Plaque Characterization of Carotid Disease Predicting Outcome

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular
• Consulting Fees/Honoraria	• Covidien
• Major Stock Shareholder/Equity	• Setajon, North Wind
• Royalty Income	• Covidien
• Ownership/Founder	• North Wind
• Intellectual Property Rights	
• Other Financial Benefit	

AT THE PRESENT TIME, WE HAVE LIMITED KNOWLEDGE OF PLAQUE CHARACTERISTICS

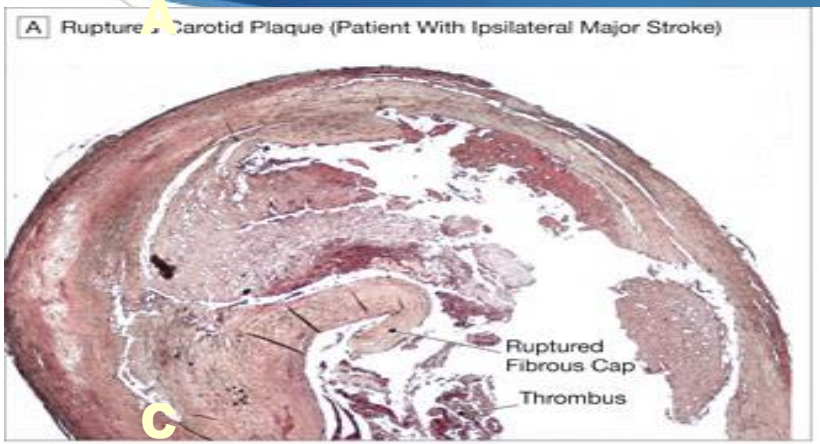
The goal is the search for the elusive plaque before it becomes symptomatic:

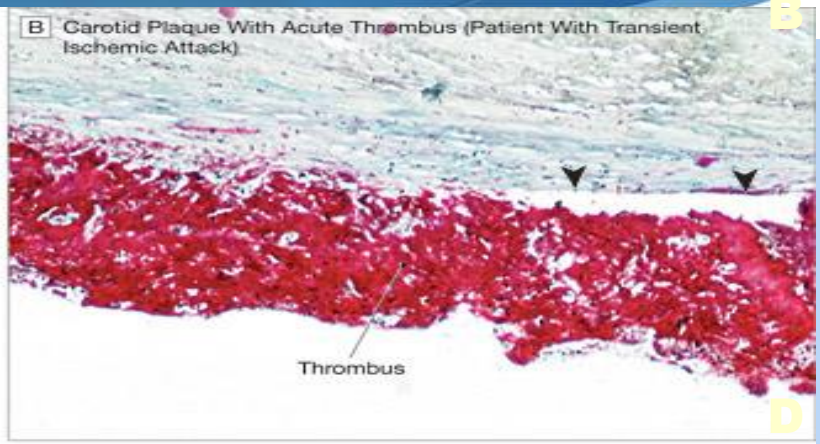
1. **Identify vulnerable plaque and TCFA**
2. **Prevent Plaque rupture**
3. **Avoid stroke**

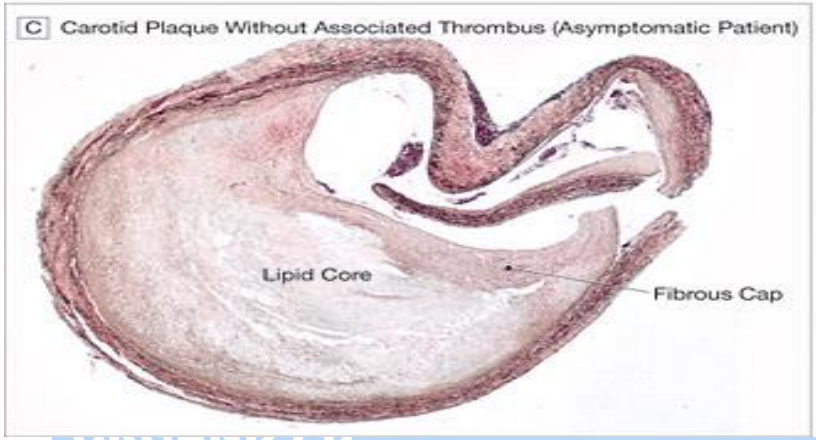
The reality of severe carotid stenosis

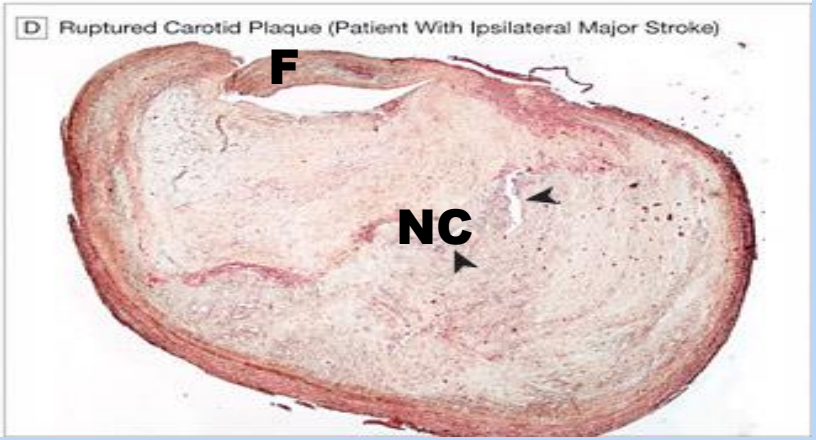
The first symptom may be a sudden permanent stroke (25% of cases)

Histopathology of Carotid Plaques with different Clinical Presentation







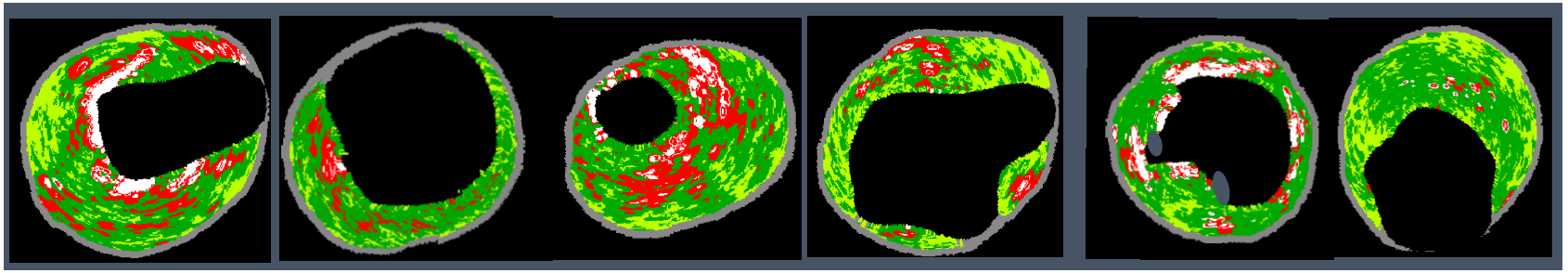


Ranking of Vulnerable Plaque

- Whereas in terms of vulnerability the ranking, based on postmortem data, might be different with the CaTCFA being allegedly most high risk plaque and FCa more stable

Considered as most vulnerable plaque

Considered as least vulnerable plaque



CaTCFA **TCFA** **CaFA** **FA** **FCa** **PIF**

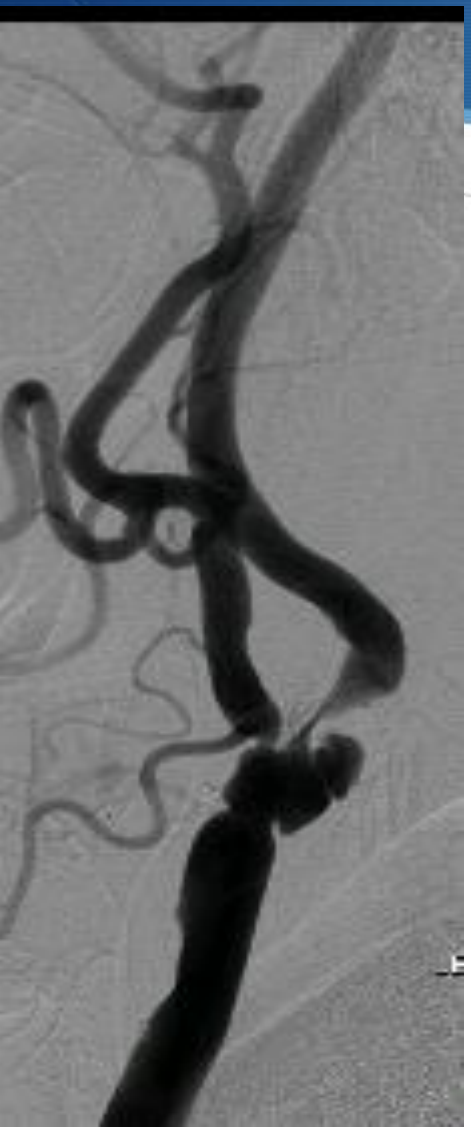
Courtesy P. Margolis, MD

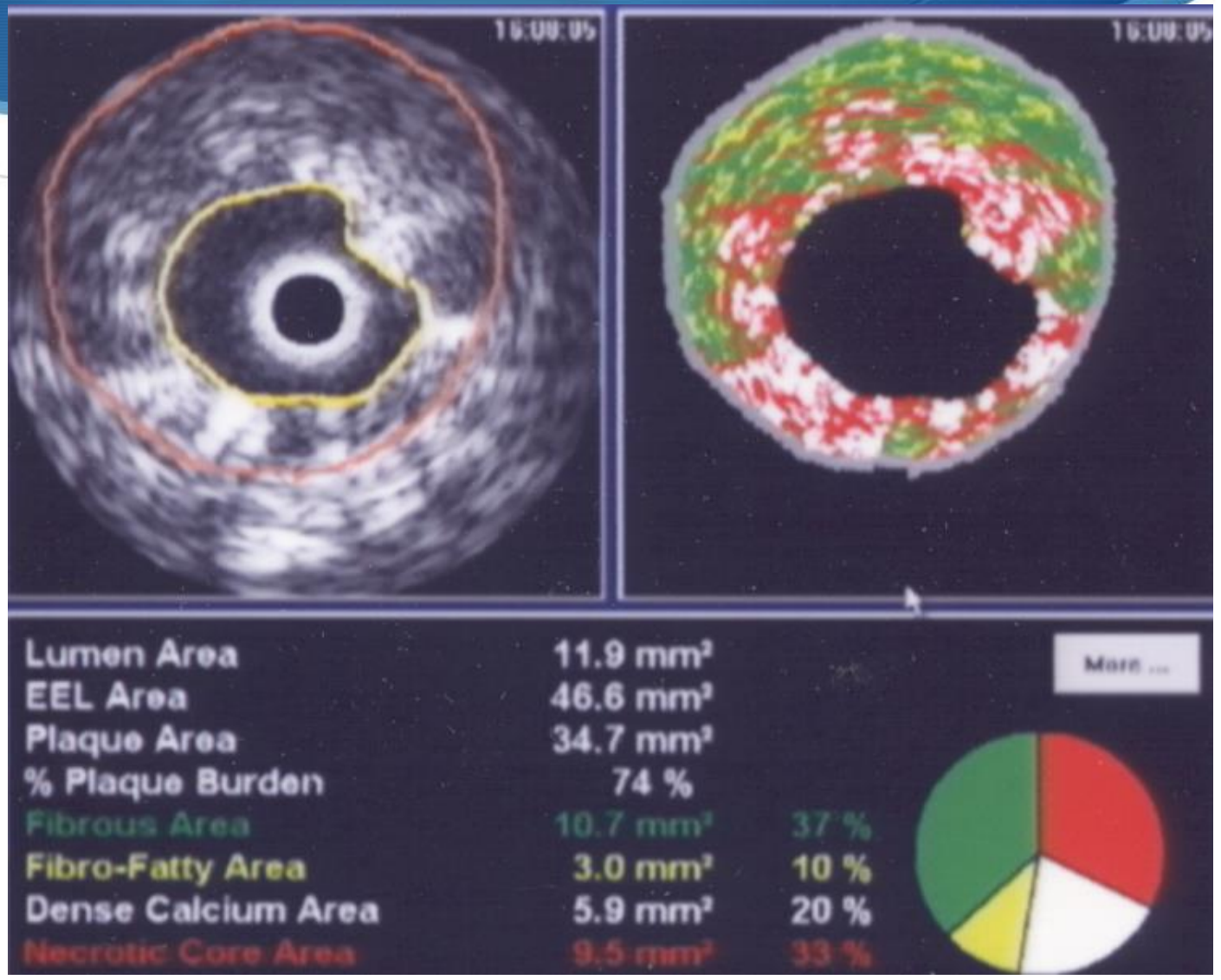
Significant Independent Predictors of Non-Cluprit Lesions

1. **Plaque Burden**
2. **TCFA by IVUS**
3. **Minimum lumen area**

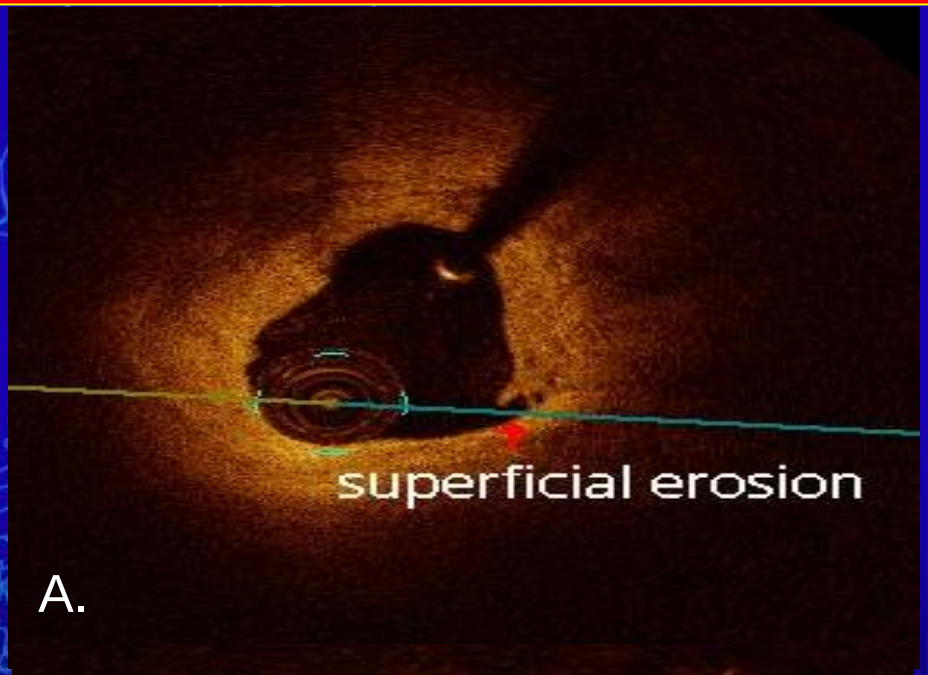
Presence of 2 or 3 of these predictors in the coronary data have a 10-18% chance of an event within 3 years

IVUS Indicates Pt Best Suited for CEA

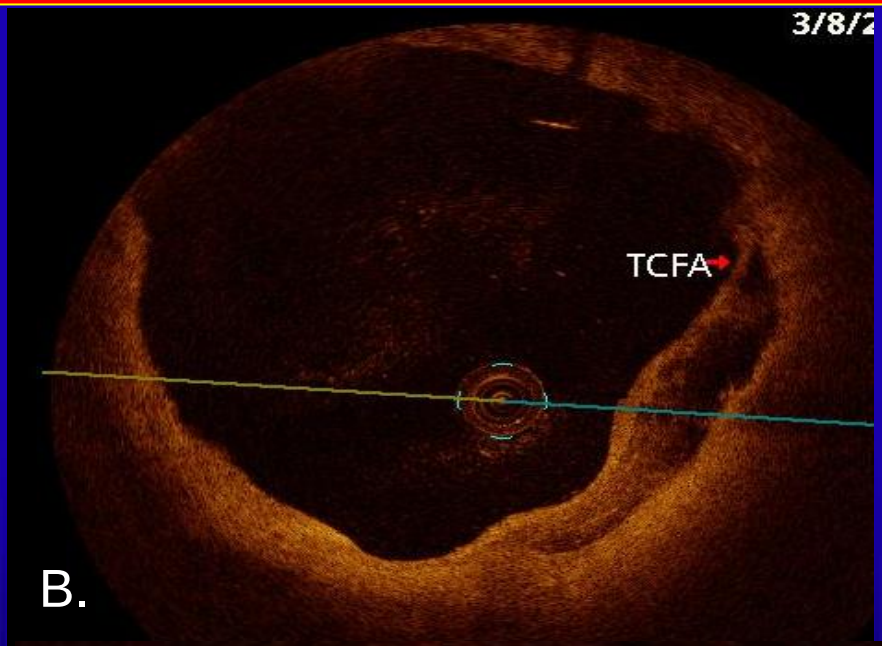




Results OCT



A.



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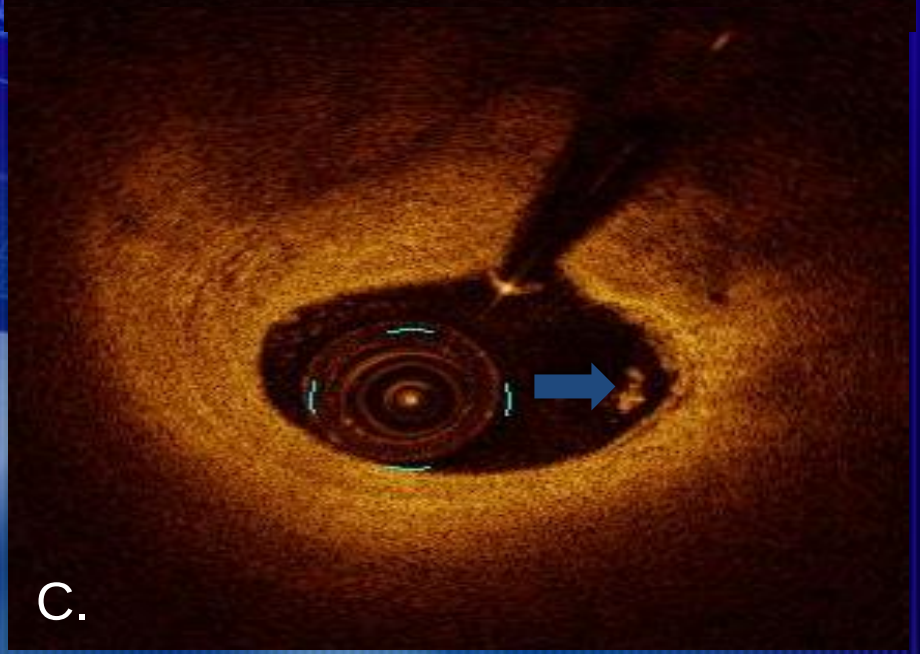

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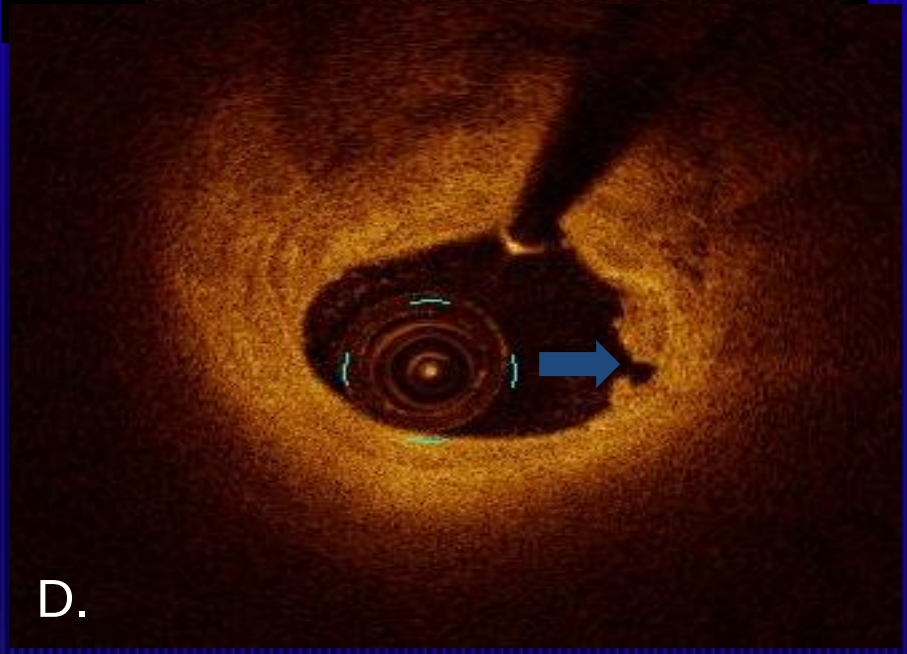


D.

