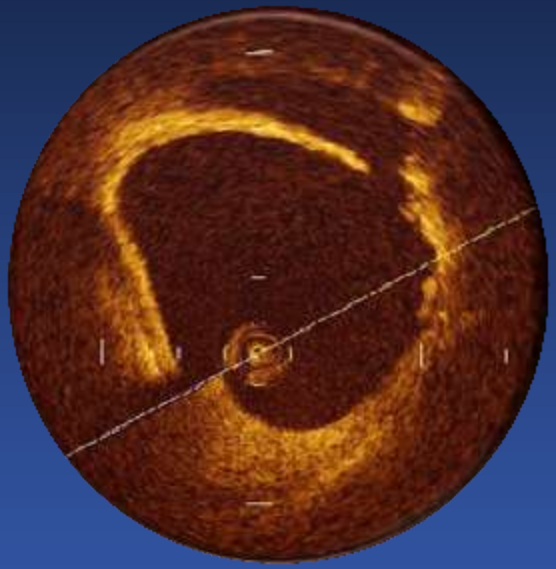
Vulnerable plaque



Konstantinos Toutouzas

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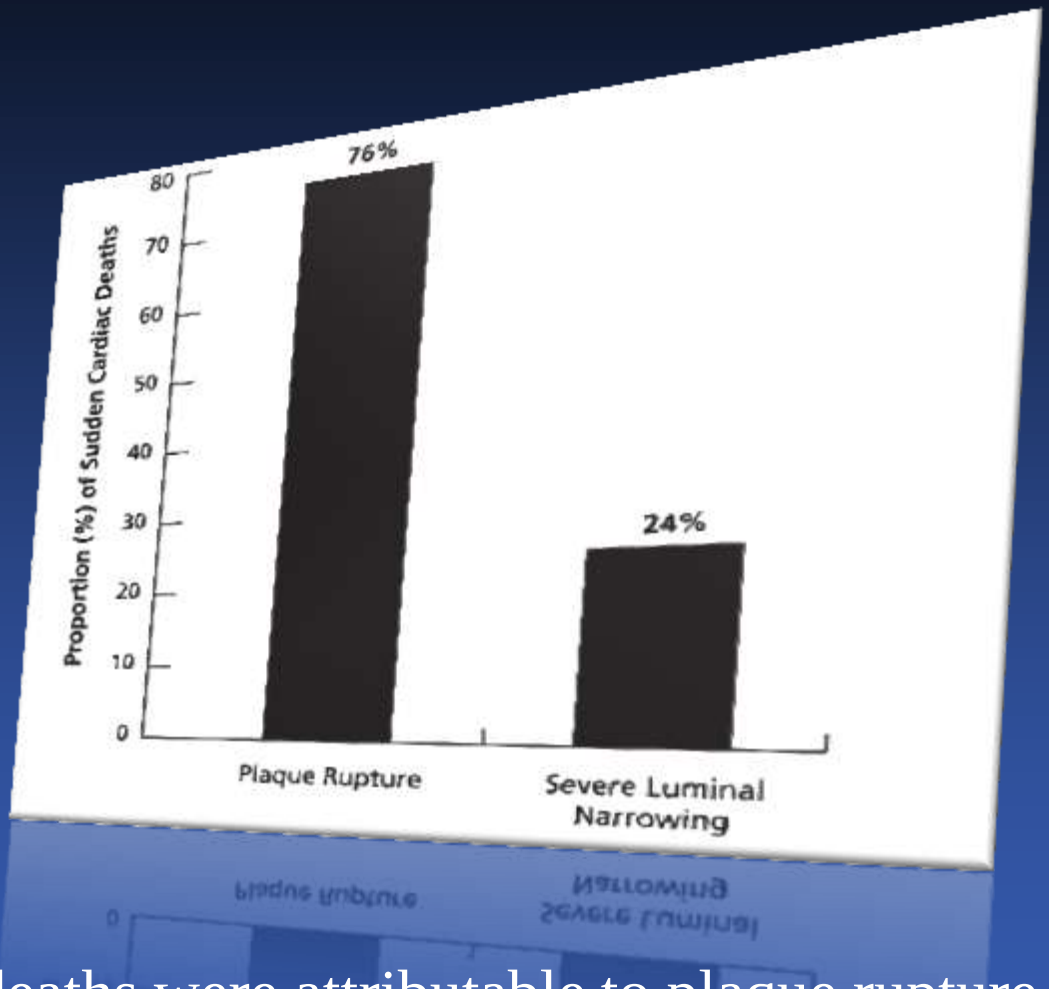
Vulnerable plaque

- From ruptured plaque to vulnerable plaque
- Tools for VP imaging
- Research applications of VP imaging
- Clinical perspective of VP imaging
- Potential for treatment

