tortousity

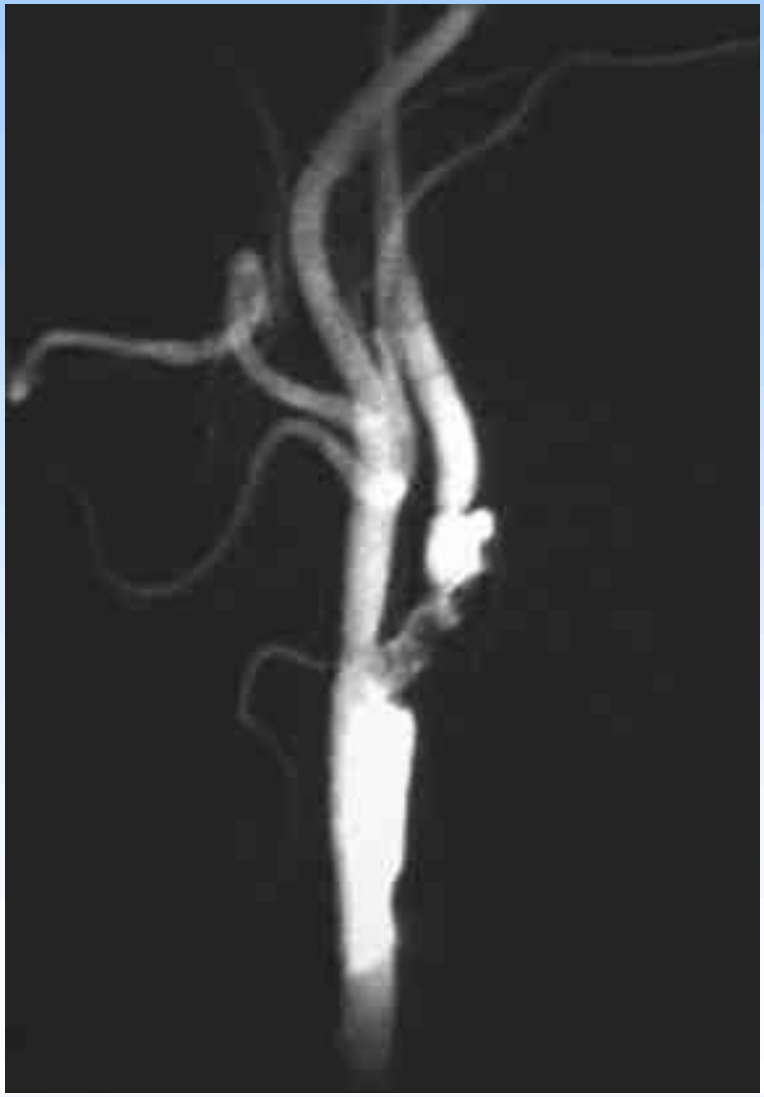




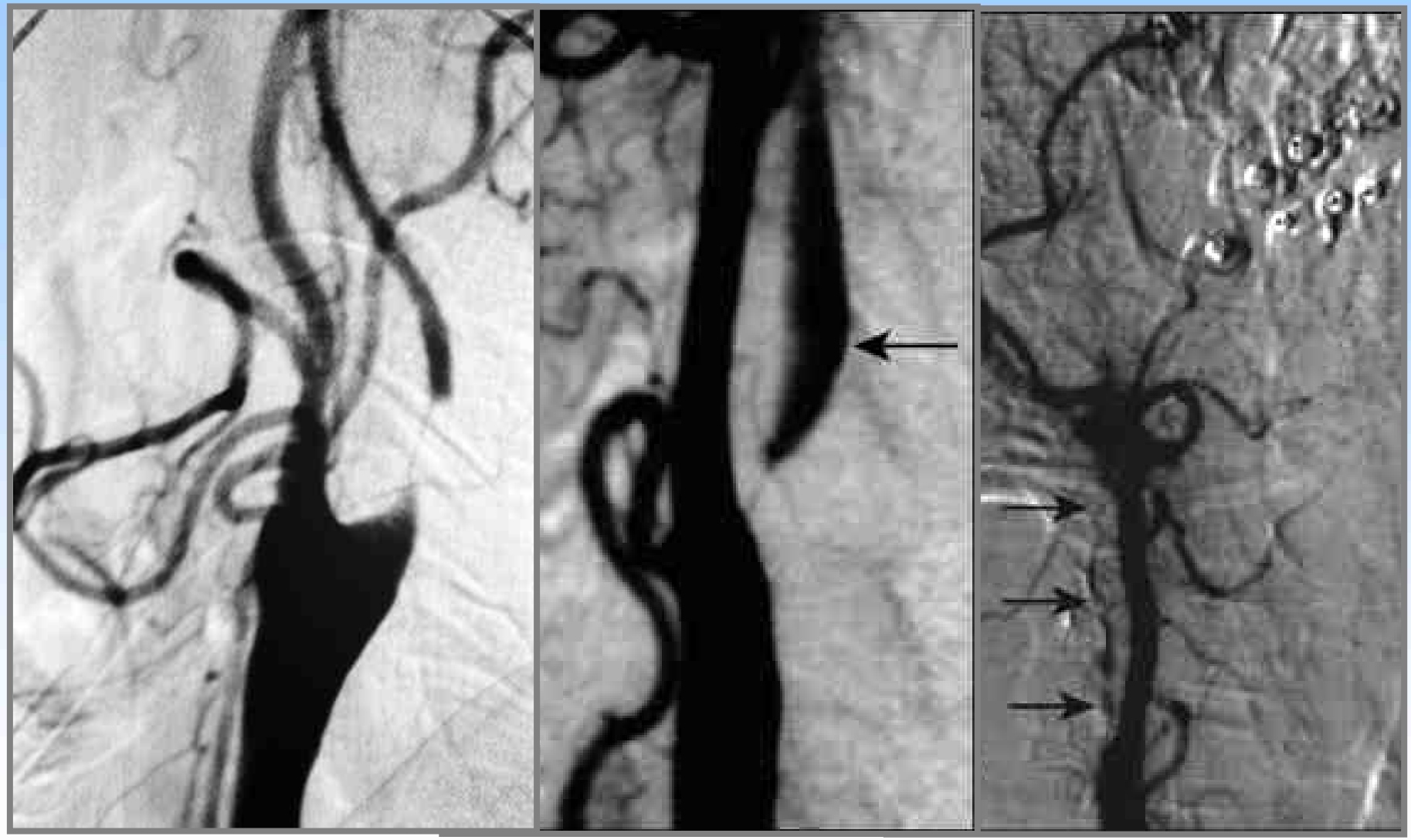

A
B

Who is at High Risk for CAS?

ICA Thrombus



What Is the String Sign?



Complications with CAS

Impact of Device Selection

I. Stent design

A. The debate of the impact of open vs. closed cell design outcome is worthwhile but the jury is still out.

II. Type of EPD

A. Although there are definite differences in the technical performance of EPDs it is unlikely that there is difference in outcome

B. Proximal protection devices have the potential to enhance procedural safety in certain clinical and anatomic patient subsets

Complications with CAS

Role of the operator

Summary

- Patient risk profiling for CAS should be done in the context of overall patient condition and operator experience
- None of the high risk elements is a contraindication for CAS on its own. However, as a rule of thumb the higher number of factors the higher the risk
- The benefit to risk ration can be optimized by:
  - Adhering to compelling indications to perform the procedure
  - Pre-procedure imaging (CTA – MRA) to optimize patient selection
  - Thoughtful procedural planning and execution