Current Imaging Techniques

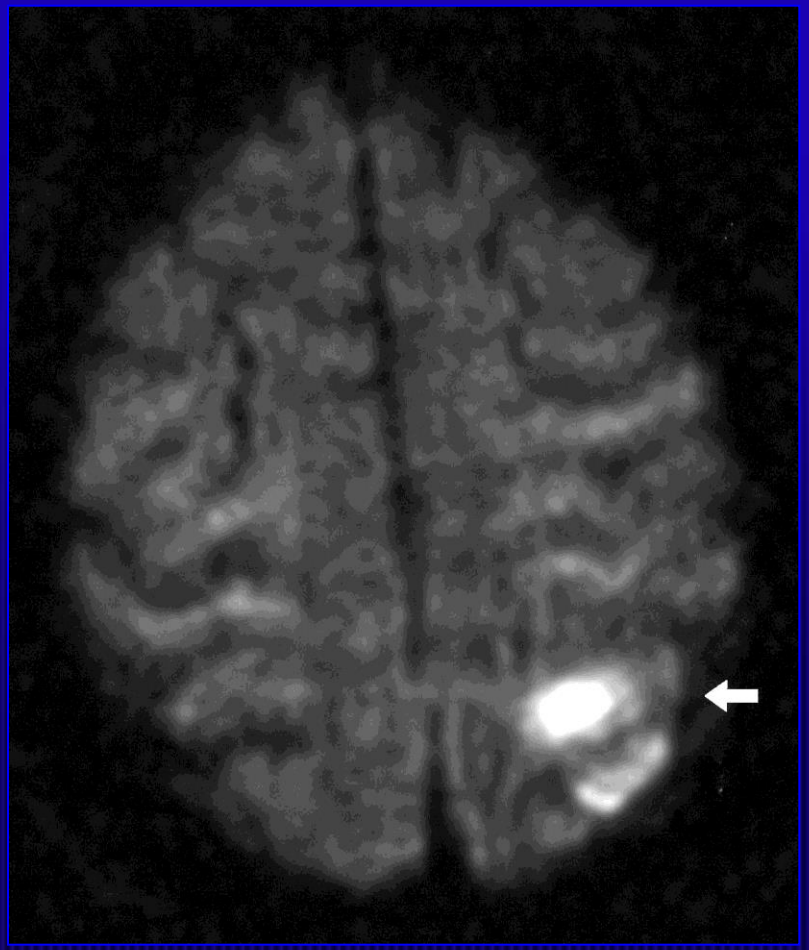
- **Essentially all trials were based on the Gold Standard**
  - **Angiography**
  - **Degree of Stenosis**

The question is how do we find these Stroke indicators

There are 14 to 20 factors that influence CAS outcomes

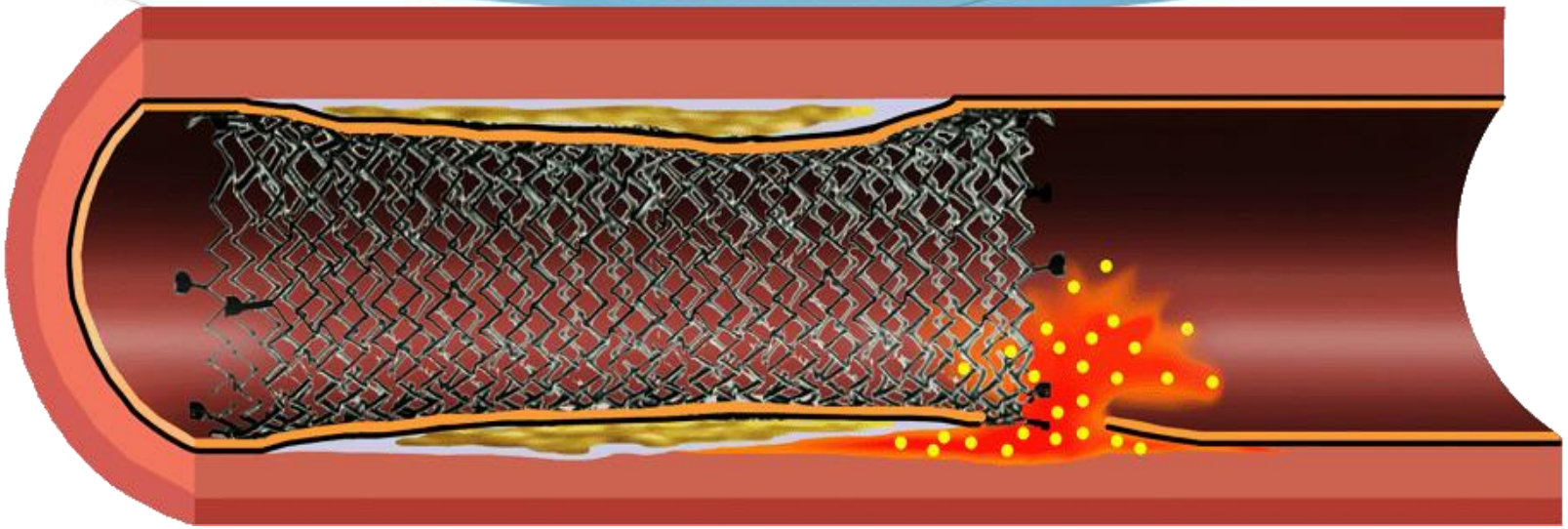
Plaque morphology is only one, but it could be the one that will separate those patients best suited for surgery vs. stenting

Ipsilateral Lesions after CAS



transient weakness of right hand: TIA

Stent erosion of Vulnerable Plaque with rupture ??

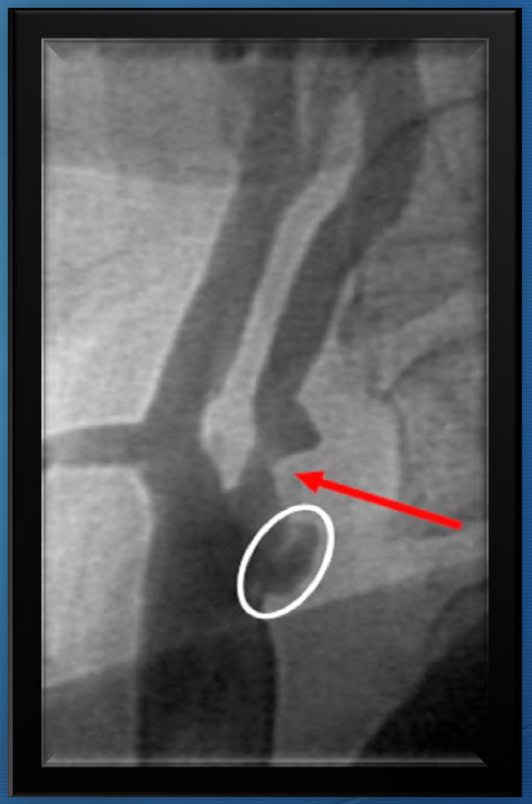


Is vulnerable plaque the culprit in procedural strokes?

The Problem

MZ, 74y,
***asymptomatic*,**
LICA stenosis 85%

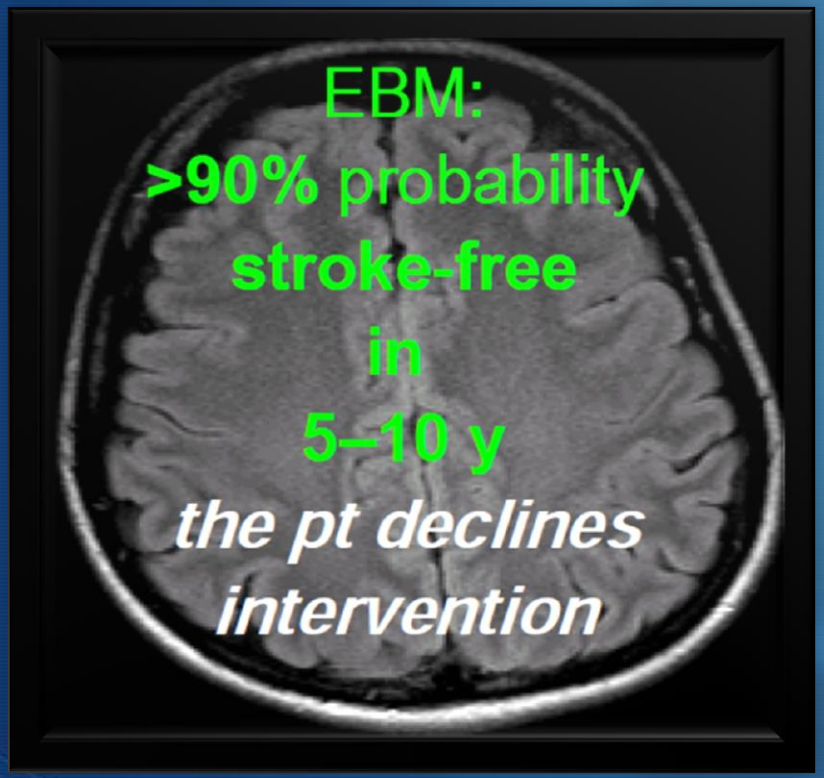
SZ, 68y, *asymptomatic*,
LICA stenosis ~40% + ulcer



QCA 43%

Which of the two plaques should be treated by (CAS) or (CEA)?

MZ, 74y,
asymptomatic,
LICA stenosis 85%



Indication to CEA/CAS

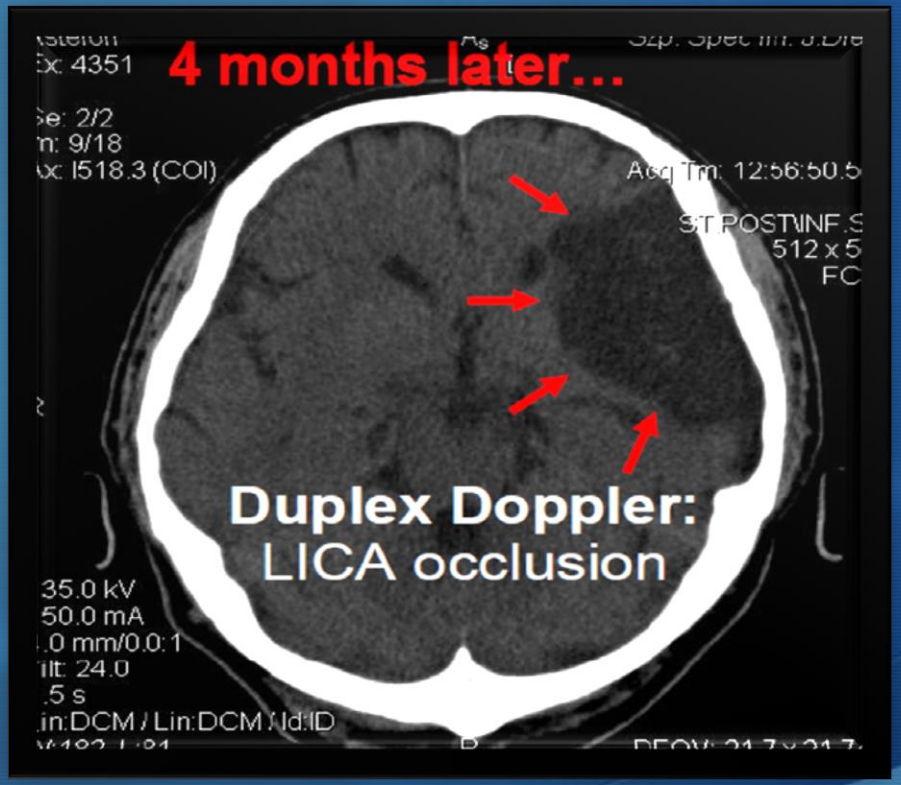
SZ, 68y, *asymptomatic*,
LICA stenosis ~40% + ulcer

NO indication to CEA/CAS

(in both – 'full' pharmacotherapy included 'high-dose' statin, ASA, ACEI)

MZ, 74y,
***asymptomatic*,**
LICA stenosis 85%

SZ, 68y, *asymptomatic*,
LICA stenosis ~40% + ulcer



Indication to
CEA/CAS

NO indication to
CEA/CAS

Motoric aphasia 4/5
Right hemiparesis 3/5

Patient selection

- 429 patients
- Male - 61.5% / Female - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceeding carotid intervention

Lesion Characteristics Based on Angiography

- **Length of lesion**
- **Percent stenosis**
- **Location of lesion (ostial vs. non-ostial)**
- **Ulceration**
- **Calcification**
- **Contralateral internal carotid occlusion**

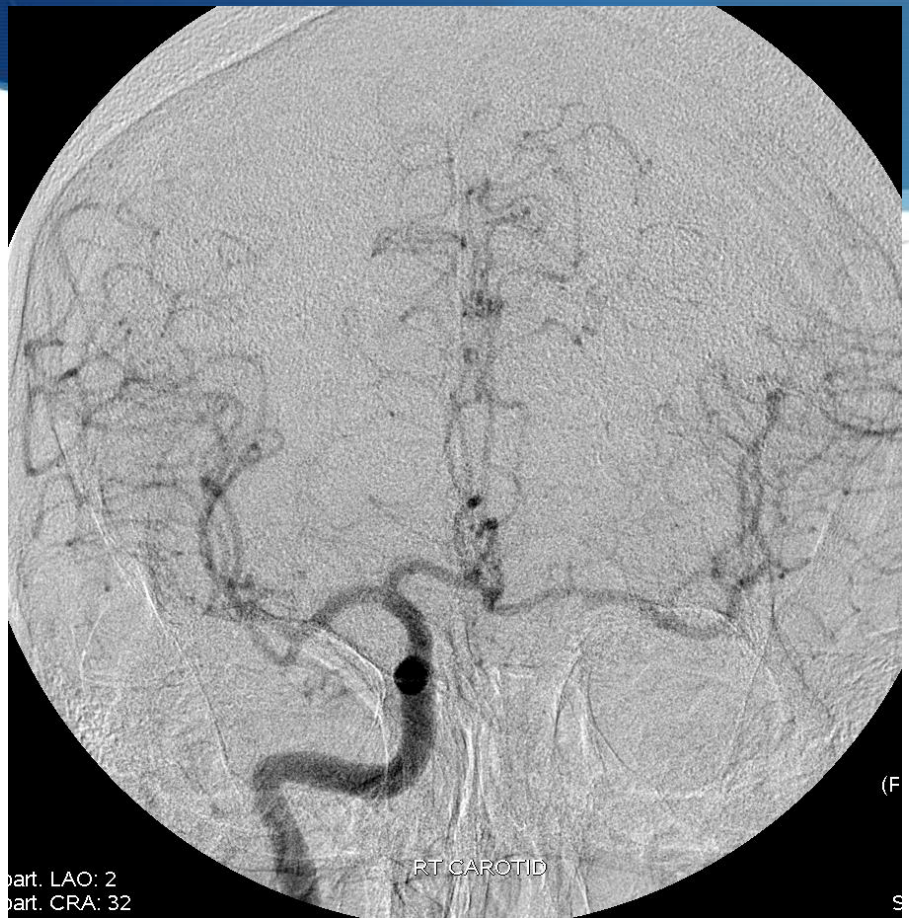
Carotid Stent Case

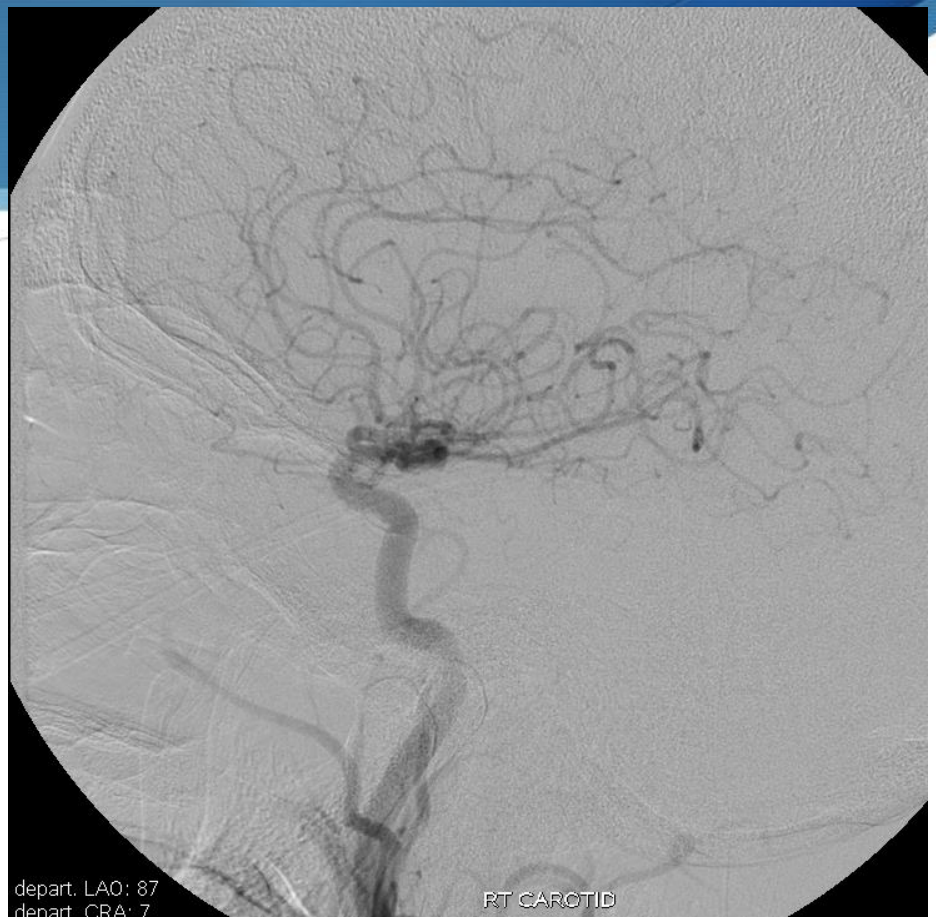
- 80 year old male with two days of right arm weakness and brief expressive aphasia
- PMH quadraperesis secondary to remote cervical fracture, previous trach, PEG
- Transferred from OSH with CTA showing high grade left carotid stenosis

RIGHT

LEFT

All flow from right side

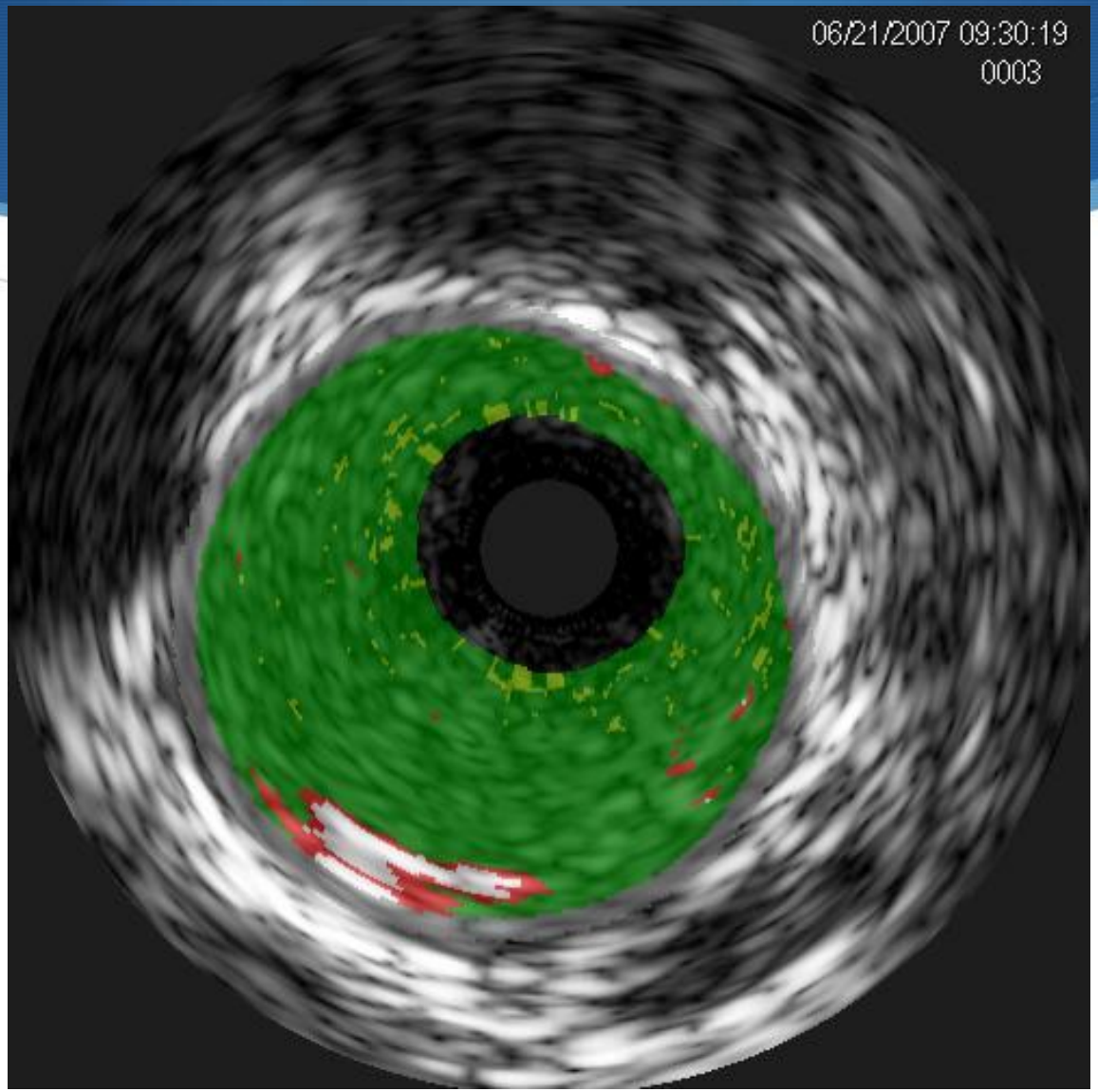




RIGHT AP

RIGHT lateral

VH in lesion(PIF)



PRE

POST

6mm straight stent 3 cm long Exact

The Challenge: Identify Unique Features Critical to Plaque Rupture

1. **Plaque Burden**
2. **TCFA by IVUS, OCT, angioscopy, MRI-C**
3. **Lumen area (minimum)**

OCT

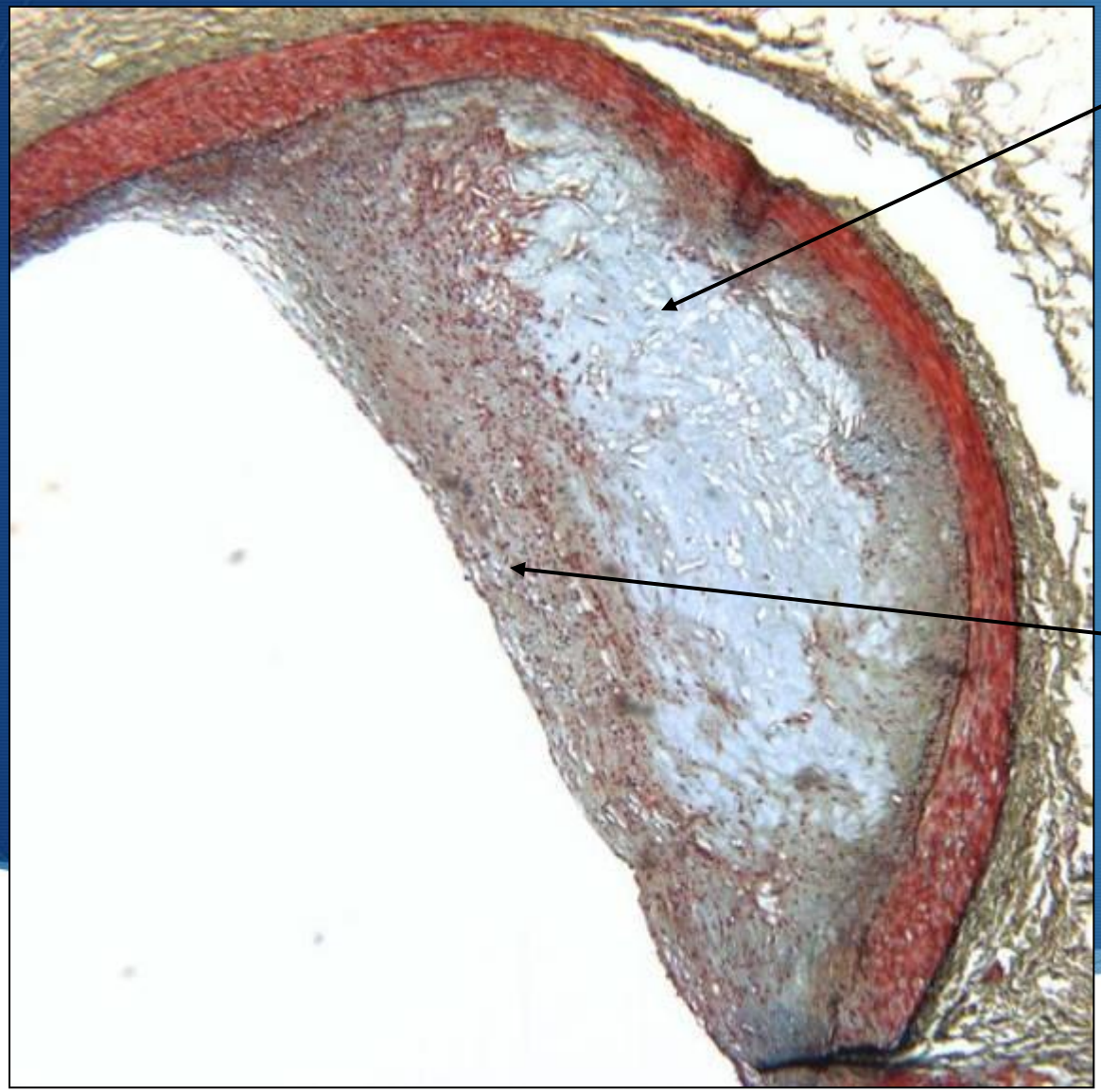
High resolution of fibrous cap thickness 10 x greater than IVUS.