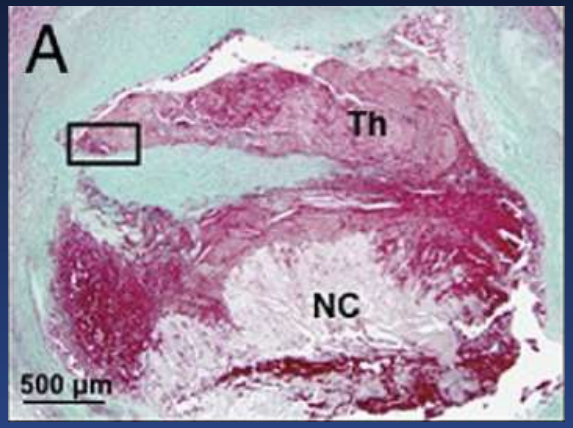
Plaque rupture impact

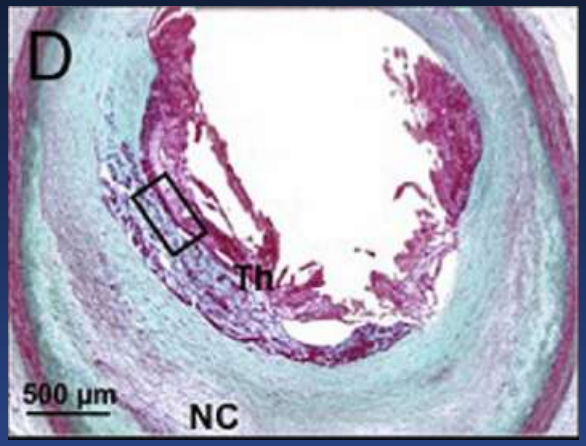


76% of sudden deaths were attributable to plaque rupture, and only 24% of MIs were associated with severe luminal narrowing.

Falk E, …,Fuster V. Coronary plaque disruption. Circulation 1995;92:657– 671

Plaque rupture vs. Plaque erosion



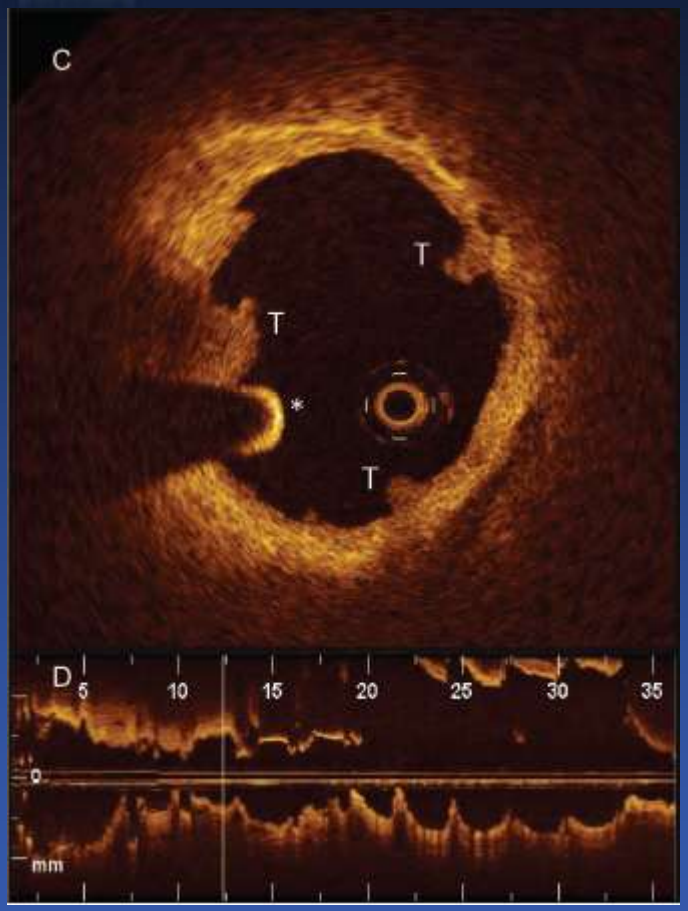


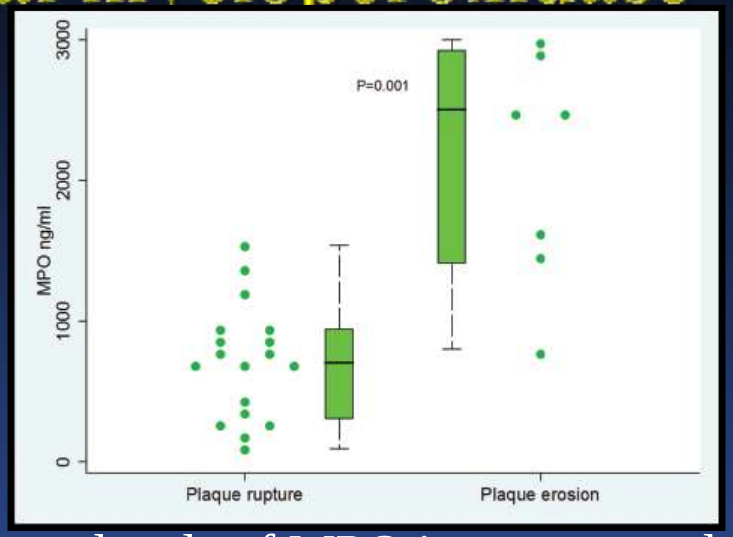
Almost half of the women under 50 years old present with fibrous cap erosion!!!

	Plaque rupture (n=65)	Plaque erosion (n=50)	p-value
Stenosis (%)	77.1±13.8	71.3±14.9	0.02
Necrotic core area (%)	38.3 ± 23.4	18.3 24.4	< 0.0001
Plaque burden	231 ± 67	190 ± 72	0.008
Intimal Macrophages (%)	3.44 ± 2.77	2.53 ± 2.65	0.03
Male Gender (%)	89	74	0.008

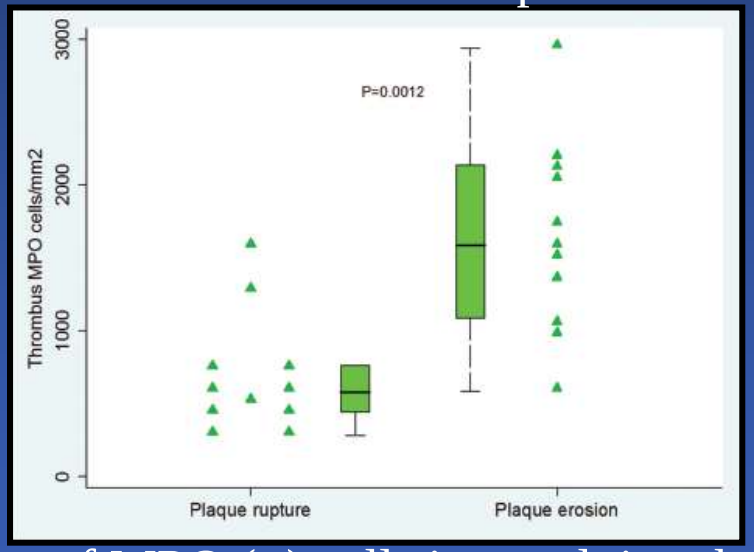
Virmani R, et al., JACC Oct 2009

Plaque erosion: Association with systemic and local myeloperoxidase





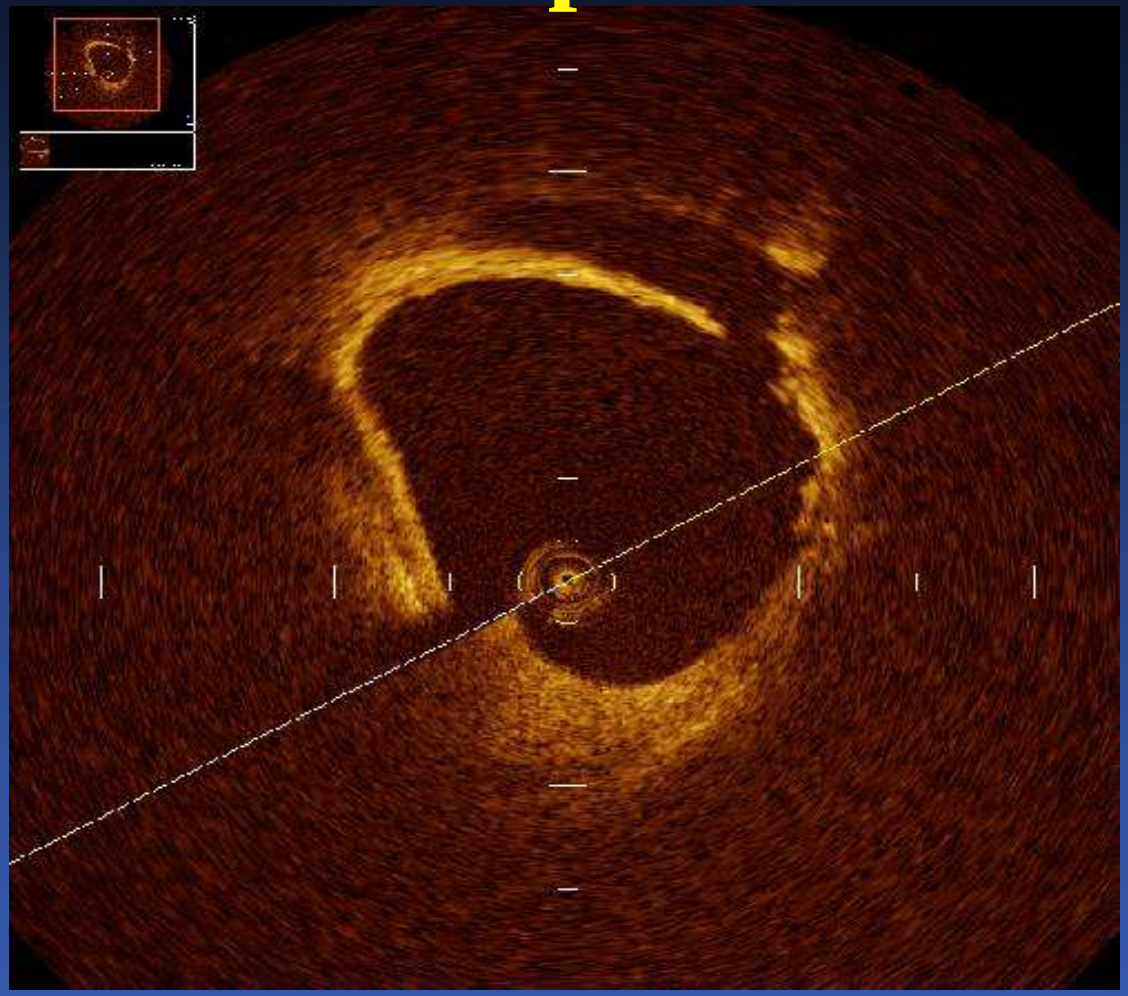
Plasma levels of MPO in rupture and erosion