Plaque characterization;

Limitation – penetration lock 3mm.

Figure 2.

FibroAtheroma (FA)

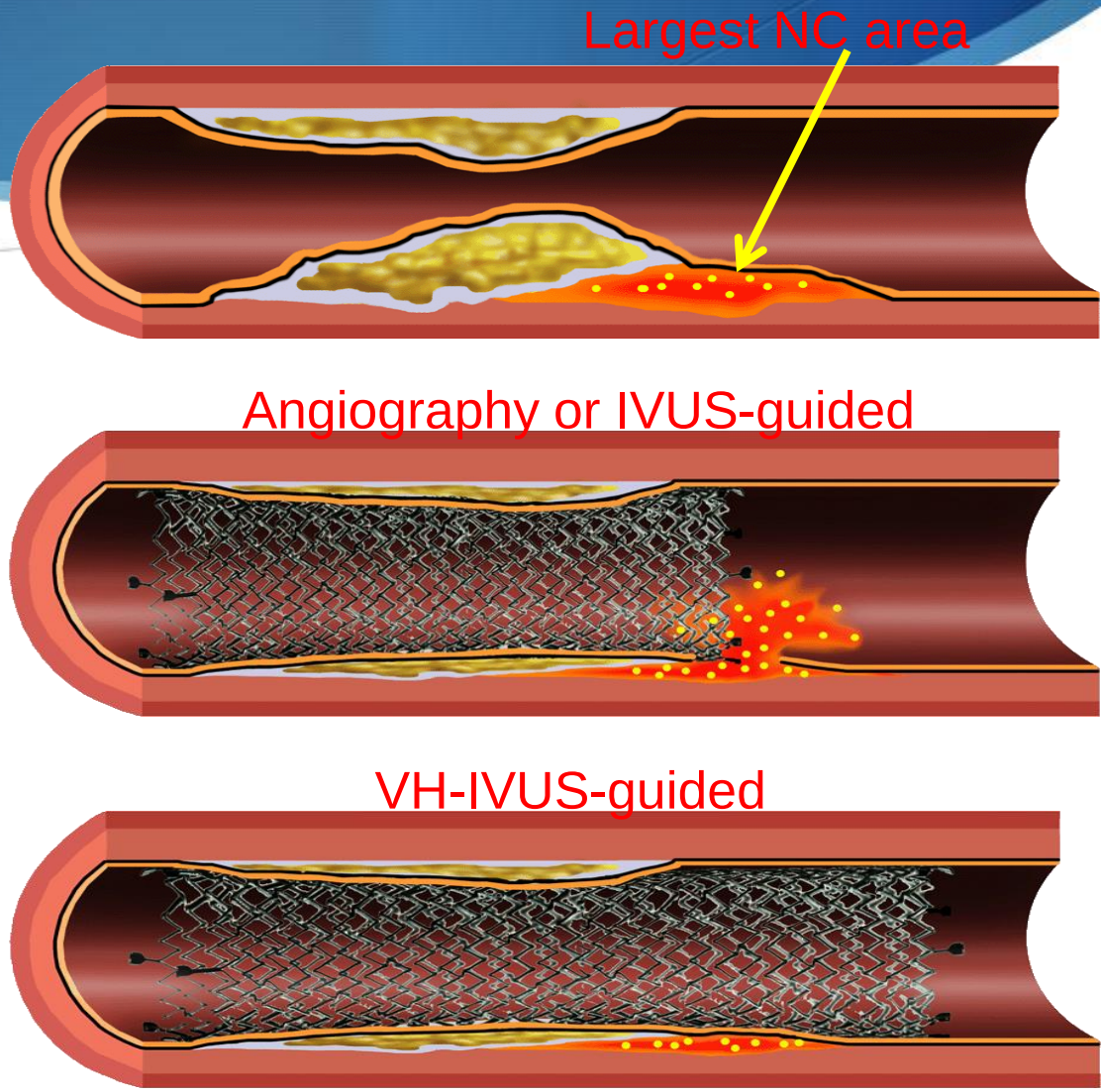


Acute Plaque rupture with thrombosis may occur in non-stenotic segment

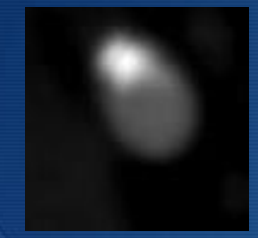
What is optimal complete lesion coverage?

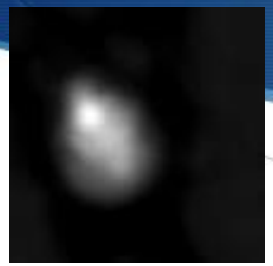
- Lack of clinical data comparing method

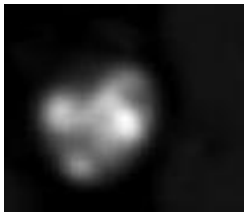
- Impact on:
  - Distal embolization
  - Stent thrombosis
  - Restenosis
  - Plaque progression

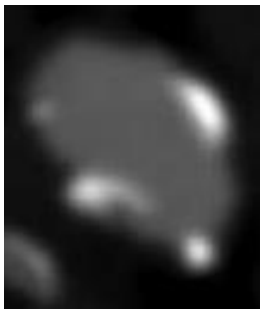


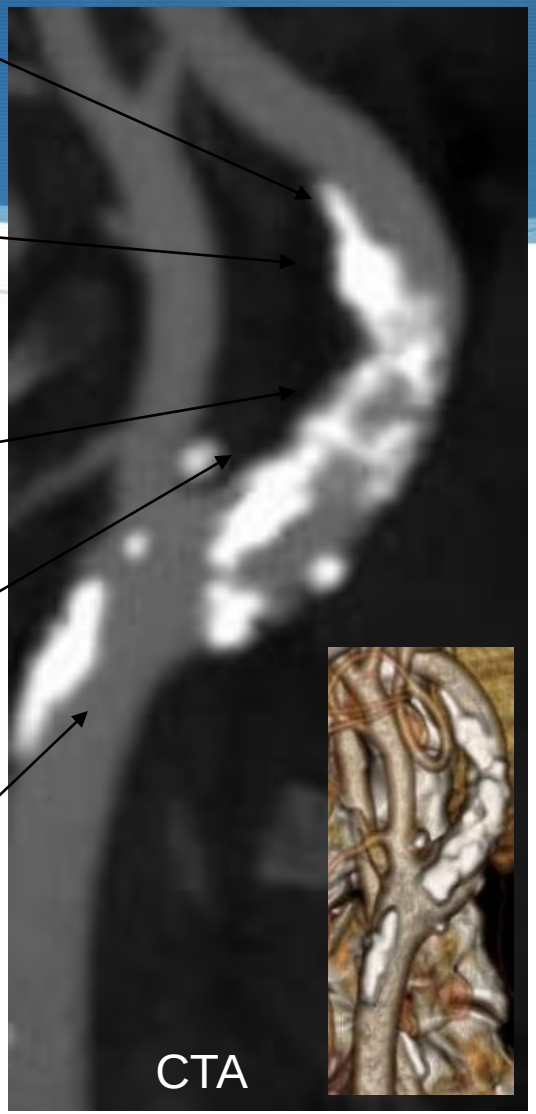
Stent may not expand



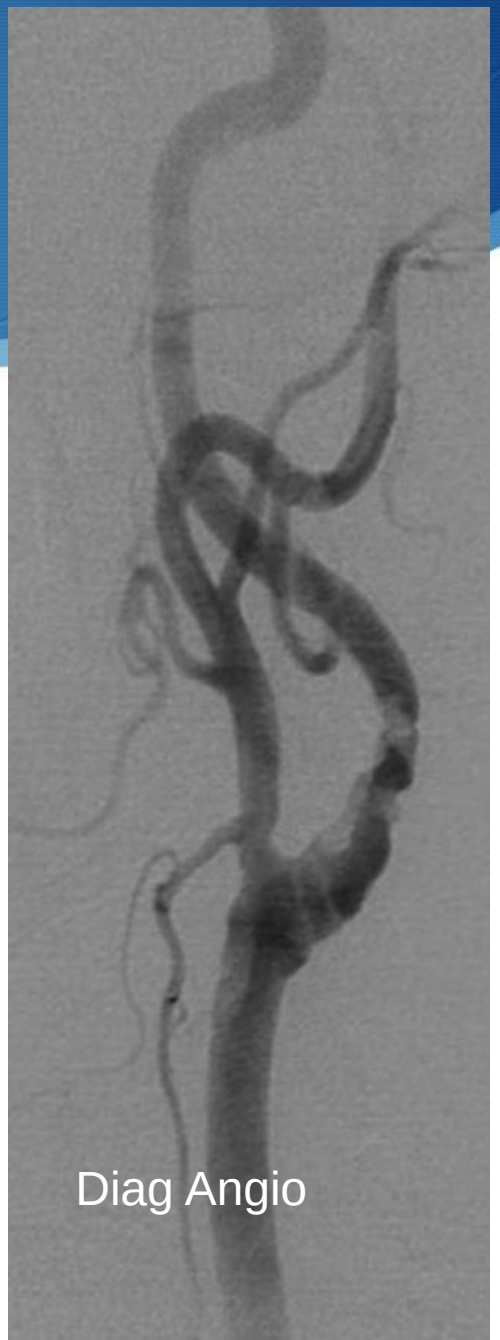






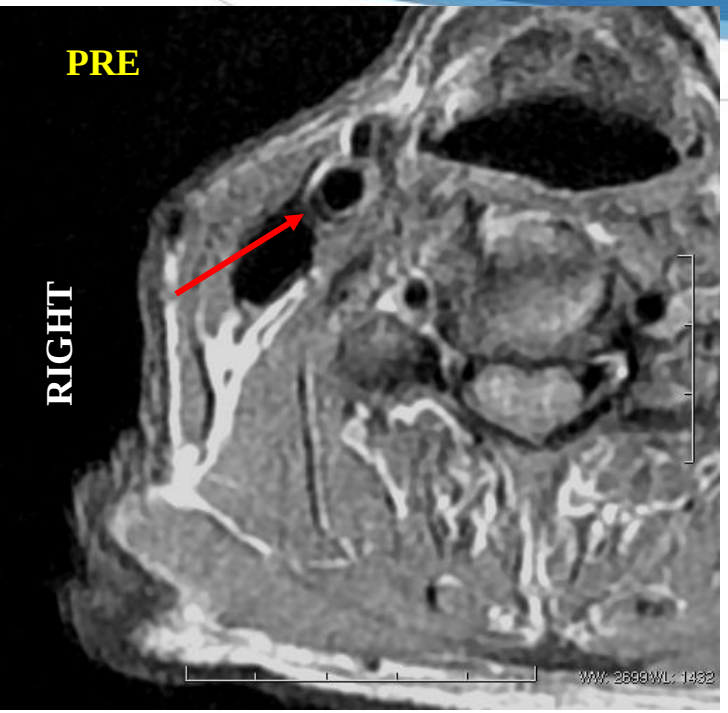


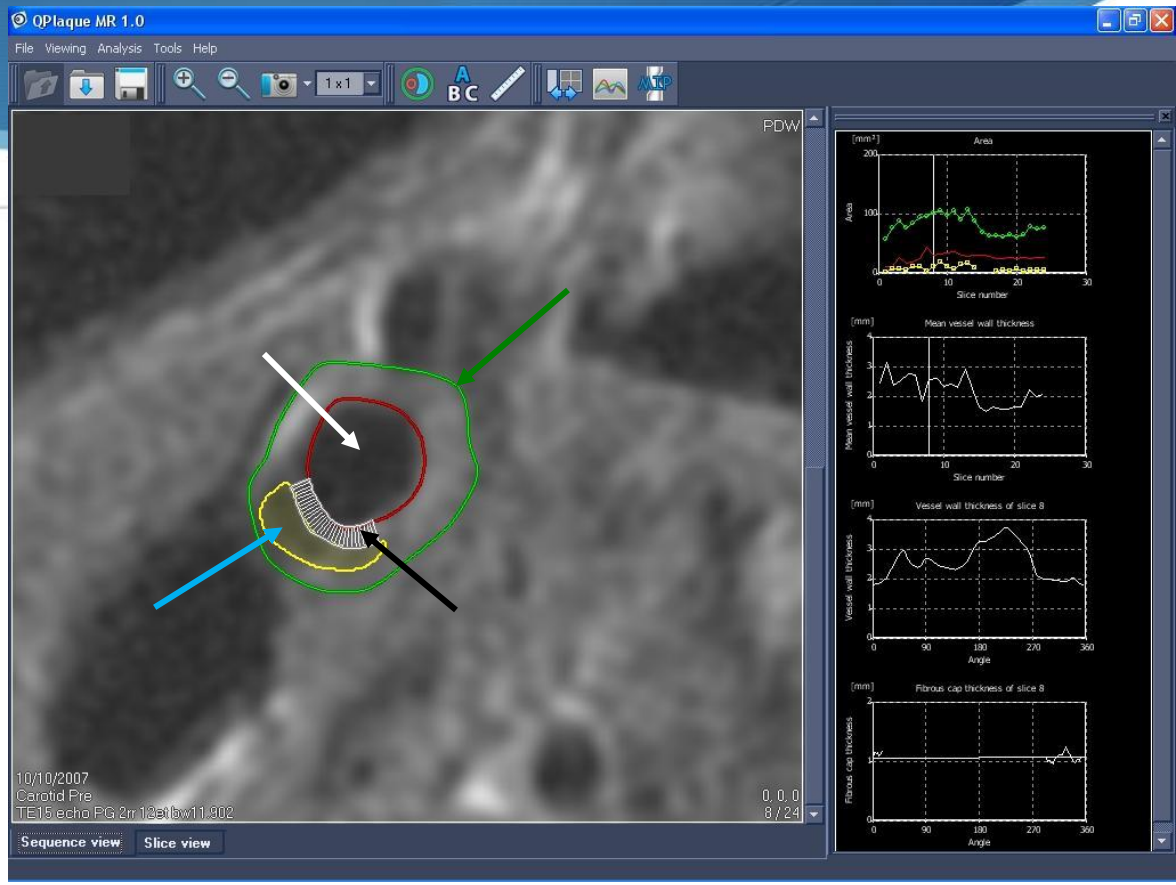
CTA



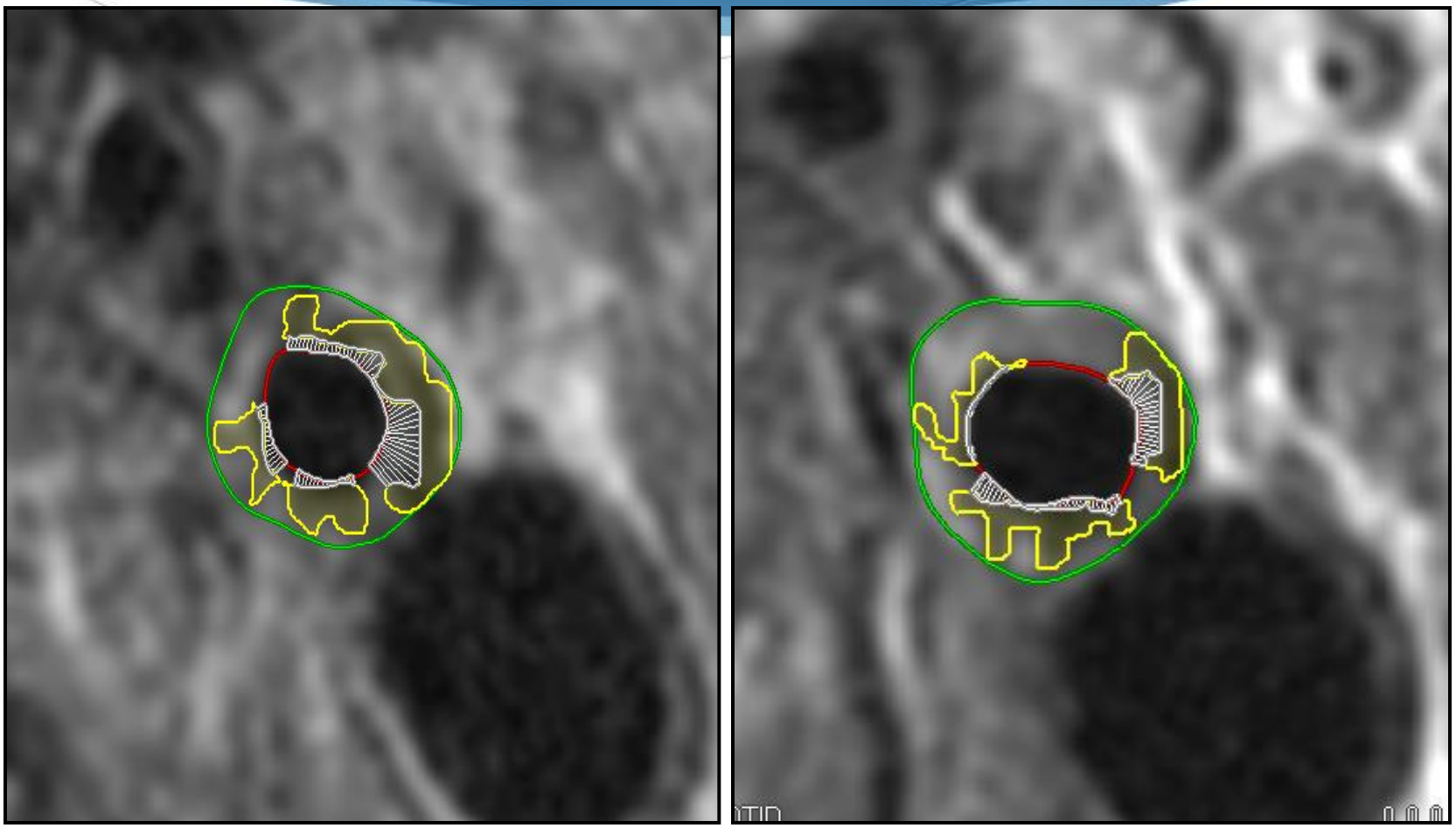
Diag Angio

Carotid plaque

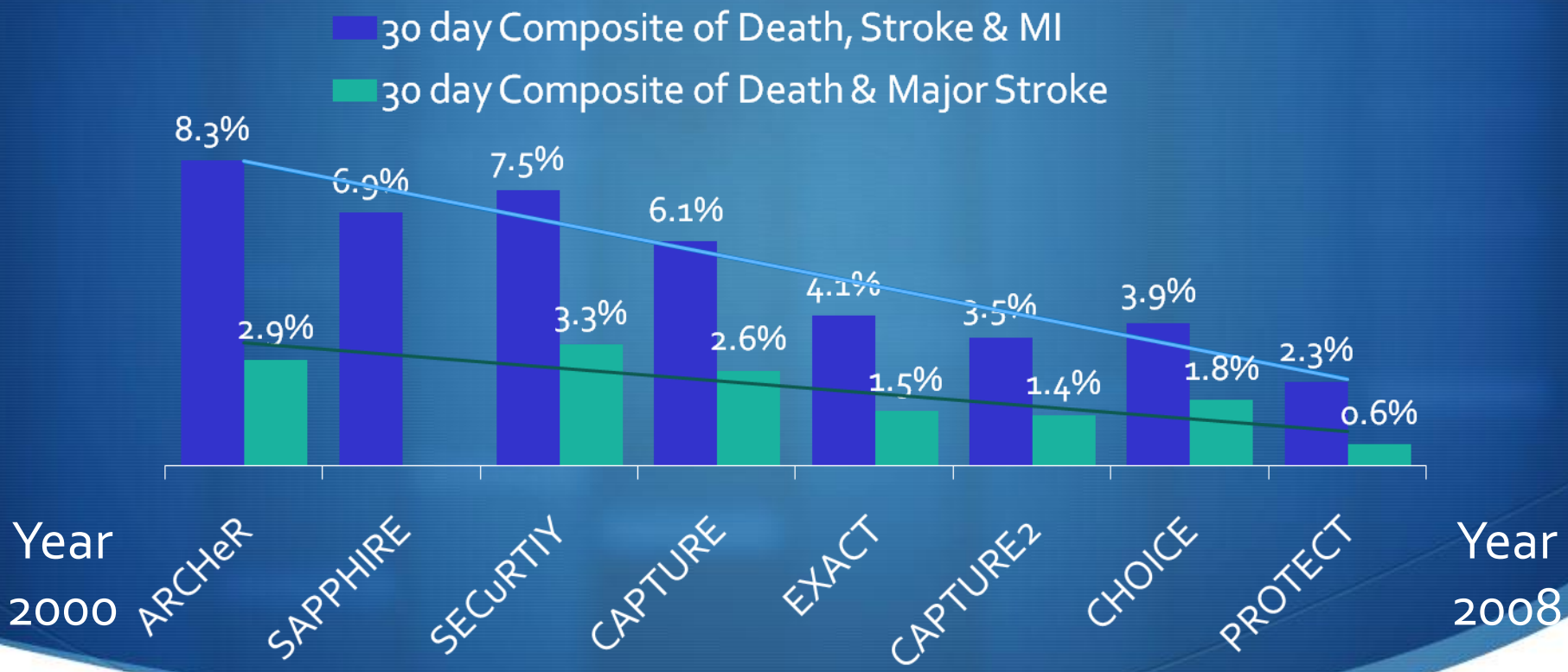




Proton Density Weighted Images of the Internal Carotid Artery at Baseline and after 12 months of Statin therapy



Outcomes of CAS Trials Over Time



SE2934600 Rev. A

(Enrollment: 2000-2008) CREST – 5.7%

(Enrollment: 2000-2008) CREST – 1.1%

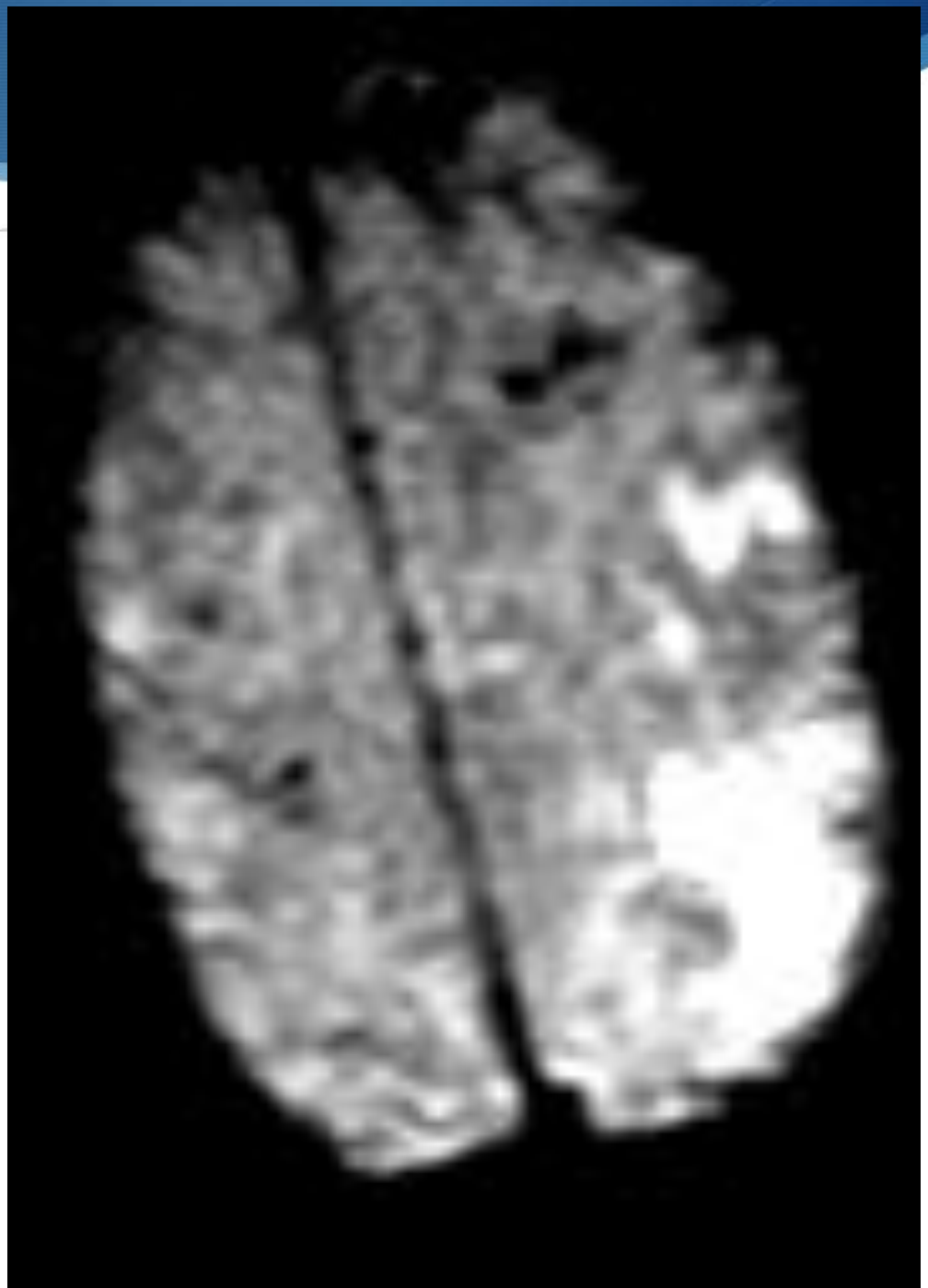
Conclusion

The imaging modalities are impressive but have inherent limitations and no single one can produce the definitive information on vulnerability.