Density of MPO (+) cells in overlying thrombus in rupture and erosion

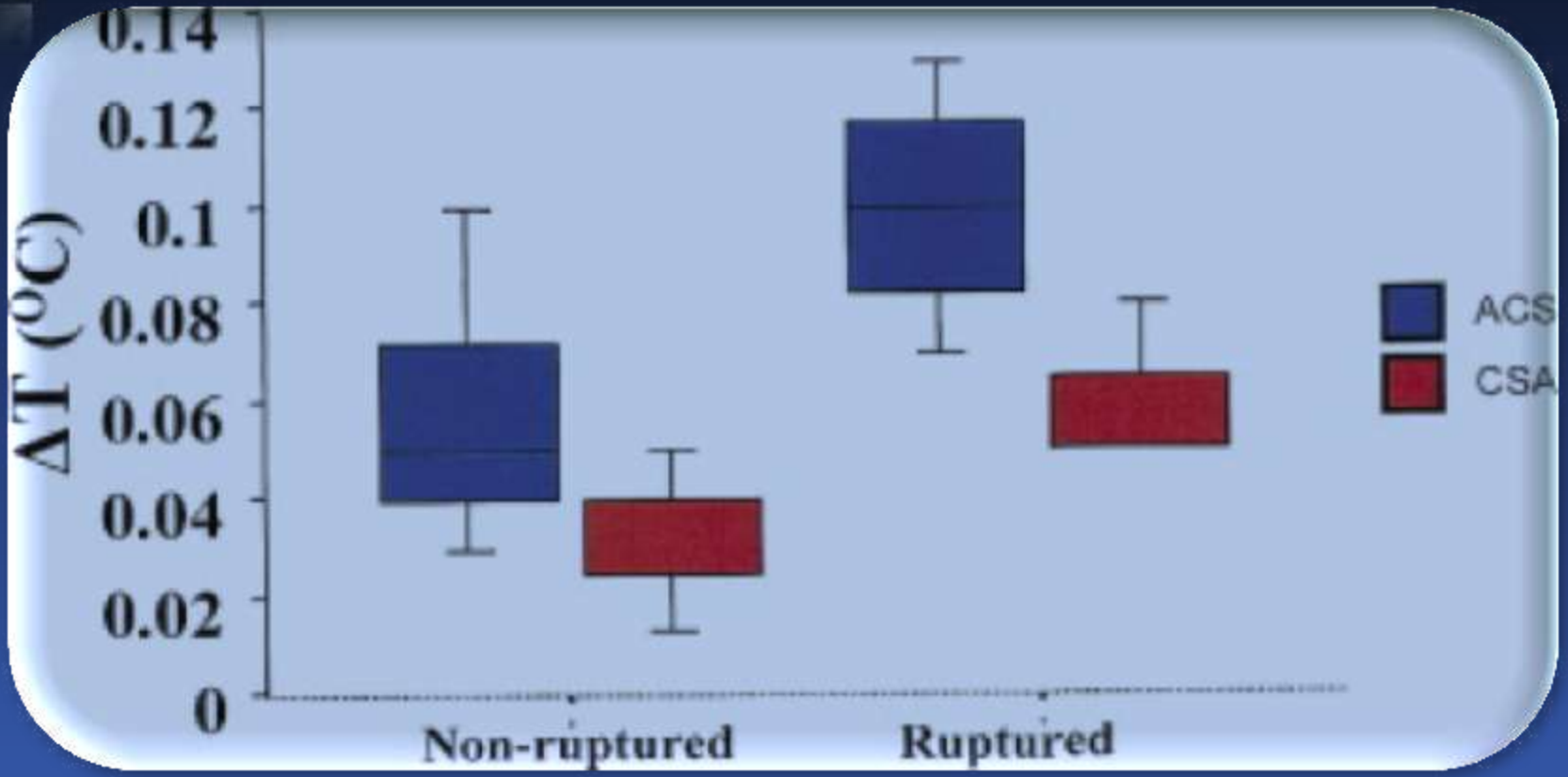
Ferrante G et al., Circulation. 2010;122:2505-2513

In vivo demonstration of cap rupture



OCT is the gold standard for imaging of plaque rupture due its highest spatial resolution.

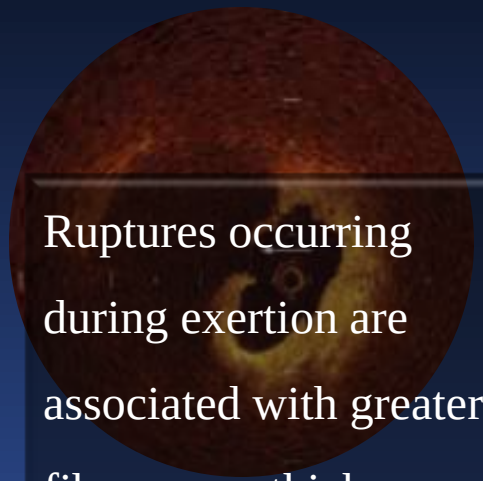
Thermal heterogeneity & rupture



Rupture had a positive correlation with thermal heterogeneity, and this correlation was more pronounced in pts with ACS.