Wallis de Vries, JVS 2008

Shower Emboli

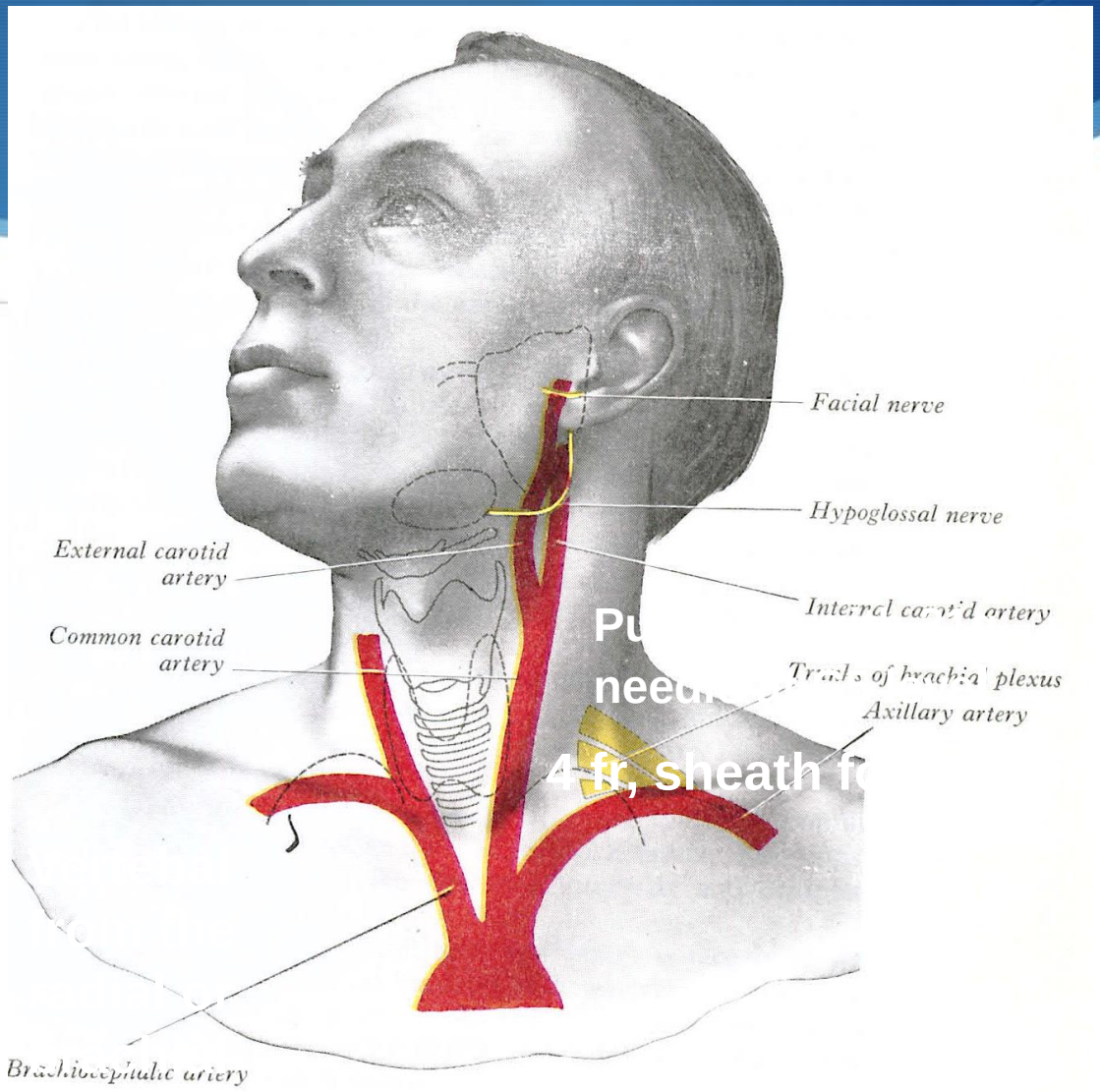
Diffusion weighted



Should we avoid the aortic arch

Bergeron Technique for direct carotid access and vertebral

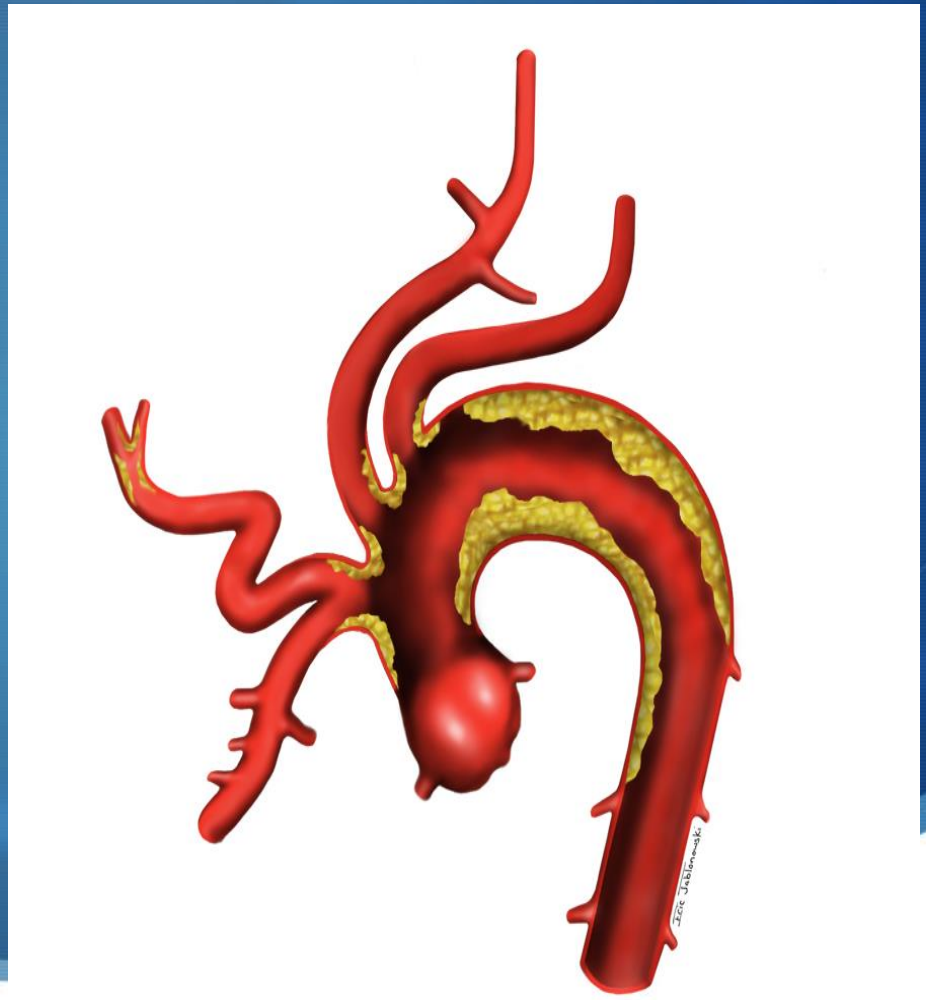
For the vertebral use radial or brachial access



Complex type 3 arch

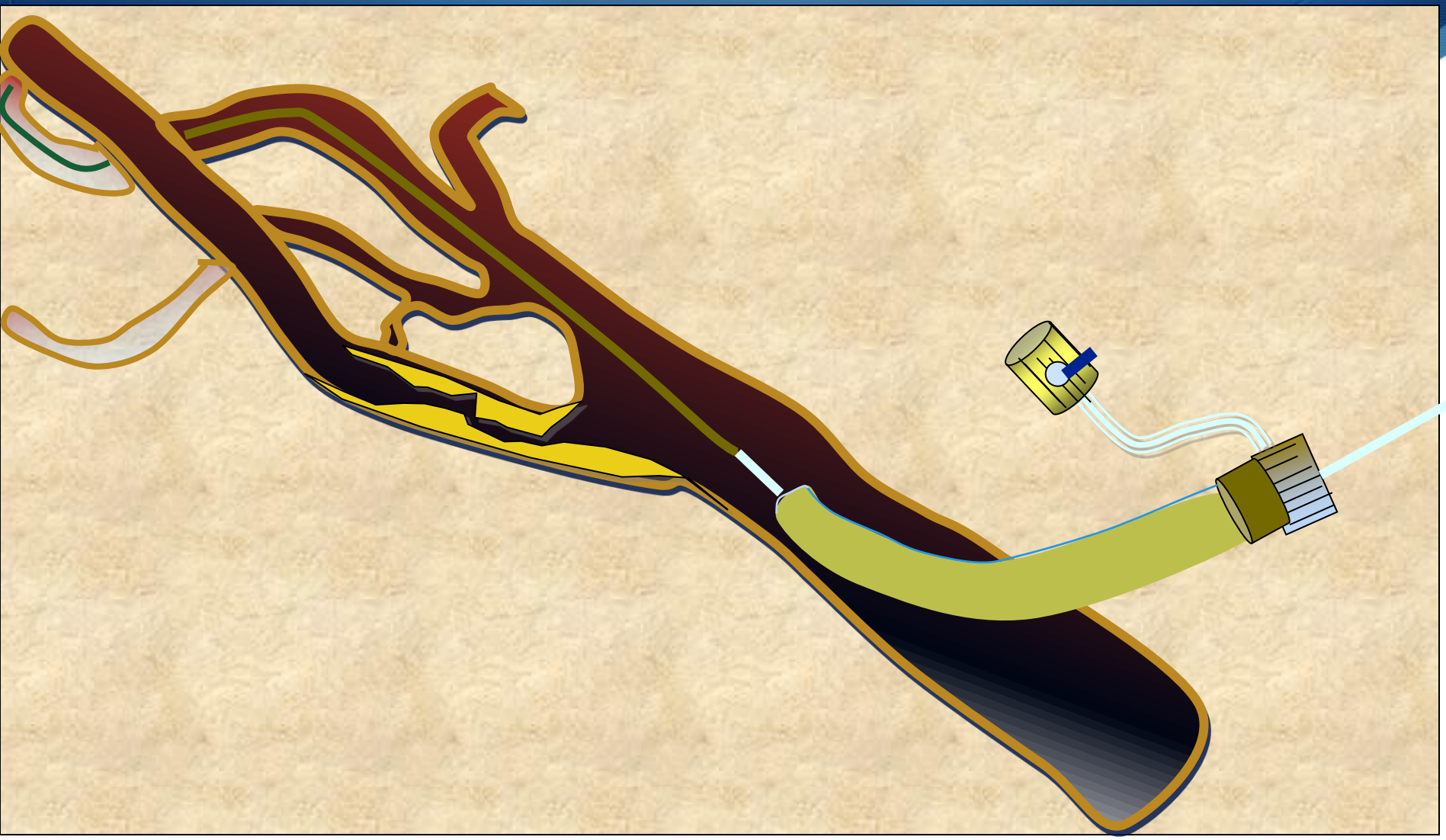
May be indication for direct carotid access or radial for vertebral basilar stroke

Too difficult from femoral approach. 18% stroke incidence from the aortic arch

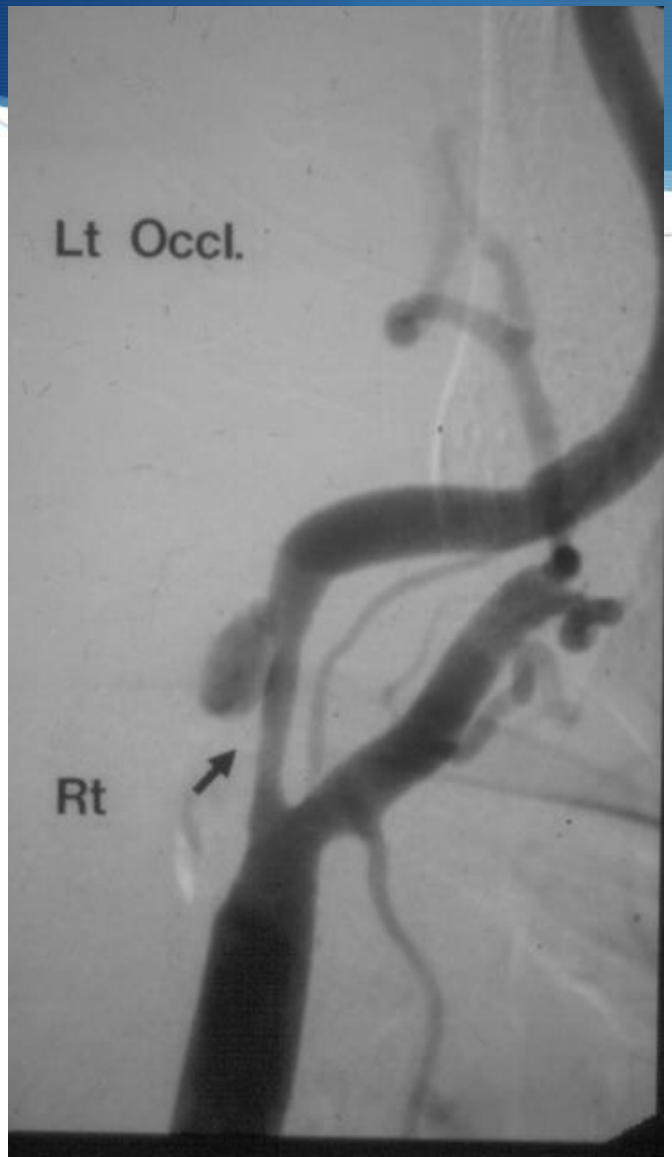


Archer Trial 2005

Remove wire, filter to internal carotid followed by pre dil and stent



SCAFFOLDING AND CONFOMABLE



Percutaneous cervical approach and closing for carotid artery stenting

N = 191

Markatis et al 2009

TABLE IV. Neurological Complications and Deaths within 30 days after CAS

1637 patients

European high volume experienced operator trial

	In-hospital	0–30 days	Overall
Death	1 (0.06)	3 (0.19)	4 (0.25)
Any stroke	8 (0.5)	11 (0.68)	19 (1.12)
Death + any stroke	9 (0.56)	13 (0.81)	22 (1.37)
Mayor stroke	6 (0.37)	3 (0.18)	9 (0.56)
Minor stroke	2 (0.12)	8 (0.50)	10 (0.62)

OCT
Reflected Infrared Light

Advantages

- Spatial resolution 10X > than US

Disadvantages

- Displace blood with saline
- Limited penetration
- Cannot do entire vessel wall

TABLE II. Operators Case Load in 2007

Institution	Enrolled Patients	Operators	Patients/ operator per year
Dendermonde	176	2	88
Cotignola	257	3	85.7
Frankfurt	80	1	80
Liepzig	188	3	62.7
Mercogliano	309	3	103
Mirano	143	3	47.7
Perugia	254	3	84.7
Siena	204	4	51

TABLE III. Procedural Characteristics

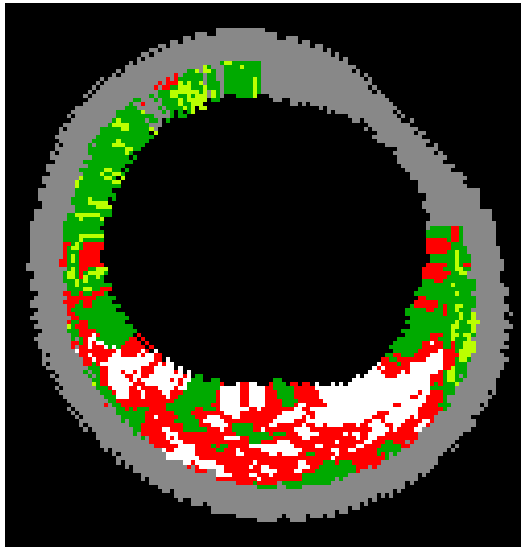
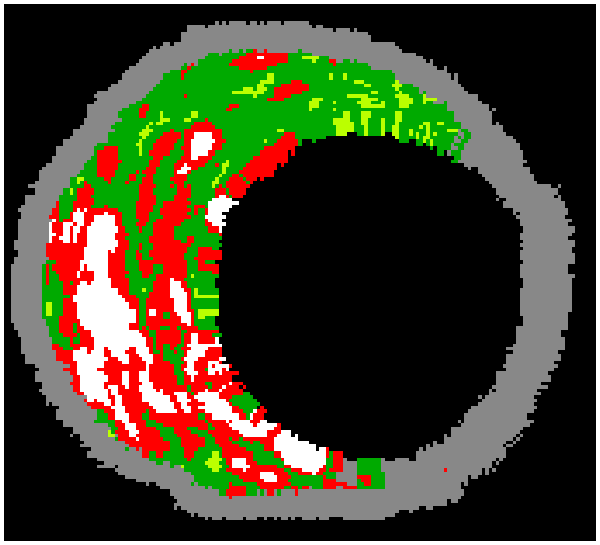
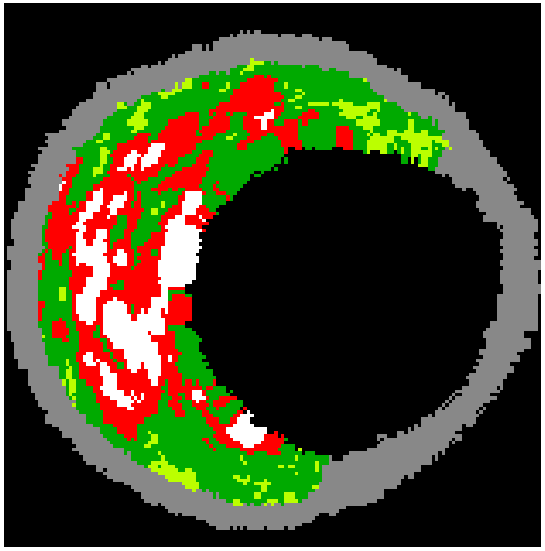
Type of embolic protection used	*N* (%)
Proximal	525 (32.6)
Distal	1,082 (67.2)
None	4 (0.3)
Embolic protection device	
Distal filter device only	1,076 (66.8)
Proximal occlusion only	517 (32.1)
Distal occlusion balloon only	6 (0.4)
Proximal occlusion and distal filter both used	8 (0.5)
None	4 (0.3)
Postdilation	1,579 (98.1)
Stent design	
Closed	104 (6.5)
Hybrid	456 (28.3)
No	1 (0.1)
Open + closed	1 (0.1)
Open + hybrid	1 (0.1)
Open	437 (27.1)
Stainless steel	611 (37.9)

Patient selection

- 429 patients
- Male - 61.5% / Female - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceeding carotid intervention

Conversely the 3 year event rate in 1650 IVUS patients was only .3% and no events in the coronary artery segment when plaque volume less than 40% (Prospect)

THIS IS THE PROBLEM

IA (IVUS Defined) TCFAs

Major limitations in relying on angiography for lesion severity and plaque composition

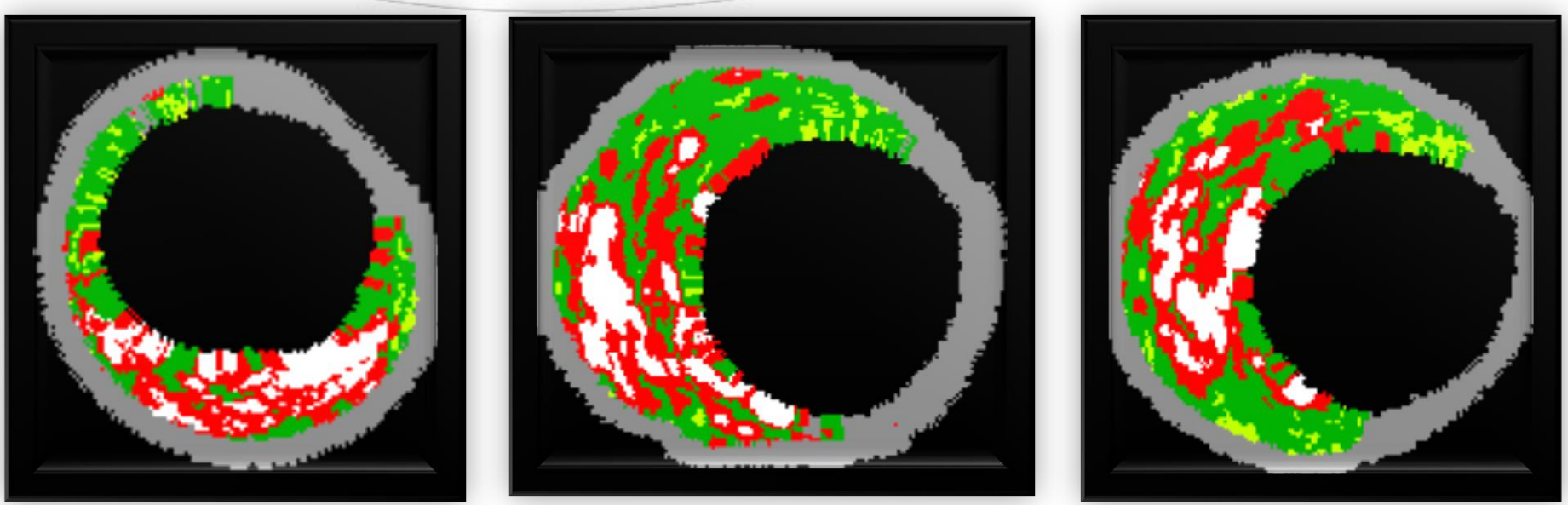
Lesion Length

Lesion Length (mm)	Peri-operative CVA (%)	30 day CVA (%)	30 day Adverse Event (%)
0 – 4.9	2.1	3.2	3.2
5 – 9.9	2.2	2.7	3.3
10 – 14.9	1.9	2.9	3.8
≥ 15	17.0	17.0	19.1

Anatomic and Lesion characteristics are not always accurate predictors of Stroke for CAS.