Toutouzas K,..,Stefanadis C, JACC 2007

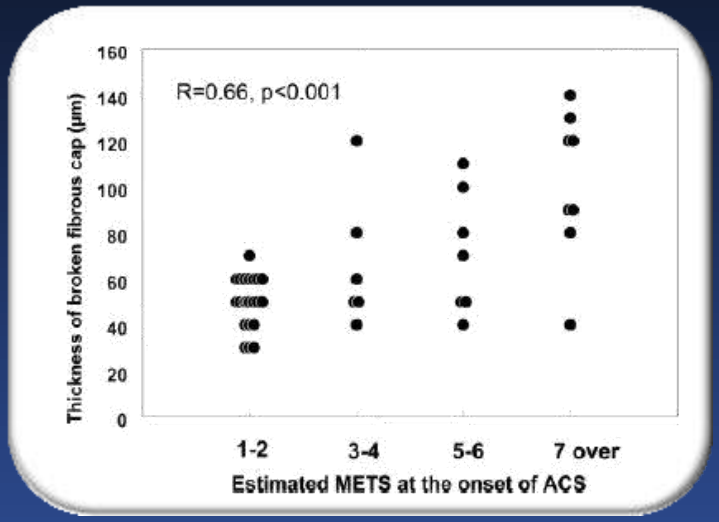
Exercise triggered rupture does not occur at "vulnerable plaques"

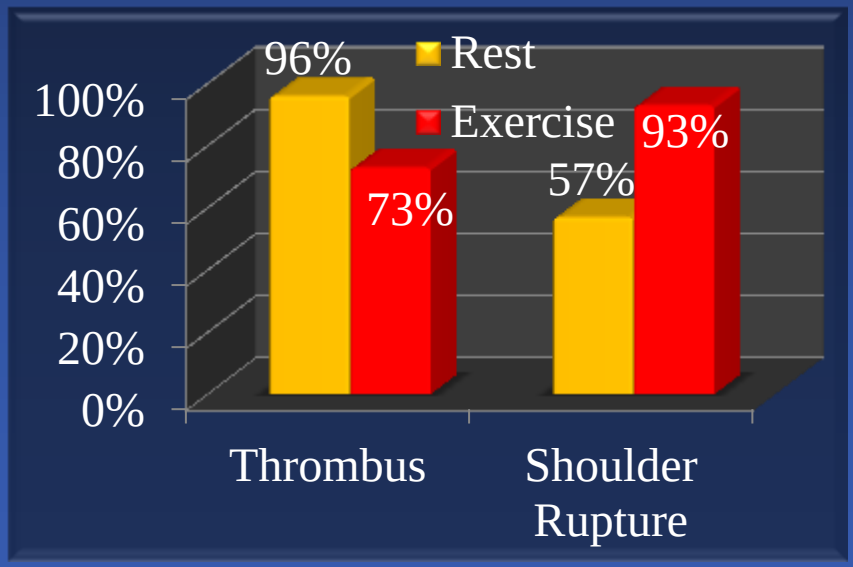


Ruptures occurring during exertion are associated with greater fibrous cap thickness and greater incidence of thrombus and are more often located at the shoulder of the plaque

Rest – Center rupture

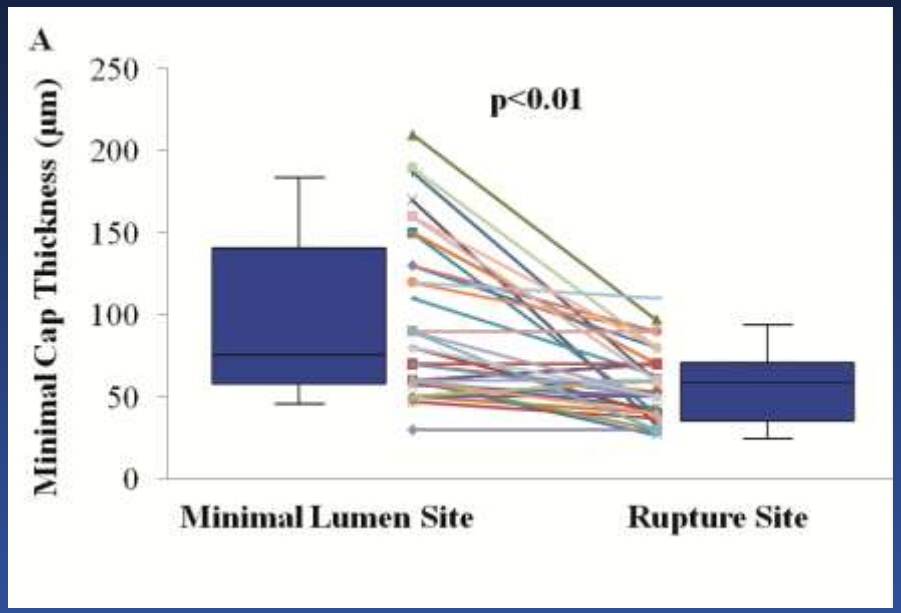
Exertion – Shoulder rupture





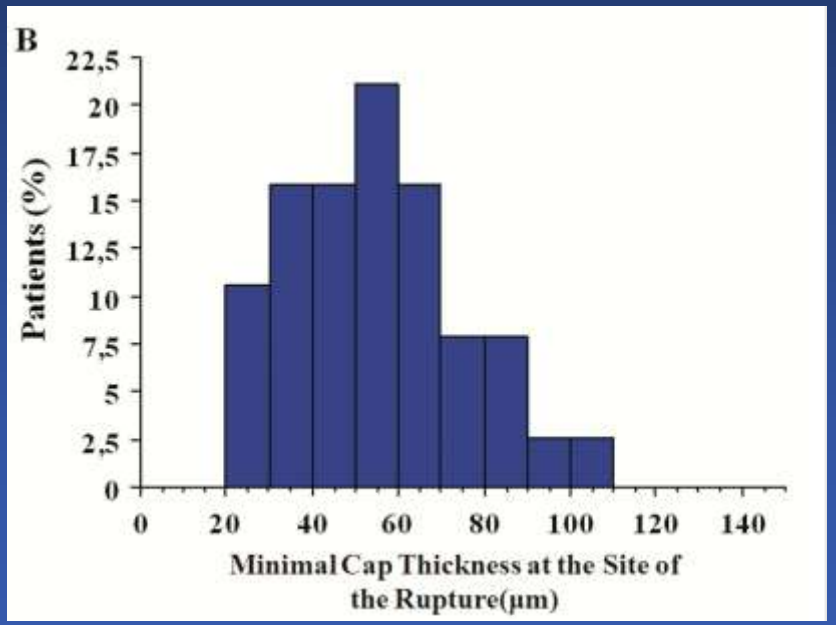
Tanaka A et al., Circulation. Dec 2008

Cap thickness in plaque rupture



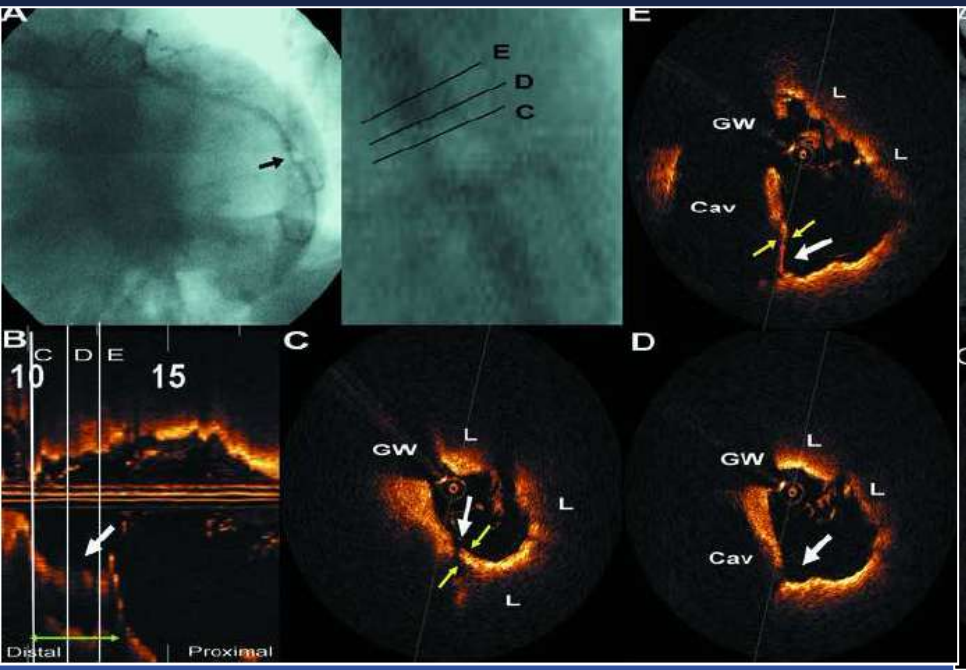
Cap thickness in minimal lumen site is higher but correlates with ruptured cap thickness

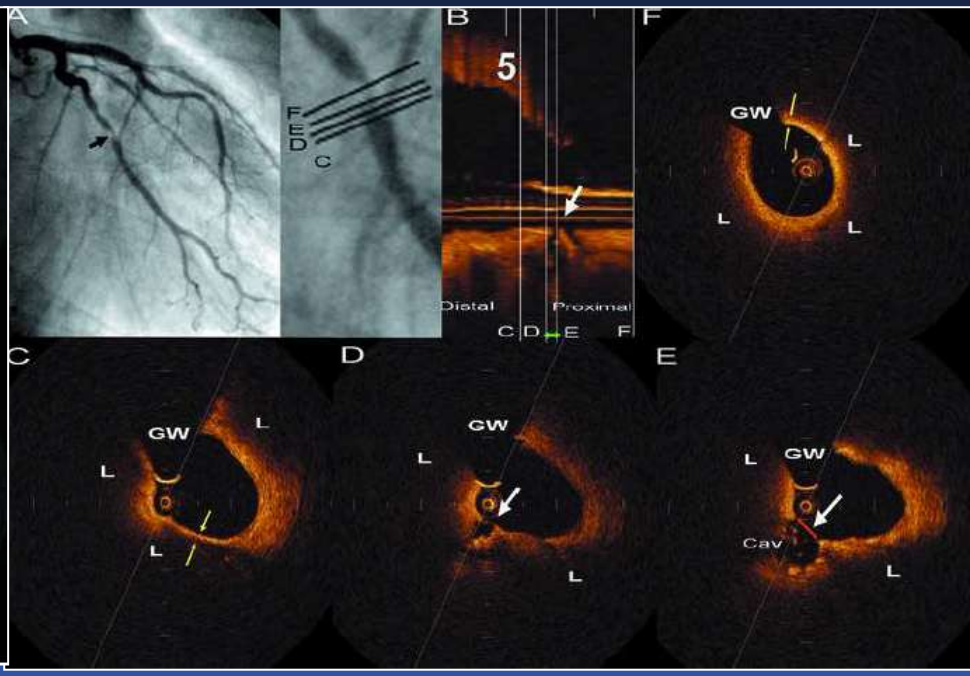
Cap thickness in 90% of the ruptures is below 100 μm



Toutouzas et al, Am Heart J 2011 Jun 161(6):1192-9.