Which test is best for this?

This Is The Problem



ID (IVUS Defined) TCFAs

The reality of severe carotid stenosis

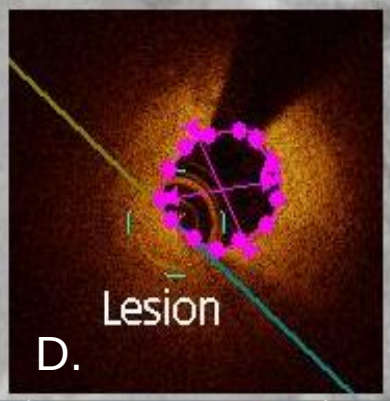
The first symptom may be a sudden permanent stroke (25% of cases)

Hallett,J ,Veith

All imaging modalities have inherent limitations

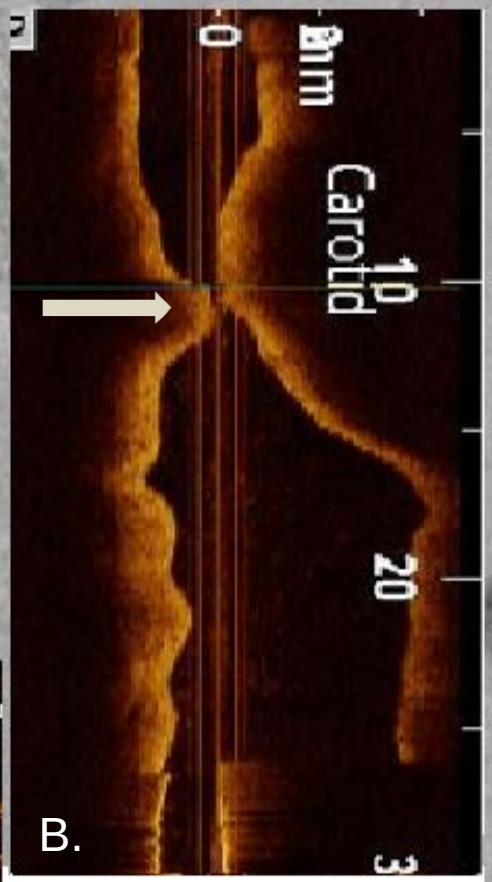
Figure 1(A-F).

C.

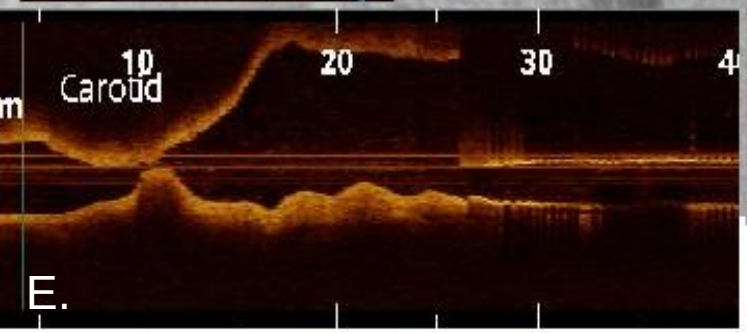


D.

A.



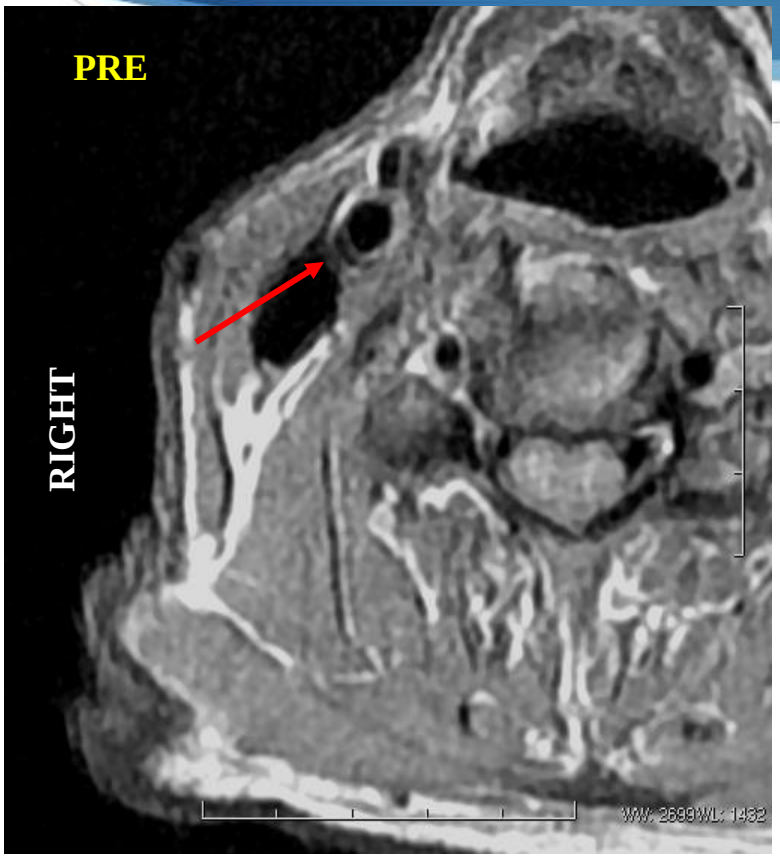
B.

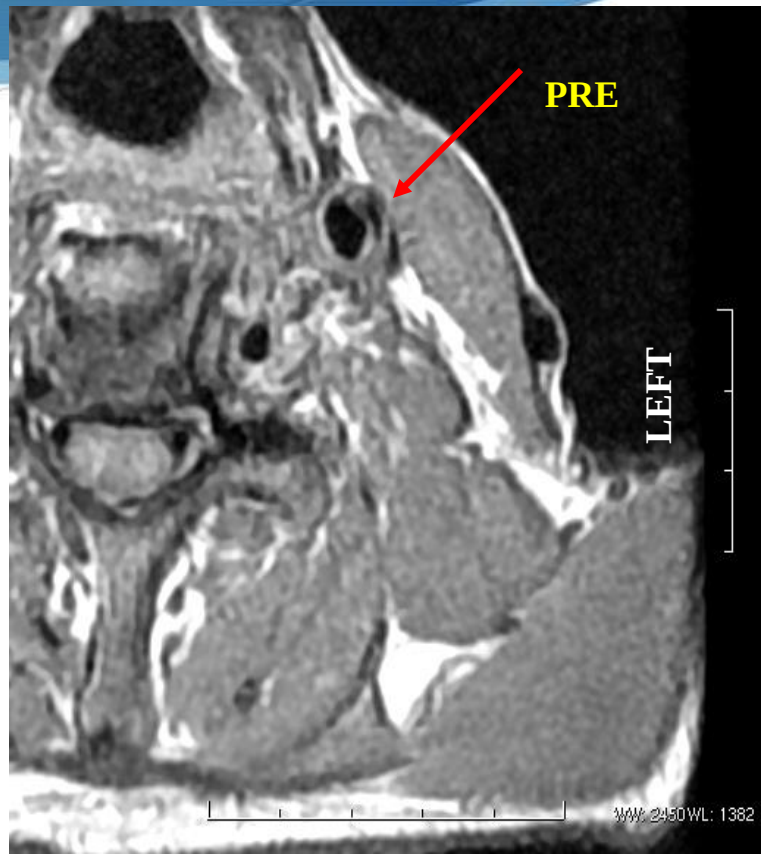


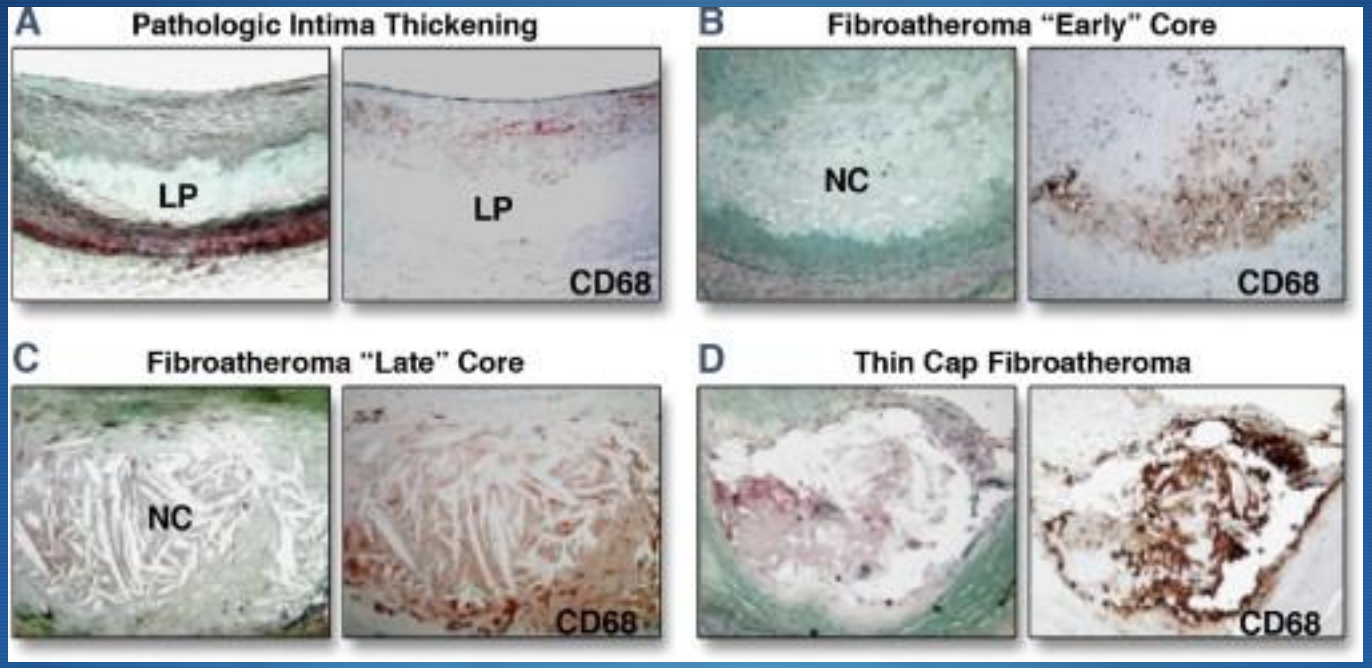
E.

F.

Carotid plaques



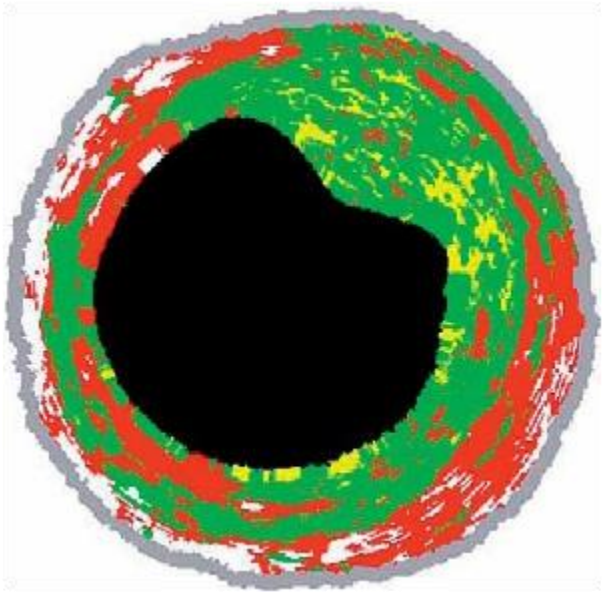




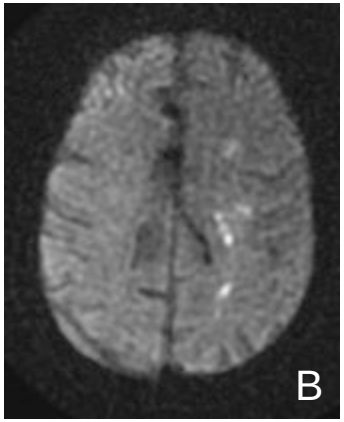
Representative Lesion Morphologies f (A) The earliest atherosclerotic lesion, pathological intimal thickening, highlighted by lipid pools (LP) in the deep intima (Movat pentachrome stain) with CD68+ ...

VH IVUS Produces a color-coded map of 4 Histological Types

- **dark green: fibrous**
- **yellow/green: fibrofatty**
- **white: calcified**
- **red: necrotic lipid core plaque**



Results (30-Day Follow-Up)



- Follow-up data were available on 56 (84%) of 67 patients in the CAS population.
- (2) major adverse events
  - Two immediate periprocedural strokes.
    - One patient (A) experienced a stroke in the distribution of the PCA as shown on CT, likely related to arch manipulATION
  - One stent thrombosis occurred, likely due to discontinuation of anticoagulation
- No strokes were reported in 2 of the 4 patients referred for CEA who were available at follow-up.

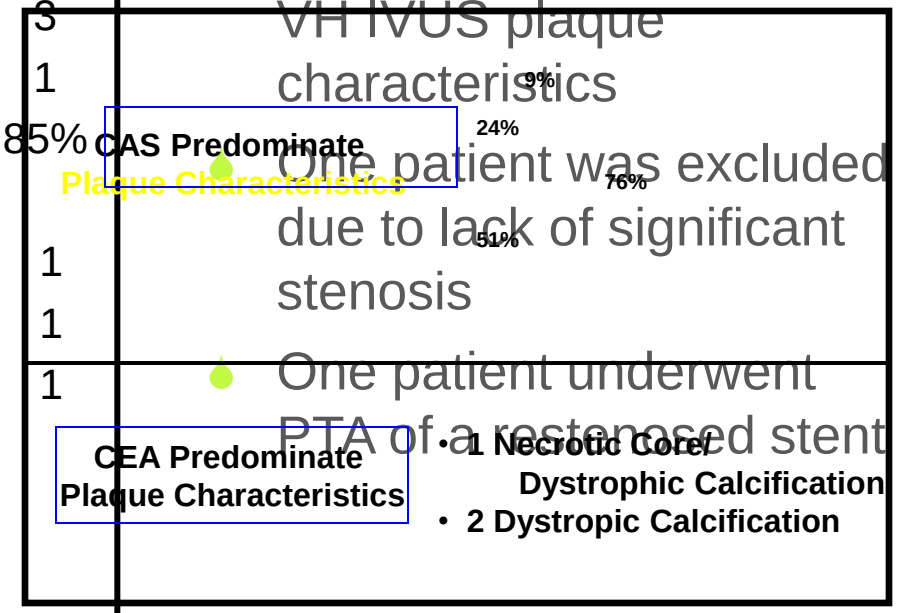
Conclusions

- Understanding plaque morphology is a crucial aspect in managing carotid occlusive disease.
- However, in this small sample population, stroke rates were not different than those reported elsewhere for carotid stenting. In these cases, VH IVUS did not offer insight into the possible causes of the events.
- Future studies are needed with prospective trials to evaluate CAS and patient outcomes correlated with VH IVUS findings.

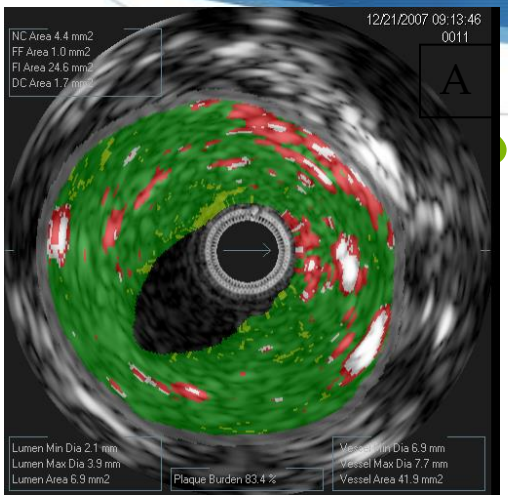
Results

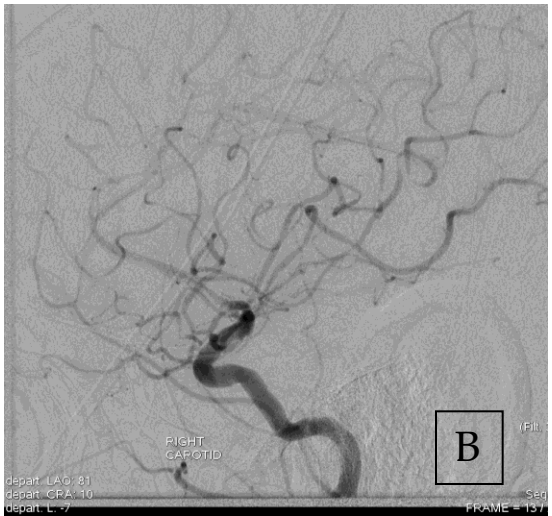
Population	CAS	CEA
Male	41 (61%)	2
Female	36 (39%)	2
Age (years)	73 ± 9.7	84
Side of ICA Lesion		
Left	31 (46%)	3
Right	36 (54%)	1
Percent Stenosis	89% ± 7.8	85%
Clinical Indication		
TIA	5	1
Amrous Fagux	2	1
Stroke	5	1
Asymptomatic	24	
Prior CEA/Stent	10	
Other	13	
Unknown	8	1

- CAS was performed in 65 of 71 patients
- Four patients were excluded and referred for CEA due to unfavorable VH IVUS plaque characteristics
- One patient was excluded due to lack of significant stenosis
- One patient underwent PTA of a restenosed stent



Adverse Events





- Two (3%) of the 59 patients undergoing CAS experienced adverse events.
  - One patient (A) suffered a minor stroke in the perioperative period due to stent occlusion related to thrombosis due to discontinued anticoagulation.
  - One minor stroke (B) in the perioperative period in the left posterior cerebral artery (PCA) distribution likely related to arch manipulation. Returned to baseline at 3 month follow-up.

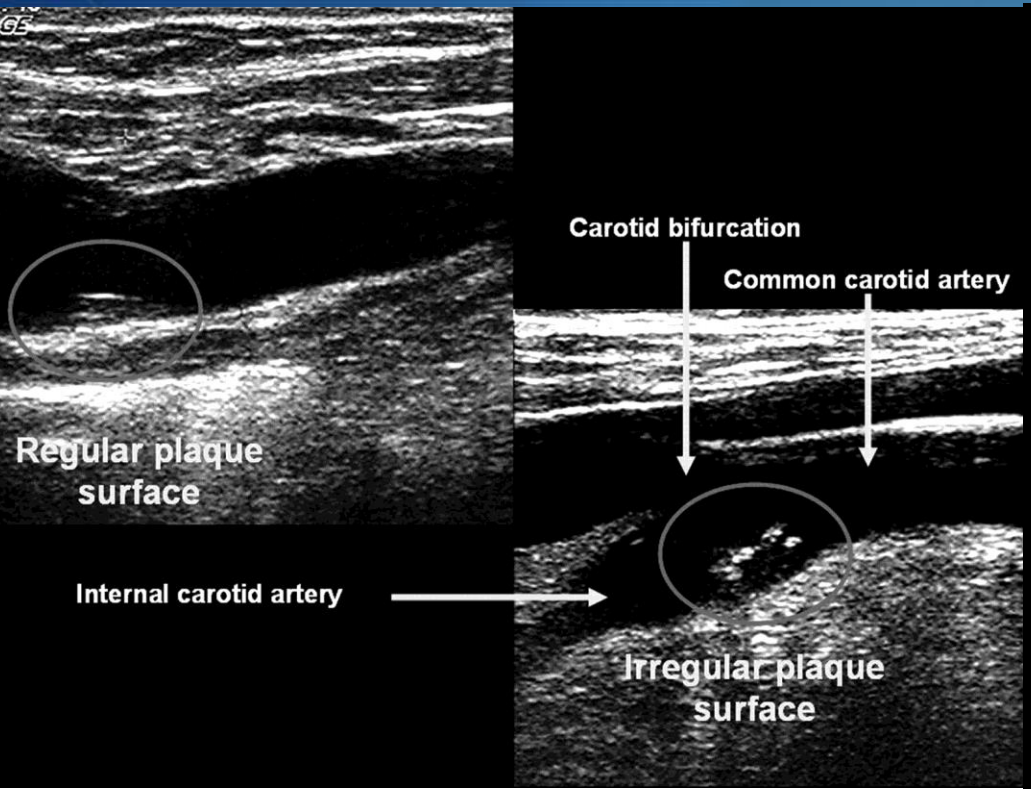
Patient selection

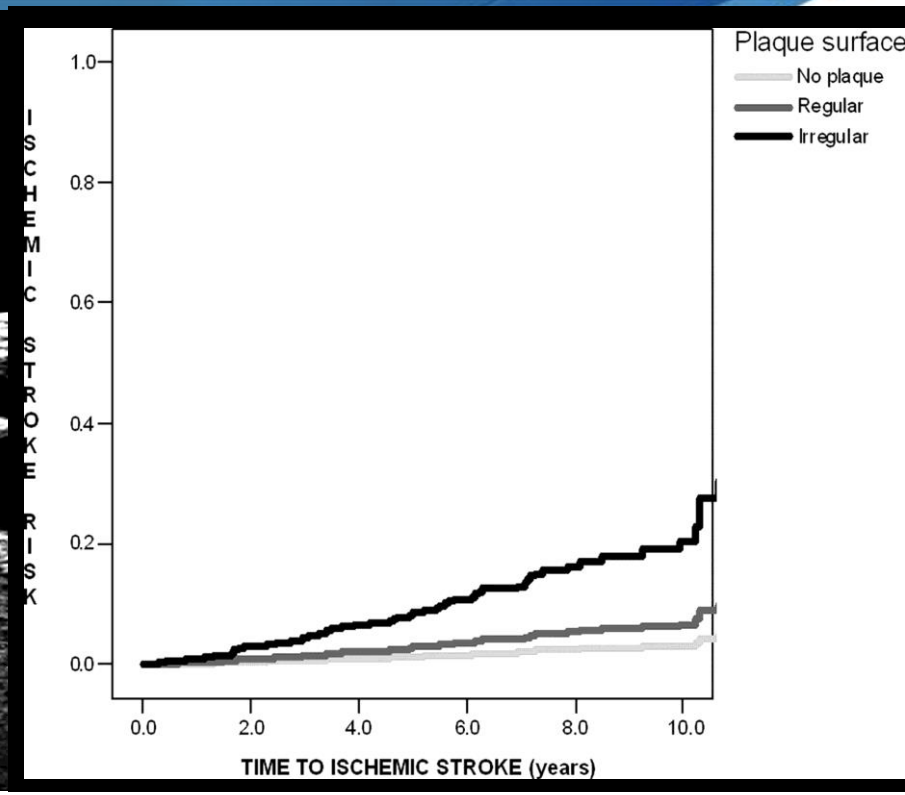
- 429 patients
- Male - 61.5% / Female - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceeding carotid intervention

Lesion Characteristics

- Length of lesion highly significant
- Percent stenosis
- Location of lesion (ostial vs. non-ostial)
- Ulceration
- Calcification
- Contralateral internal carotid occlusion

Plaque Surface Irregularity





Prabhakaran, S. et al. Stroke 2006;37:2696-2701

Hazard Ratio 3.1

Stroke

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A Division of American Heart Association

Ultrasound

- **Computer assisted analysis suggested that increased echolucency of plaque was a risk factor during and immediately post stenting**

Biasi, Circulation 2004

Acute Plaque rupture with thrombosis may occur in non-stenotic segment

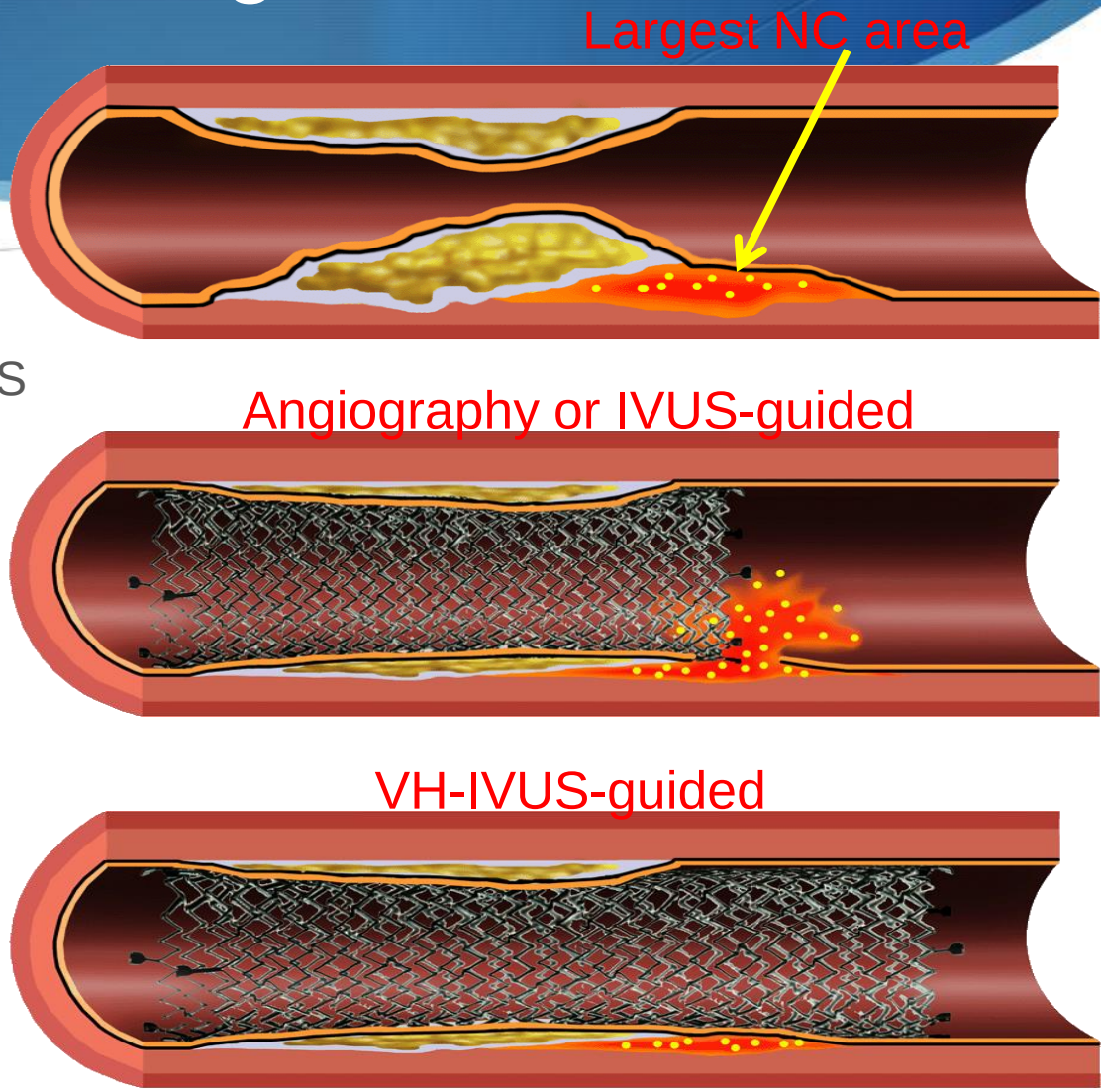
Patient Selection

- 429 patients
- Male - 61.5% / Female - 38.5%
- Symptomatic (35%) and asymptomatic (65%)
  - Symptomatic
    - TIA, amaurosis fugax, or CVA with clinically, lateralizing symptoms ≤ 60 days preceeding carotid intervention

What is Optimal Complete Lesion Coverage?

- Lack of clinical data comparing
  - VH-IVUS guided vs. angiography/conventional IVUS guided PCI

- Impact on:
  - Distal embolization
  - Stent thrombosis
  - Restenosis
  - Plaque progression

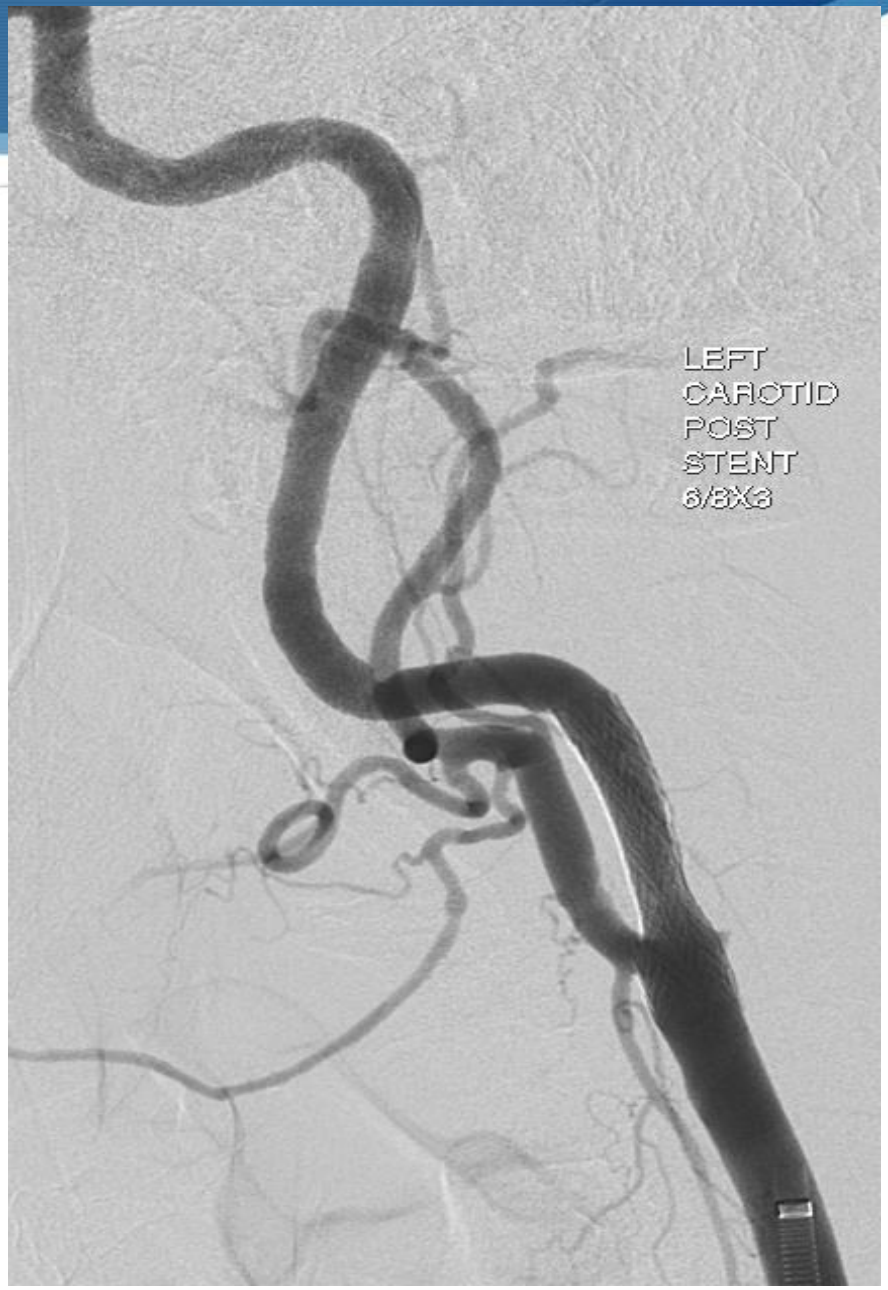


TYPE A Lesion

TYPE 4 ARCH

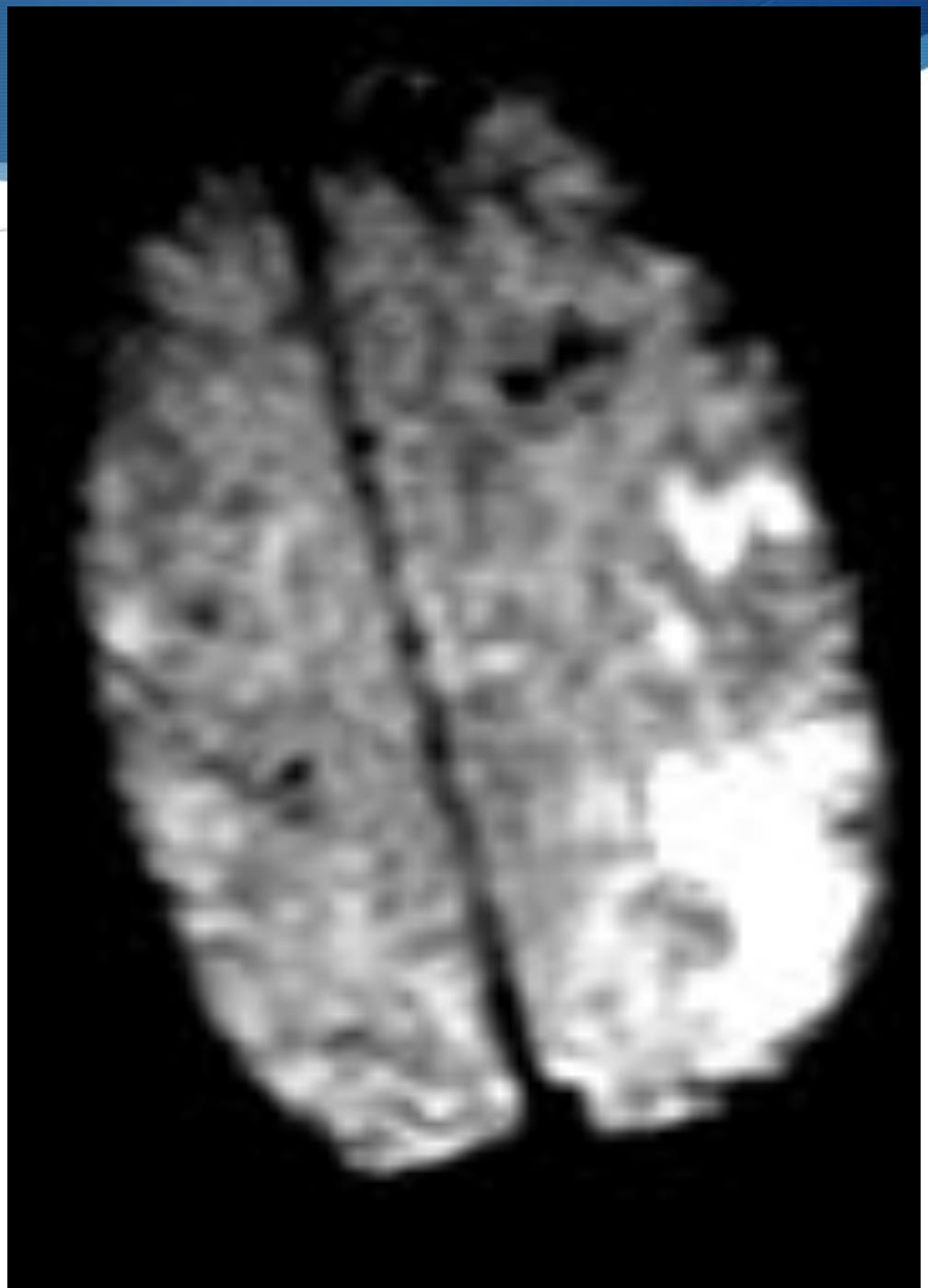
Procedure completed

FILTER REMOVED

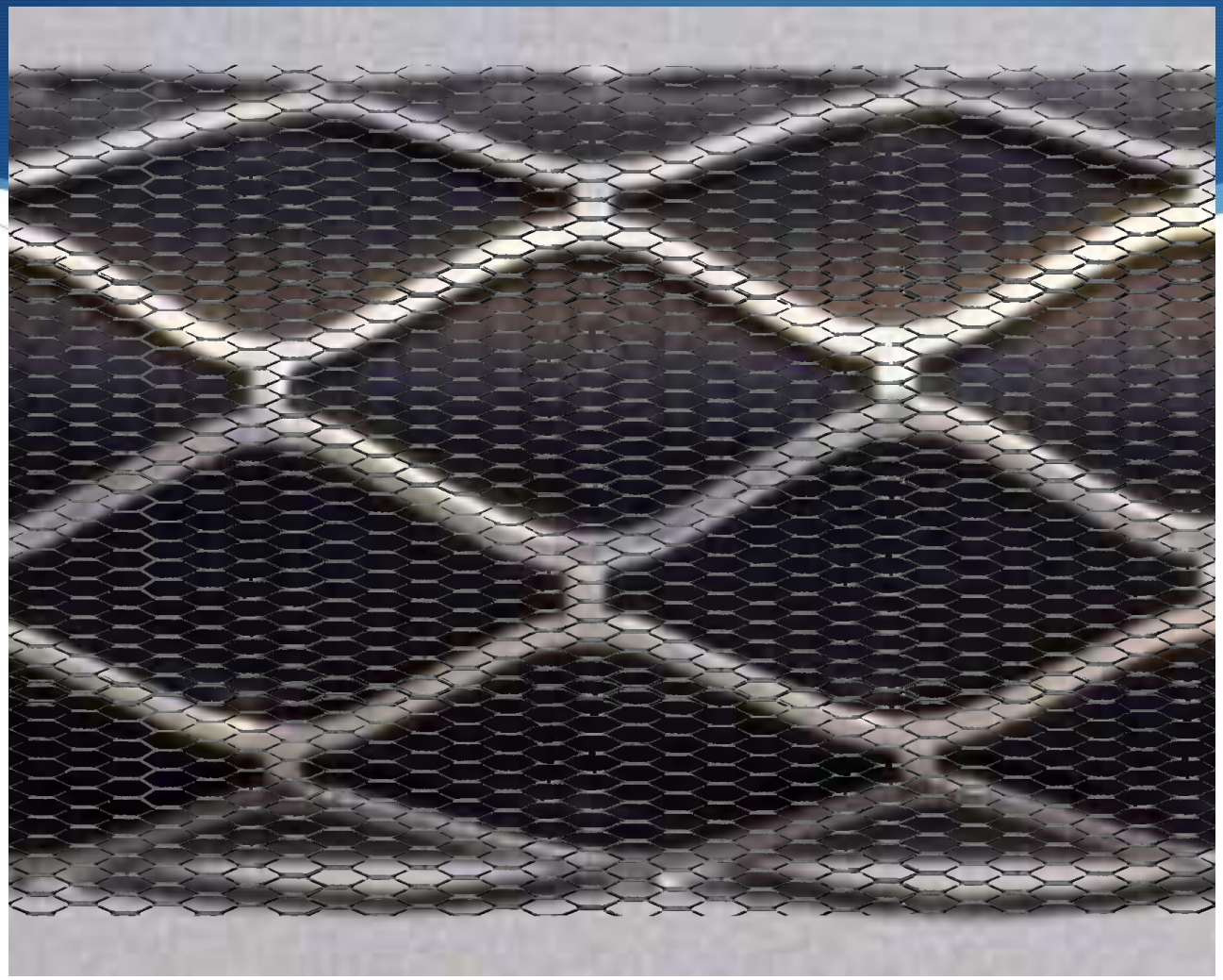


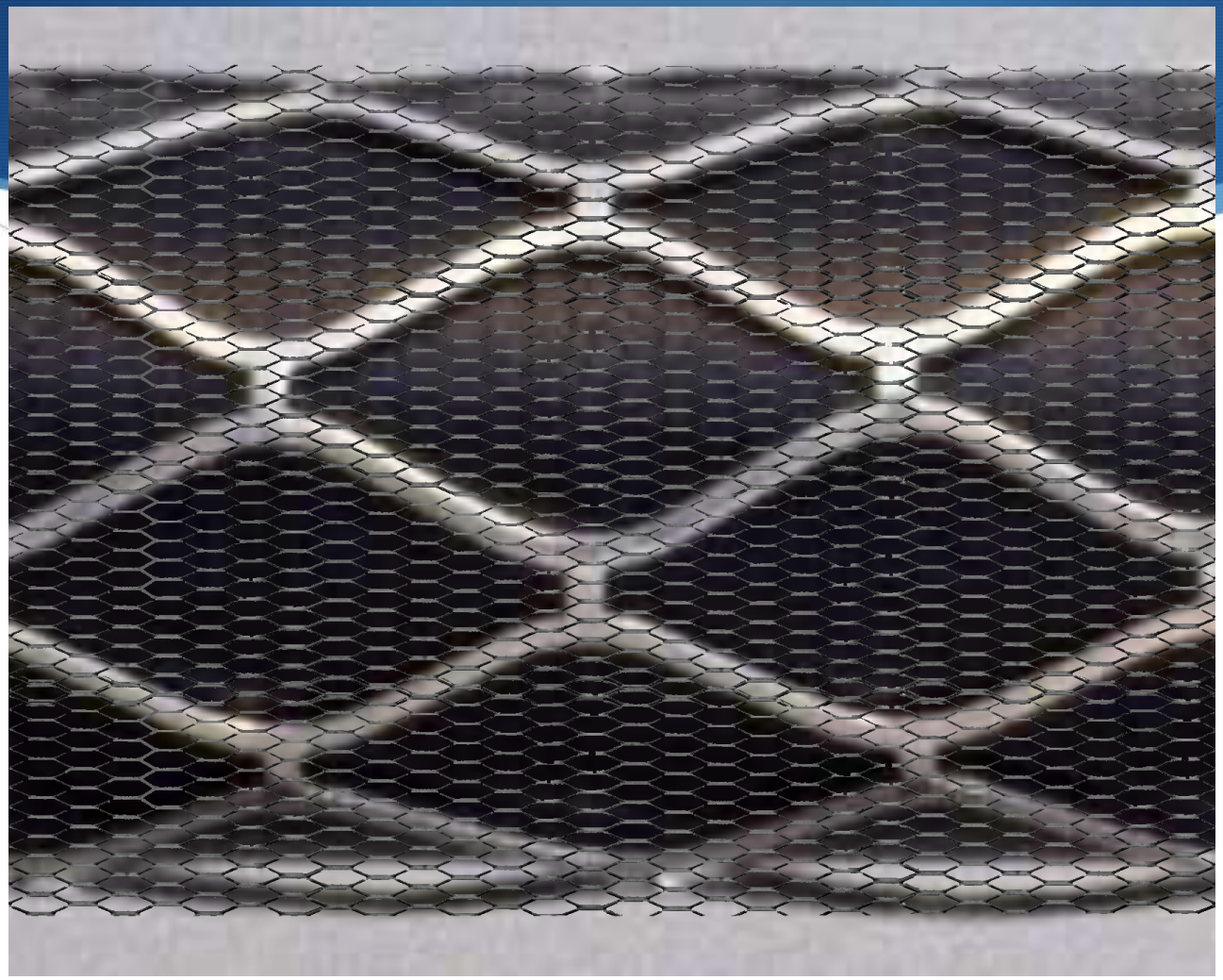
Shower Emboli

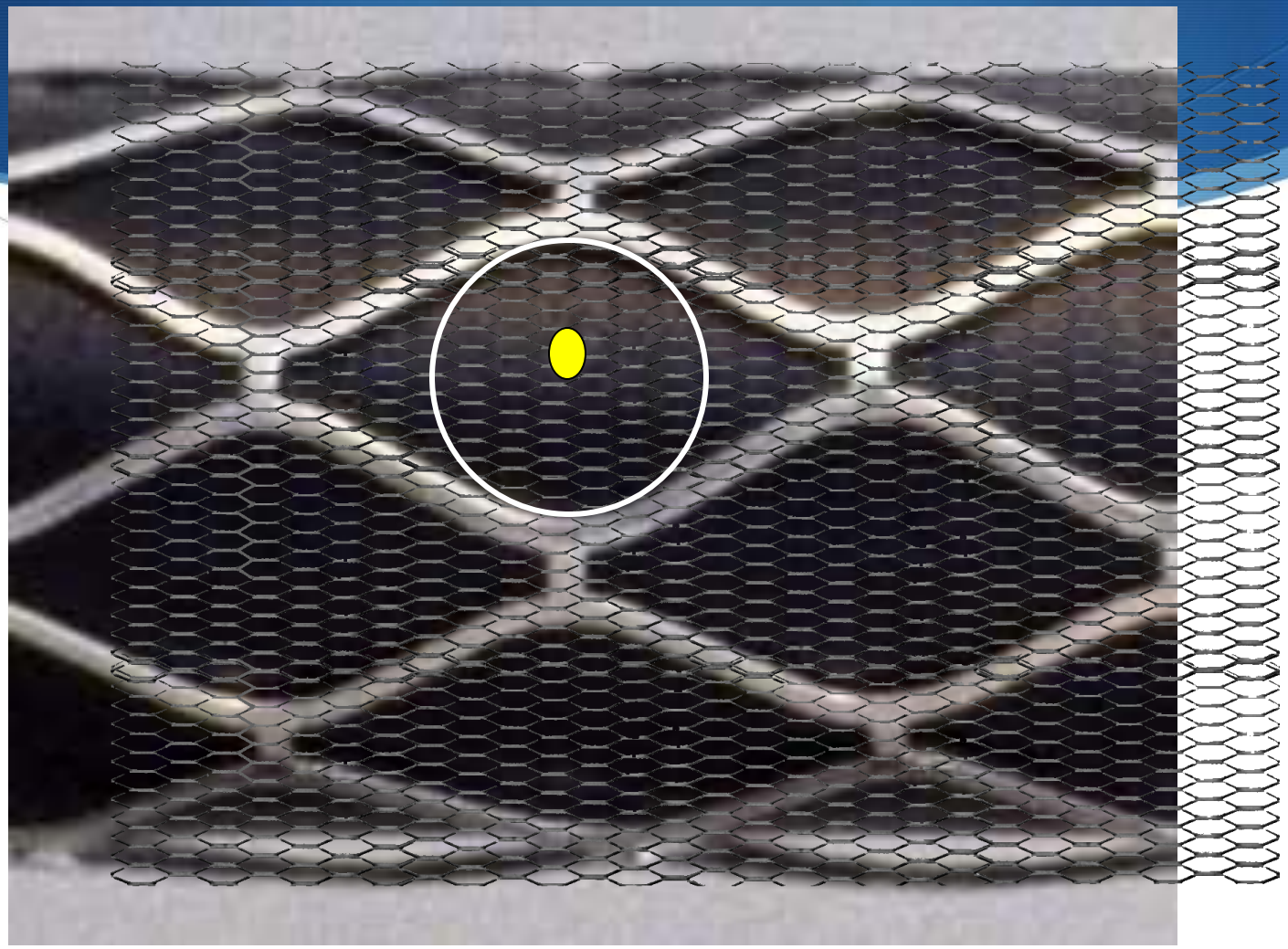
Diffusion weighted



Presence of 2 or 3 of these predictors have a 10-18% chance of an event within 3 years





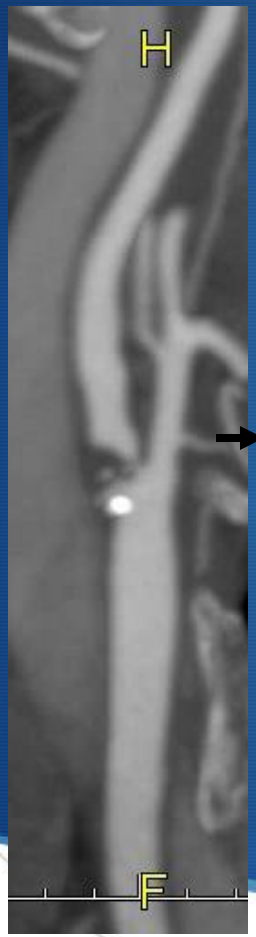


Acute Plaque rupture with thrombosis may occur in non-stenotic segment

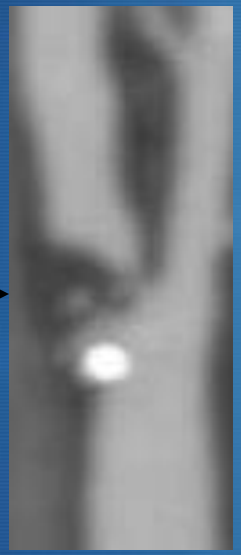
TIP 5 - Continued

Figure 2.