Difference in rupture between STEMI & NSTEMI





STEMI NSTEMI

STEMI patients have greater rupture length and greater length of missing fibrous cap than NSTEMI patients

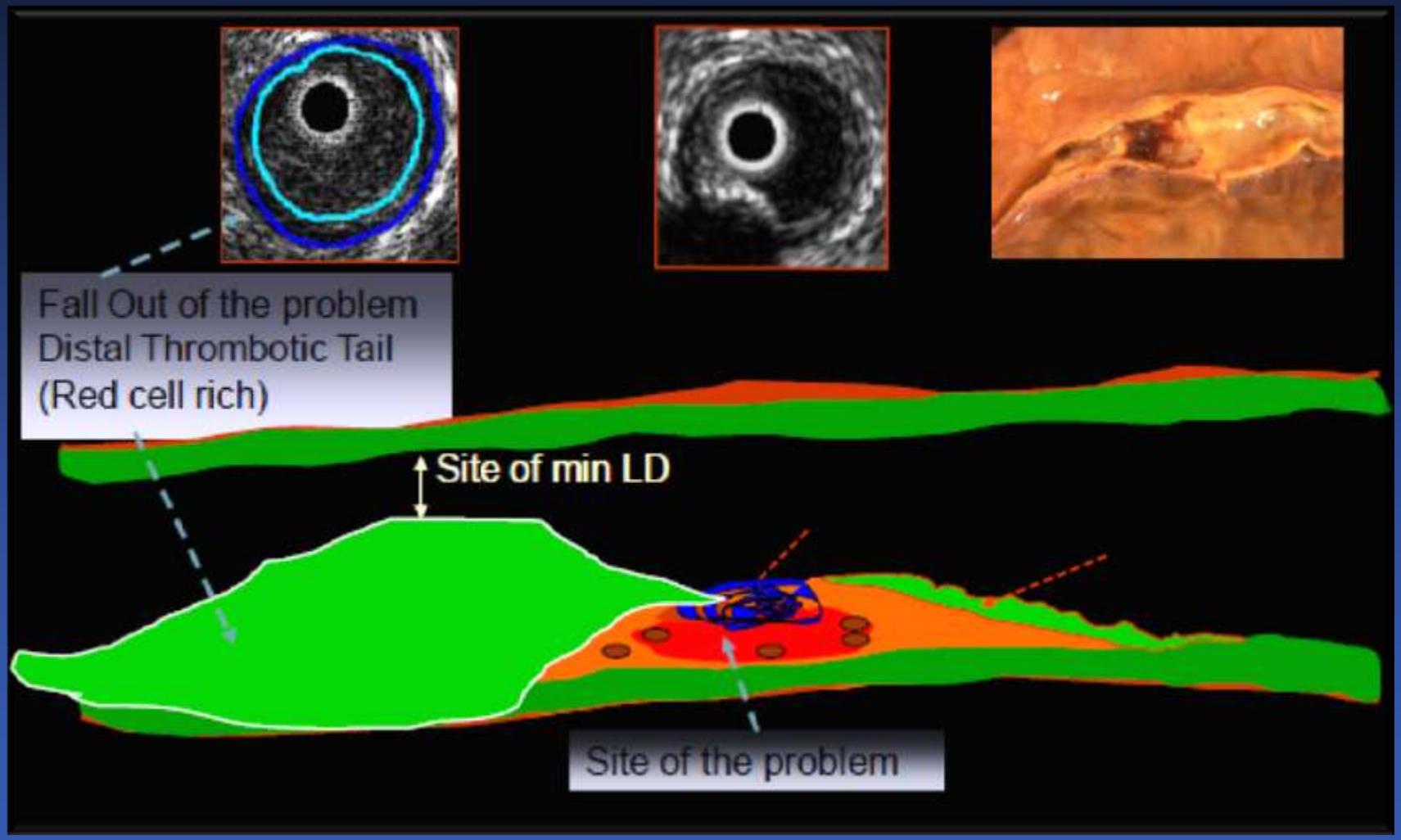
Toutouzas et al, Am Heart J 2011 Jun 161(6):1192-9.