Can Carotid CTA Characterize Plaque Too High Risk For CAS?

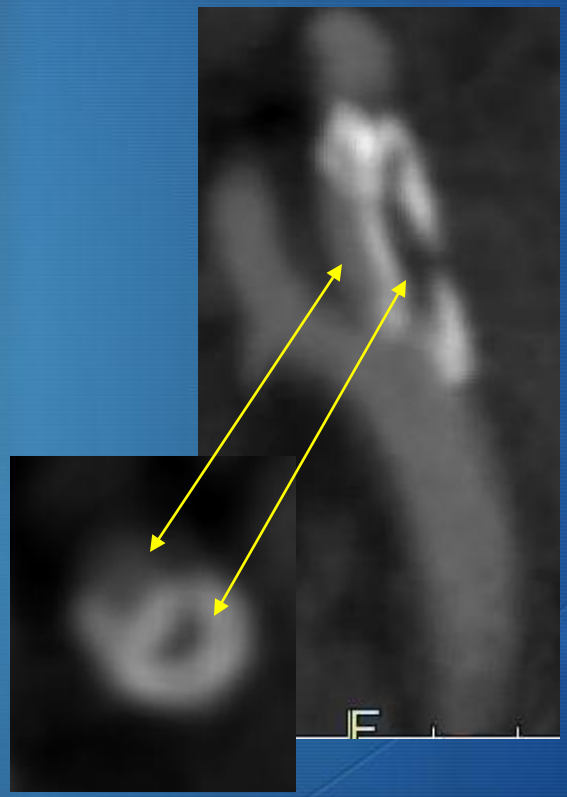


Dangerous: Soft Plaque



67 Female with TIA's referred for CEA; Path reports soft, atheromatous lesion

Plaque Analysis: Are These Necrotic Cores?

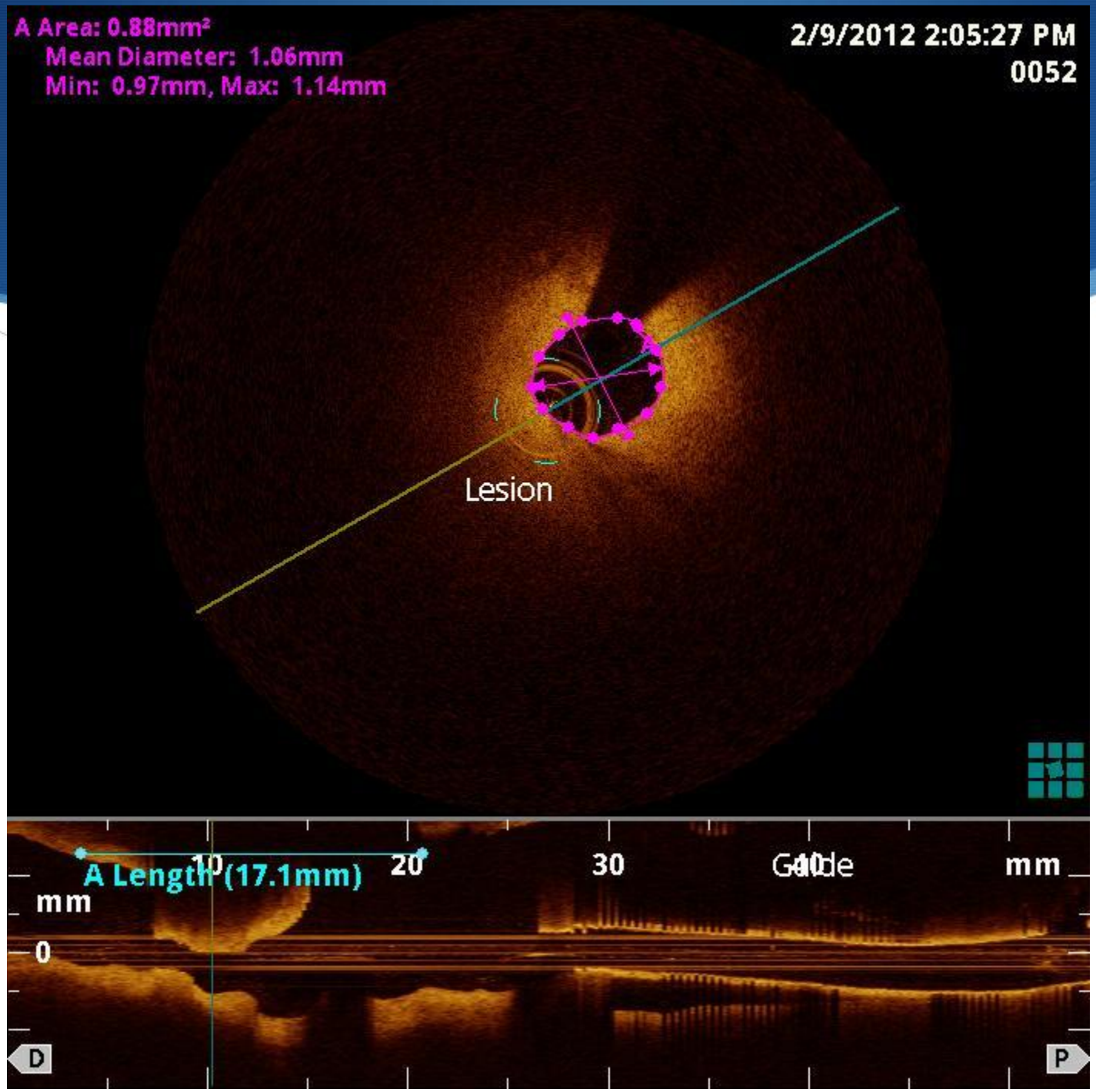


Both Patients referred for CEA instead of CAS

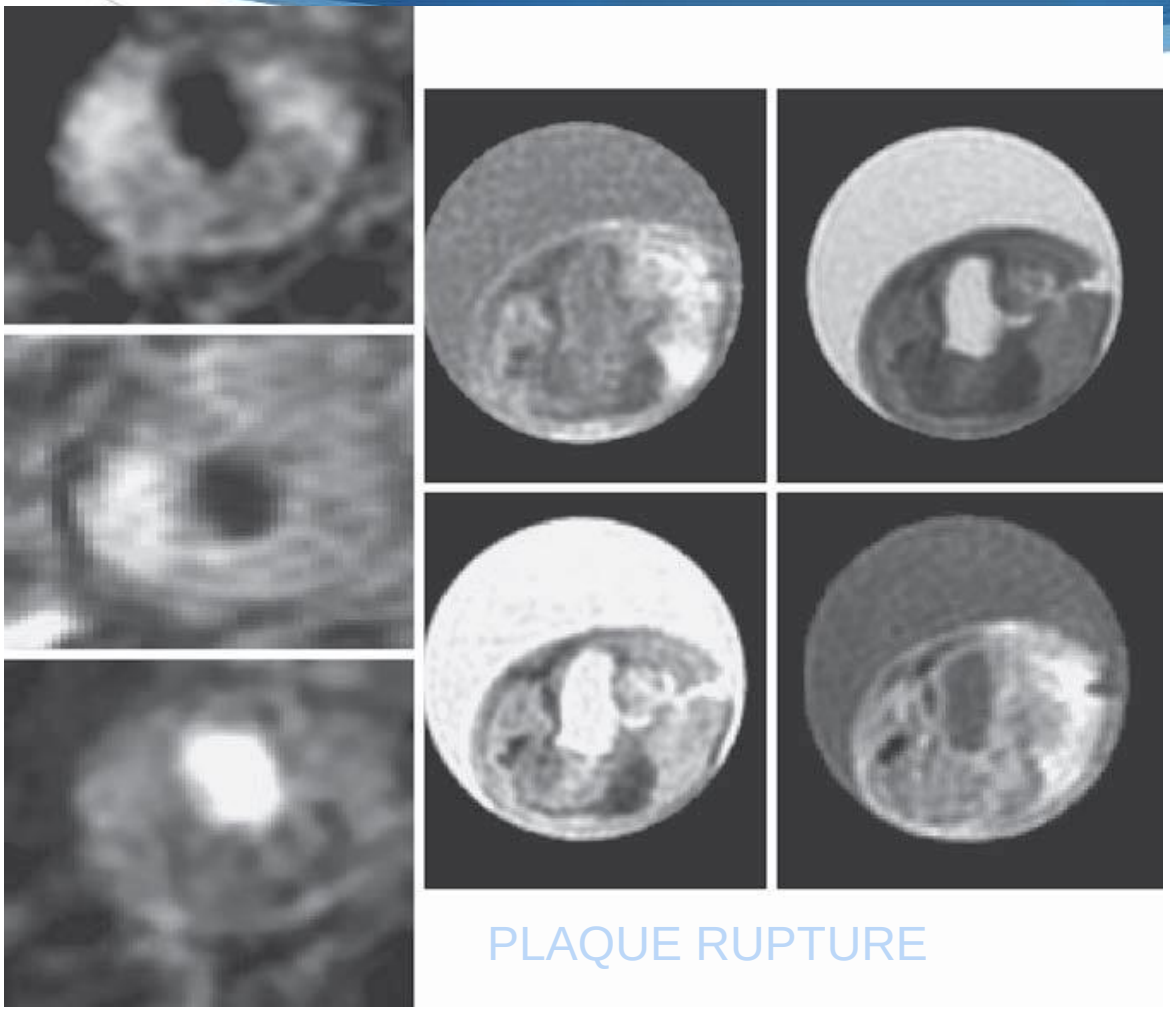
CTA

- Arterial wall assessment of morphology is less impressive than degrees of stenosis.

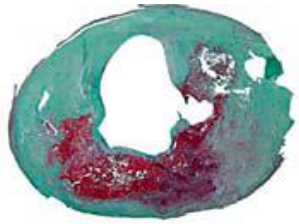
- **Calcification is the only histologic content** using CTA

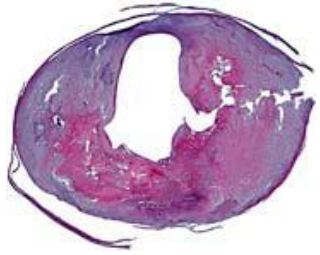

A Area: 0.88mm²
Mean Diameter: 1.06mm
Min: 0.97mm, Max: 1.14mm
2/9/2012 2:05:27 PM
0052
Lesion
A Length (17.1mm)
10
20
30
40
mm
mm
0
D
P

•**MRI with plaque rupture and intra plaque bleed**



PLAQUE RUPTURE





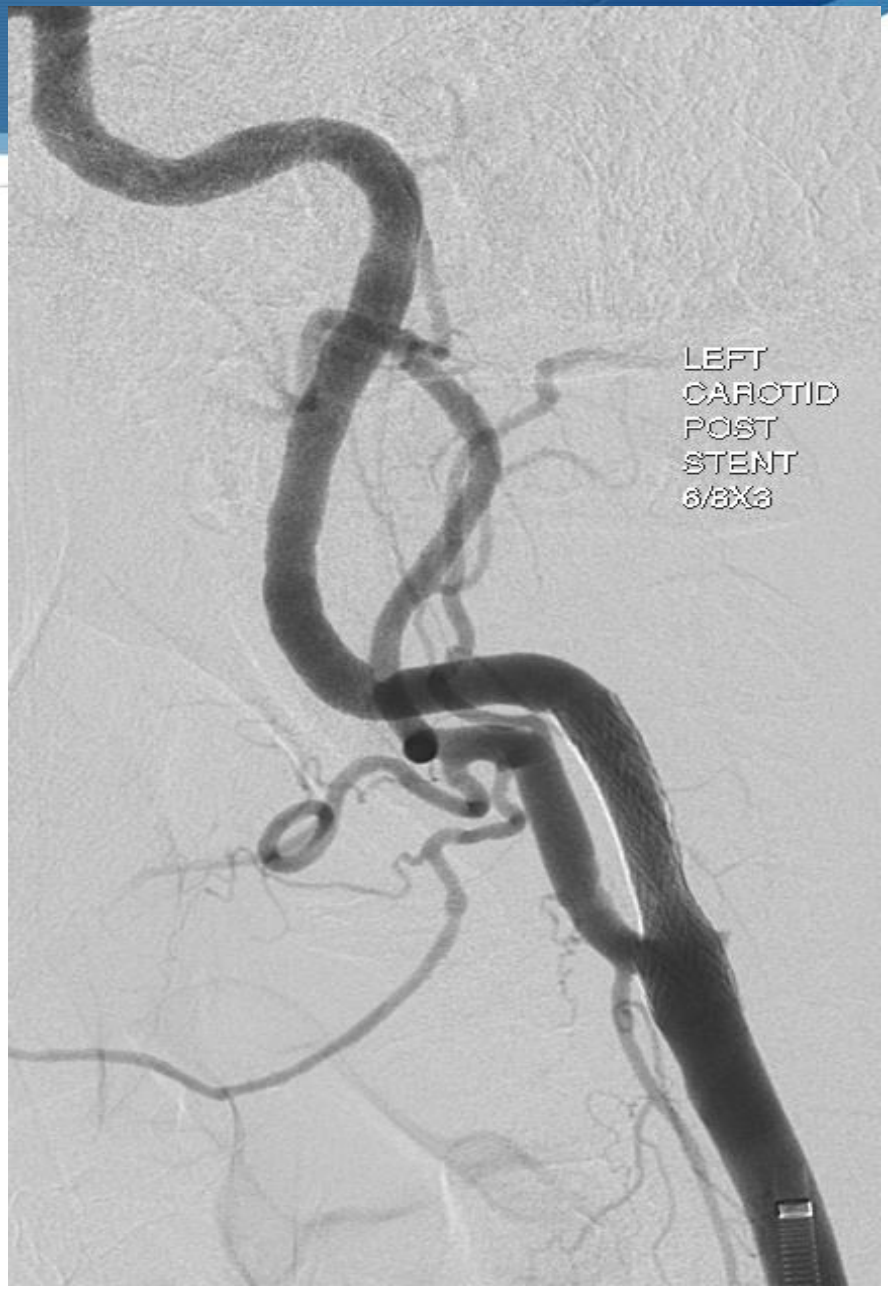
Gao et al., *Cerebrovasc Dis*, 2009

TYPE A Lesion

TYPE 4 ARCH

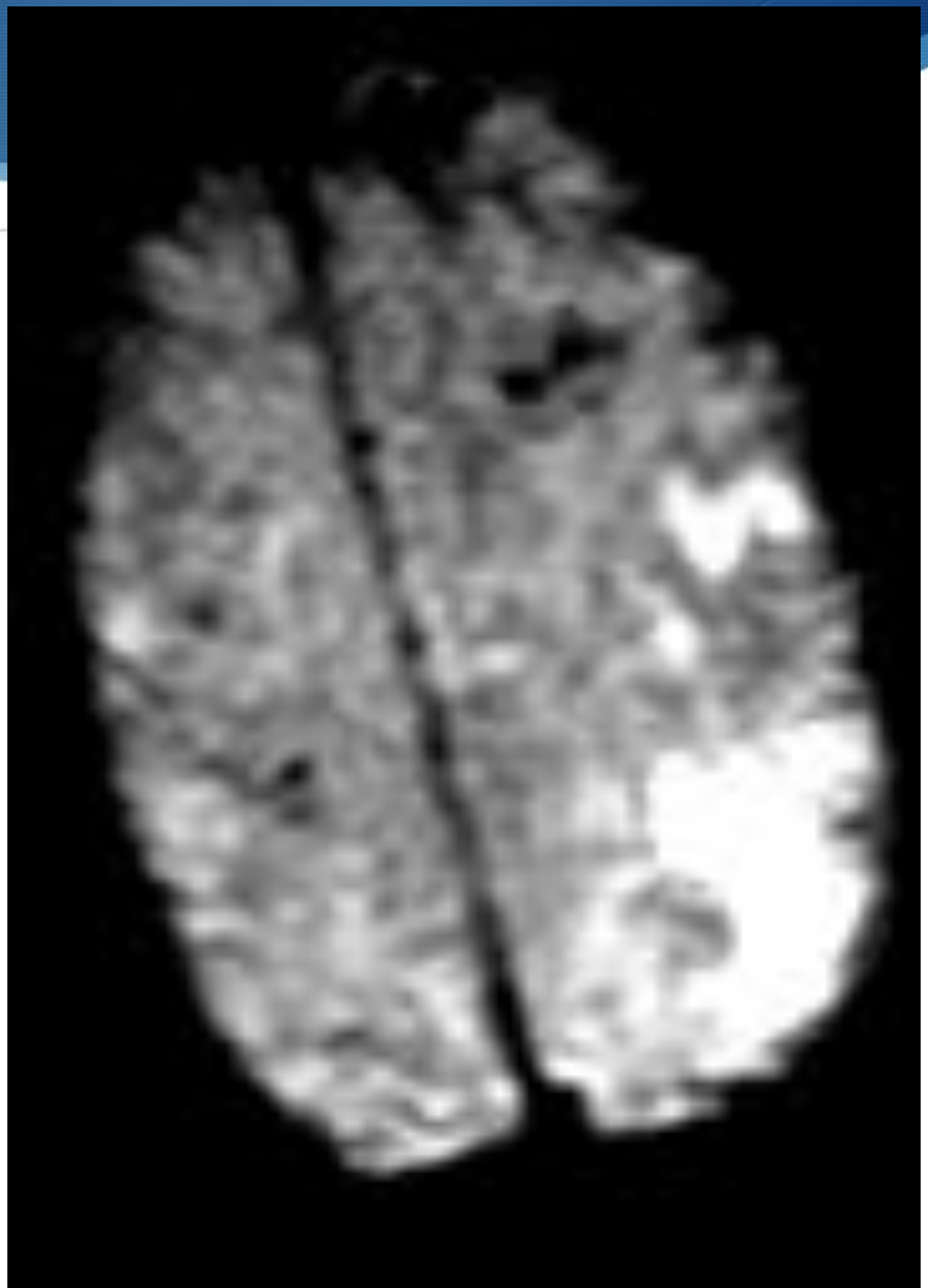
Procedure completed

FILTER REMOVED



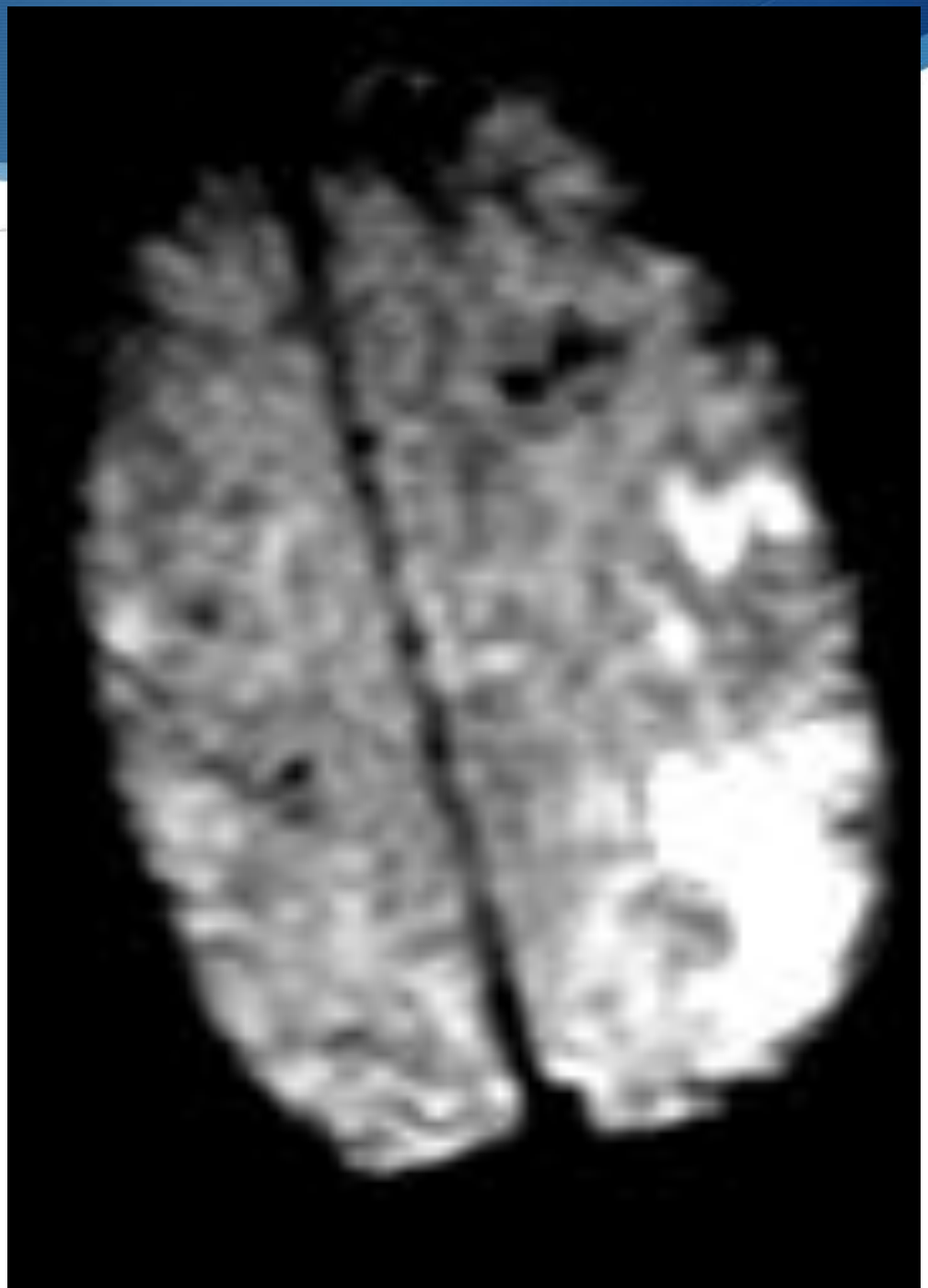
Shower Emboli

Diffusion weighted



Shower Emboli

Diffusion weighted



ADVANTAGES

- Procedure time
- Less contrast media
- No aortic arch manipulation
- No contralateral or vertebral embolisation

What have we overlooked in the neurovascular evaluation

The aortic arch as a source of vulnerable plaque whether diagnostic or interventional procedures are being done

21 g needle at C5
p

Conclusions

Administration of lipid modulating agents appears to have initial paradoxical effects on lumen size:

- **A decrease in vessel wall area and lipid area is accompanied by a decrease in lumen area**
- **An increase in vessel wall area and lipid area is accompanied by an increase in lumen area**

Conclusion

- Percent stenosis provides relatively little information about vulnerability of *de novo*, statin-naive carotid plaques.

- As most current imaging studies concentrate on plaque stenosis, a more appropriate focus on plaque composition provides a more robust quantifiable volumetric metric and may be more indicative of the underlying pathology by high-resolution 3D CMR.

Carotid Plaque Analysis

- Images were acquired in axial projection in a 2D and 3D manner
- via QPlaque (Medis, The Netherlands). Plaque morphology determined by T1, T2/PD CMR.
- Windows and level settings were set to constant levels to standardize signal intensities for each analyzed image.
- Manual contours identified:
  1. Fibrous cap
  2. Lipid pool
  3. Outer and inner wall contours
  4. T2 images were reviewed to determine/confirm lipid core determination with the T2 image used to confirm lumen contour.

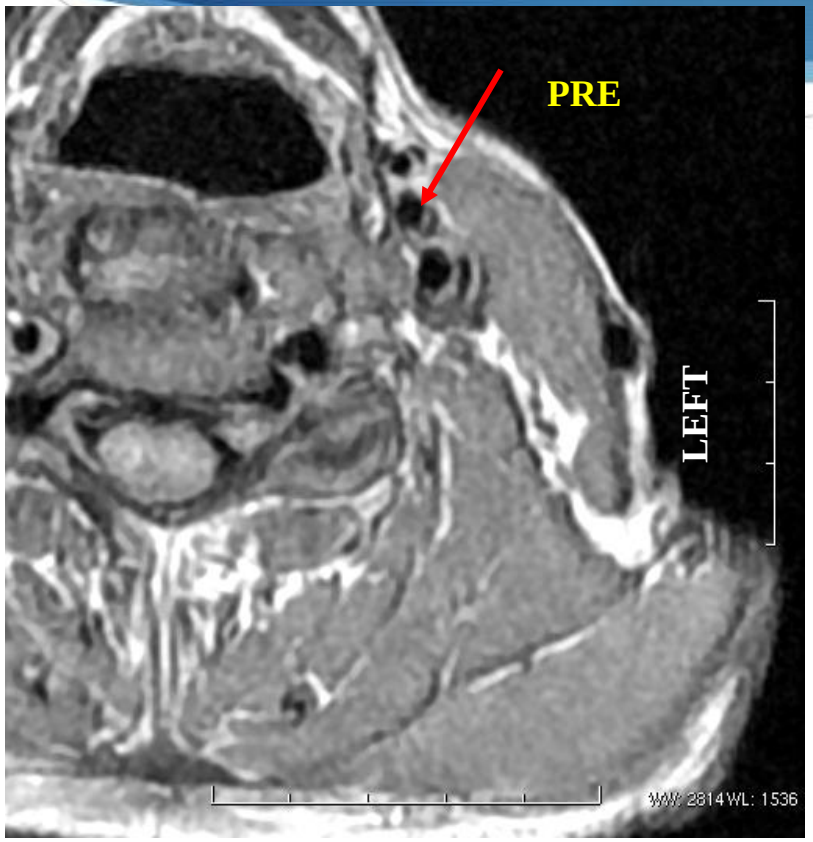
– Fasting lipid profiles drawn on day of MR imaging

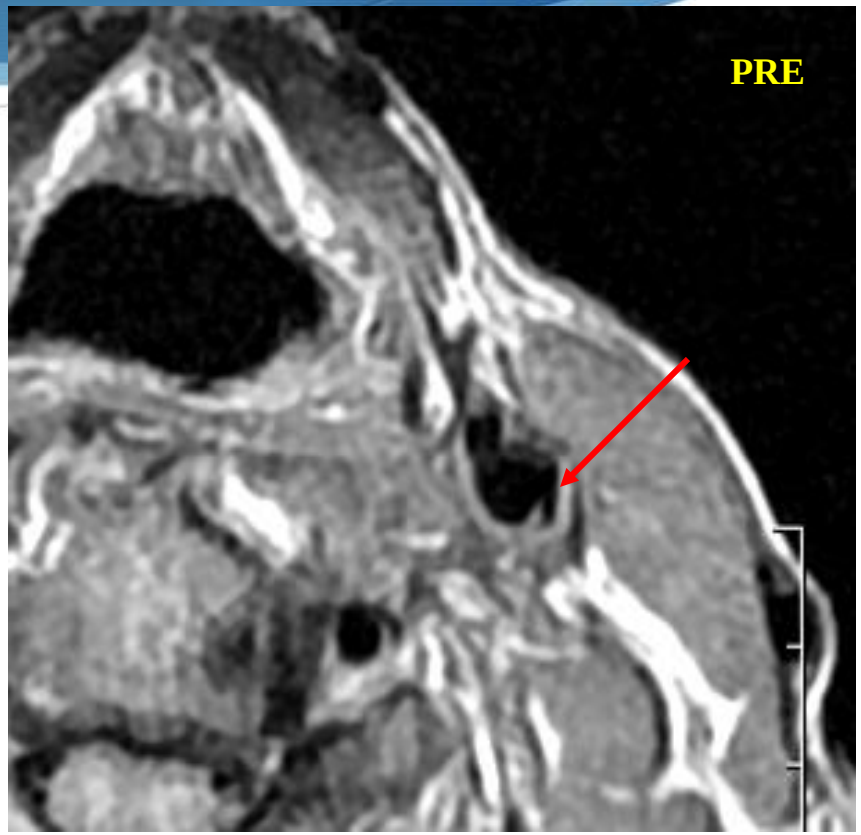
Current Imaging Techniques

- Essentially all trials were based on the Gold Standard
  - **Angiography**
  - **Degree of Stenosis**

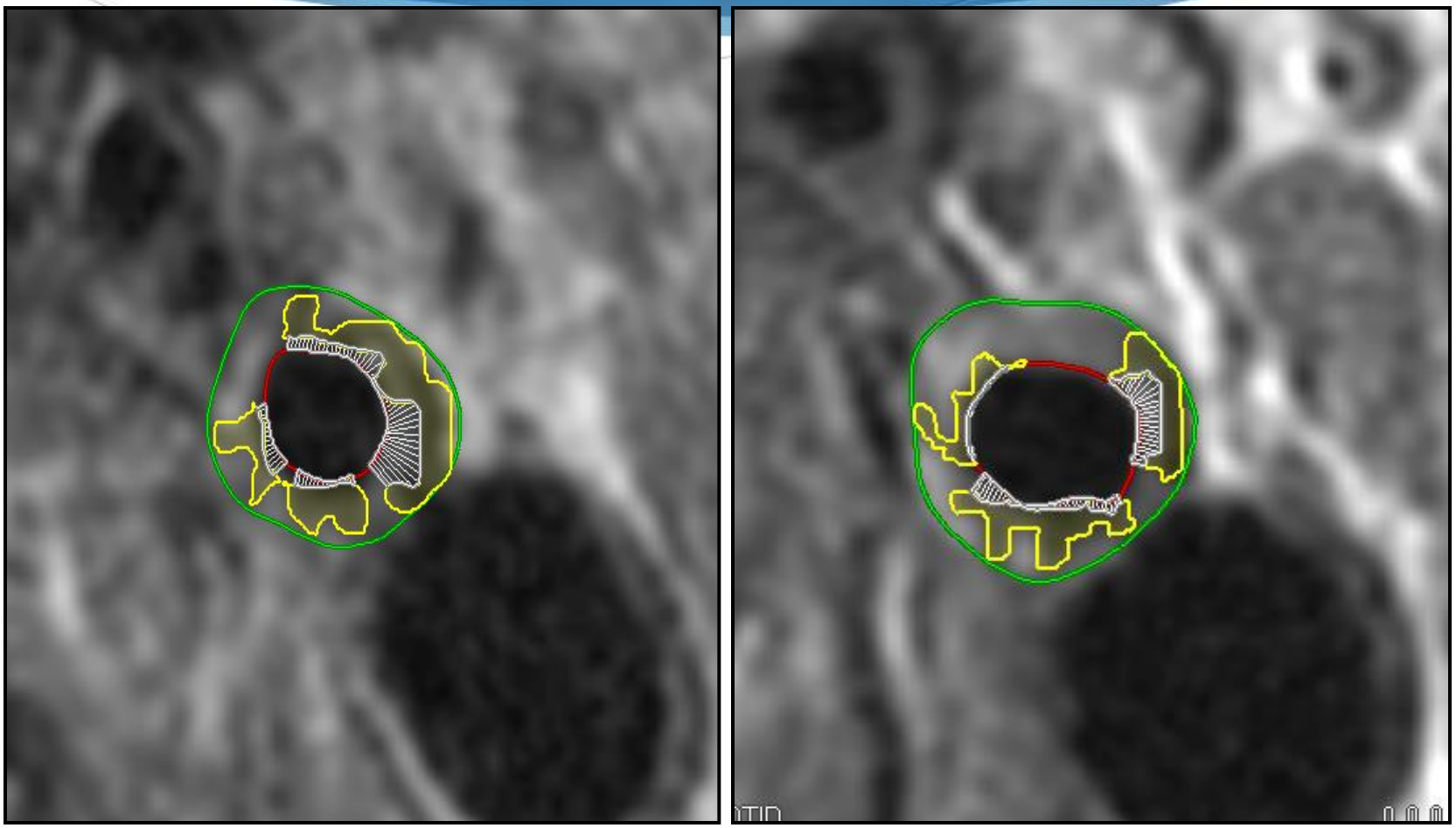
CAN IVUS FINDINGS DURING CAS PREDICT OUTCOME?

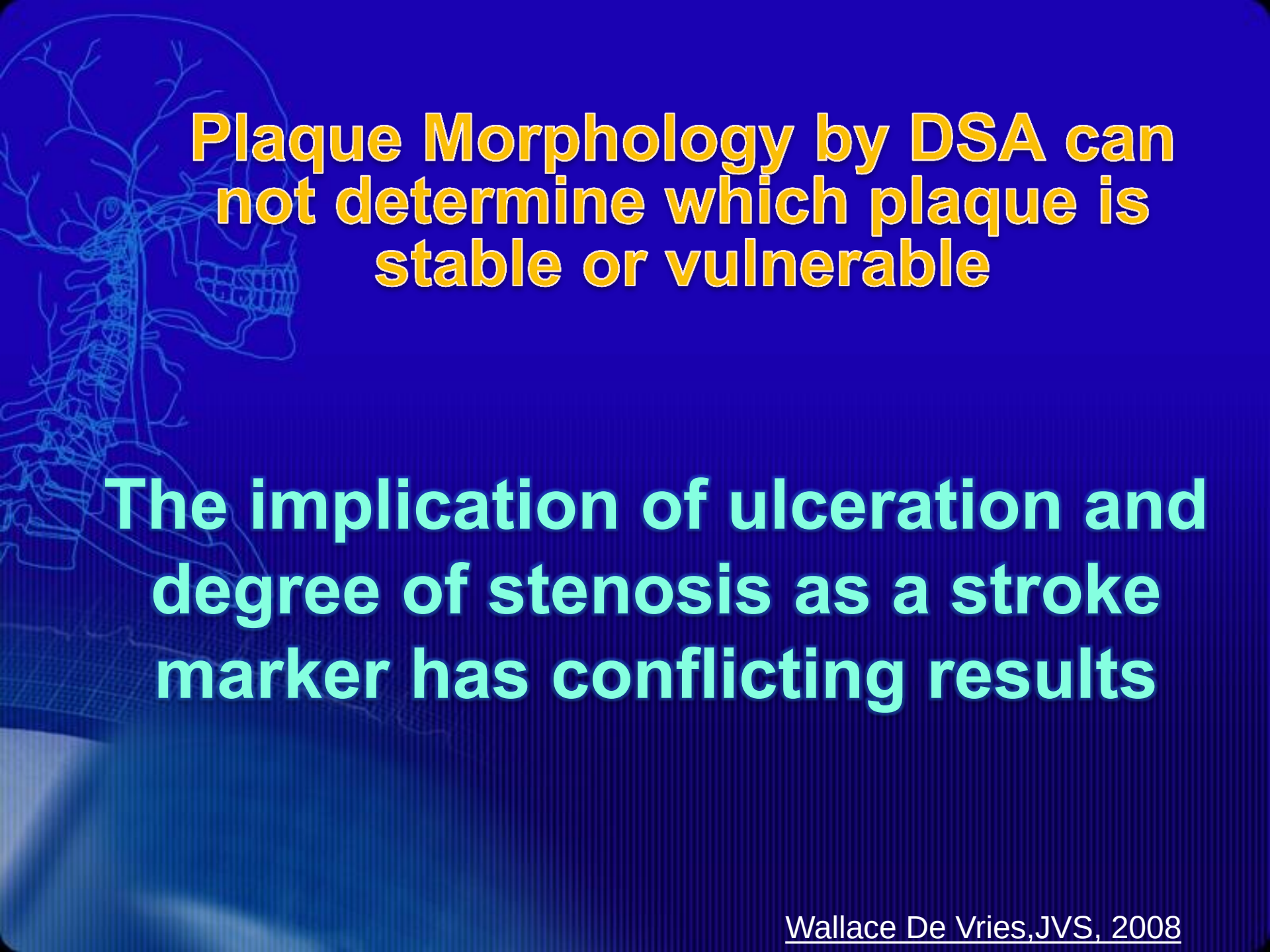
Carotid plaques





Proton Density Weighted Images of the Internal Carotid Artery at Baseline and after 12 months of Statin therapy

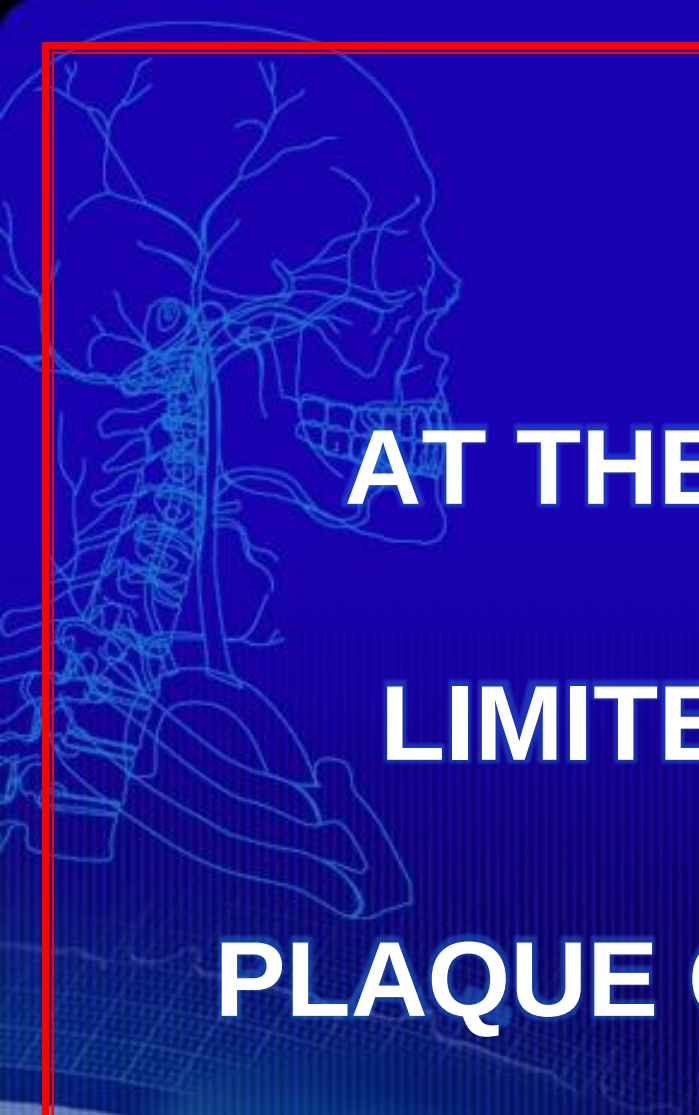




Plaque Morphology by DSA can not determine which plaque is stable or vulnerable

The implication of ulceration and degree of stenosis as a stroke marker has conflicting results

Wallace De Vries,JVS, 2008



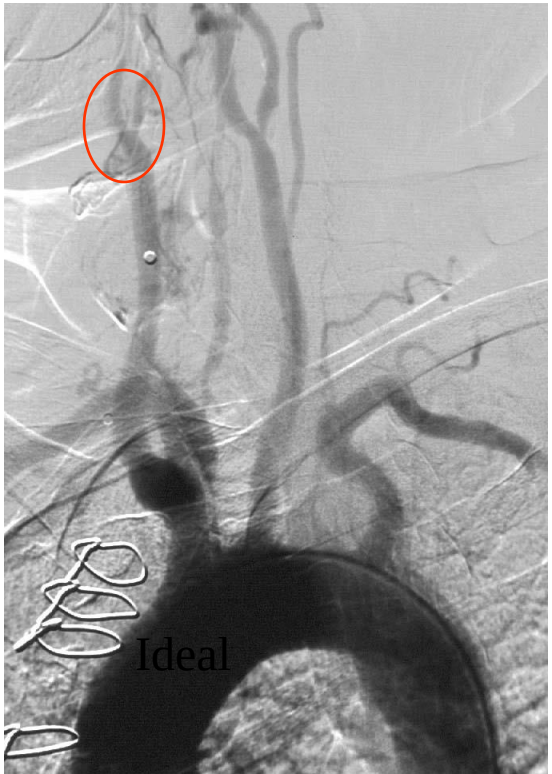
AT THE PRESENT TIME, WE HAVE LIMITED KNOWLEDGE OF PLAQUE CHARACTERISTICS

Outcomes of CAS Trials Over Time

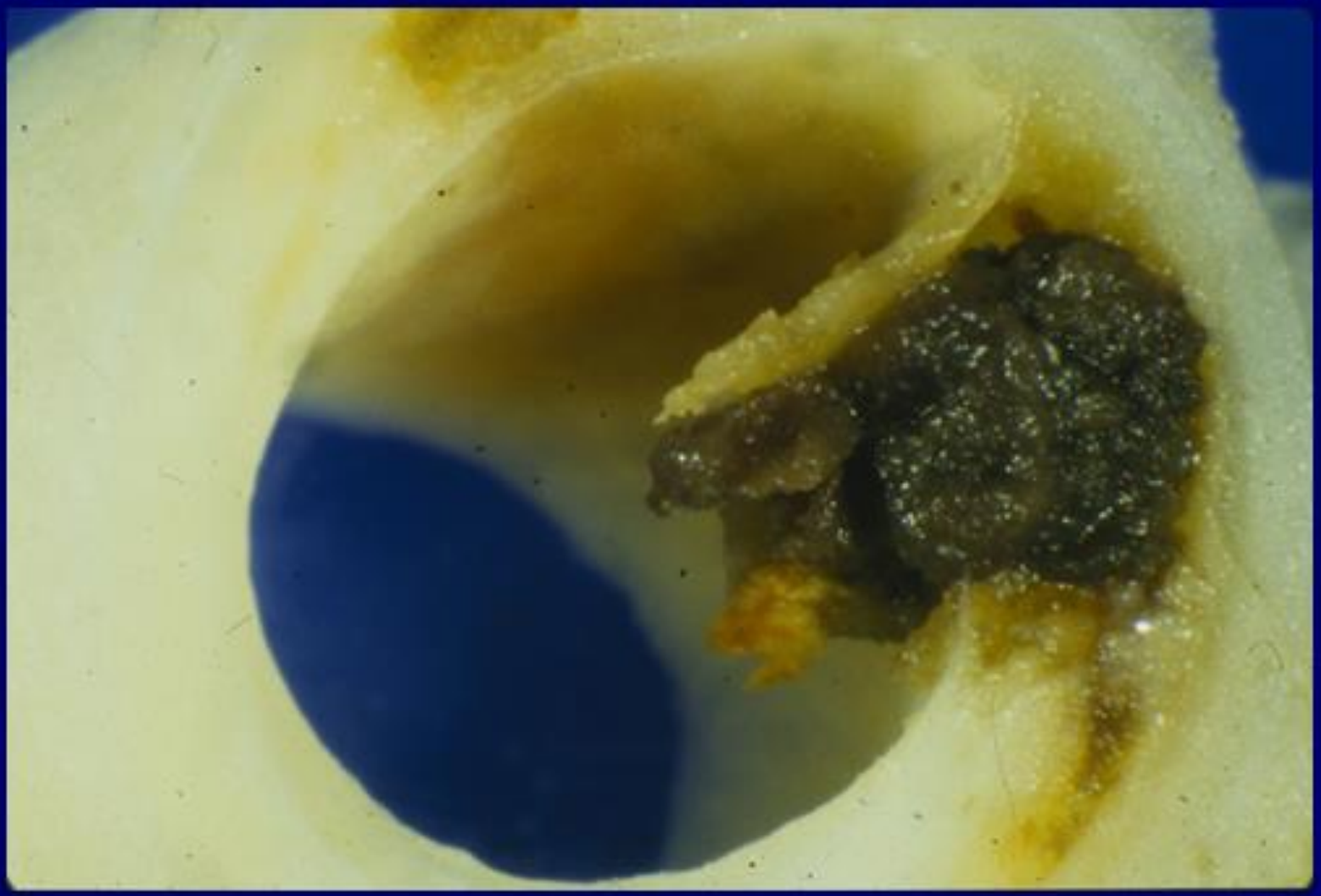
- CAS results have vastly improved over time due to: (1) more experienced operators; (2) better patient selection and; (3) a wider spectrum of technology
- CAS outcomes have evolved over time similarly to CEA

PROBLEMS of the aortic arch

Complexities of the aortic arc are responsible for almost all technical failures



MINIMAL PLAQUE WITH THIN CAP: RUPTURE-CLOT



Major limitations in relying on angiography alone for lesion severity and plaque composition

All imaging modalities have inherent limitations