Rupture location in ACS

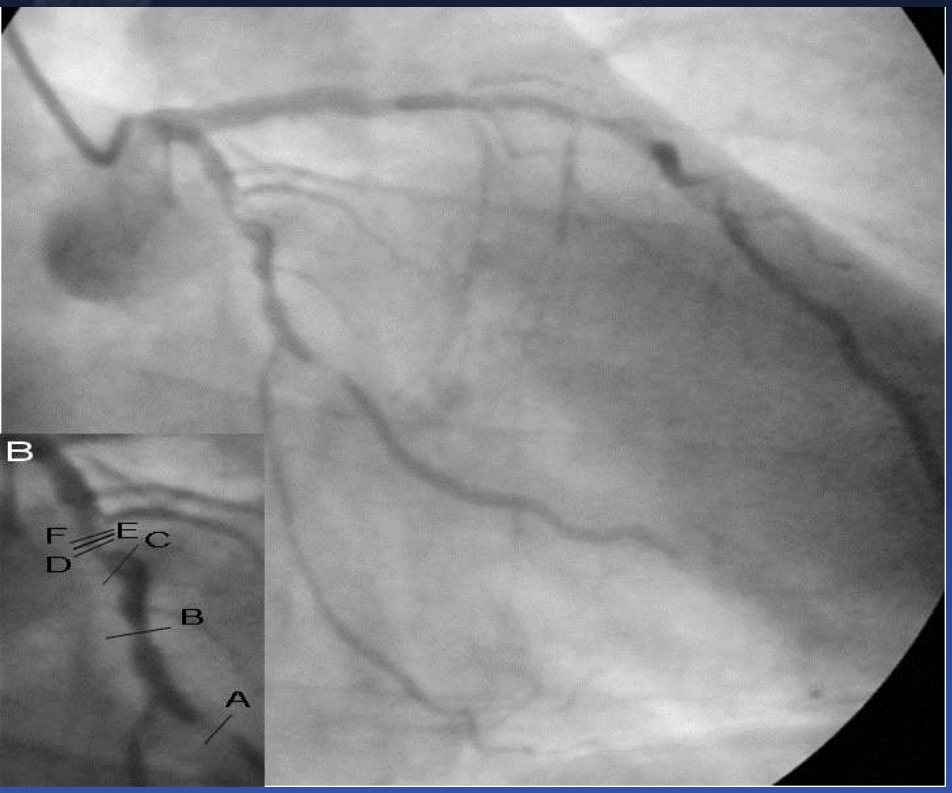
Rupture Characteristics	
Rupture Length(mm)	2.27±1.70
Location of rupture	
Distal to the MLS	14(36.8)
MLS	14(36.8)
Proximal to the MLS	10(26.3)
Distance from MLS(mm)	2.01±2.10
Cross Sectional Area(mm2)	4.12±2.68
Minimal Cap Thickness(μm)	59±21μm
Rupture at cap shoulder	26(68.4)
Length of missing fibrous cap(mm)	0.53±0.27

Toutouzas et al, Am Heart J 2011 Jun 161(6):1192-9.

Plaque rupture and minimal stenosis

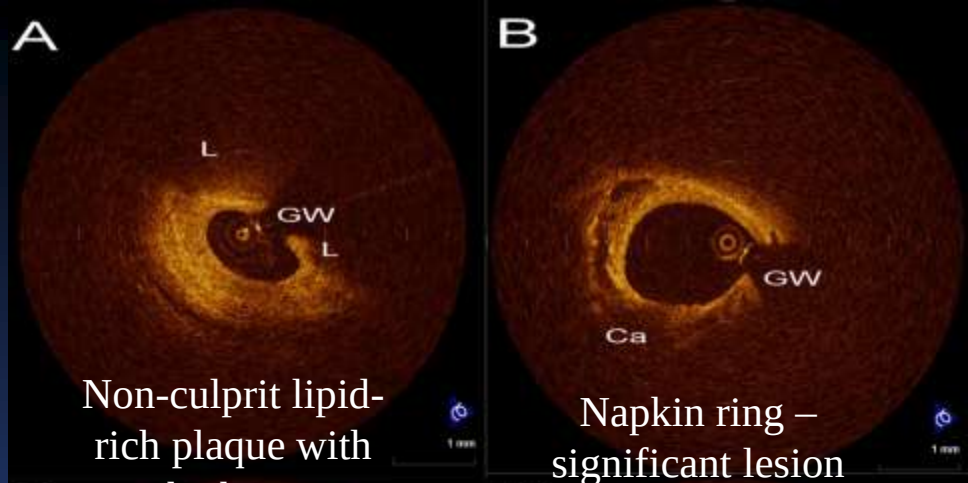


OCT imaging in ACS



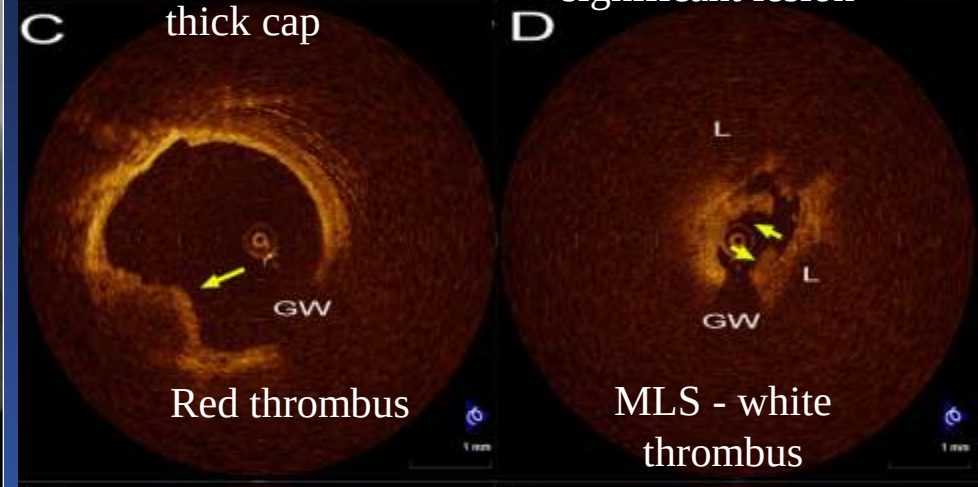
Evaluation of culprit lesion in ACS revealed multiple morphologies

Toutouzas et al, Heart July 2010



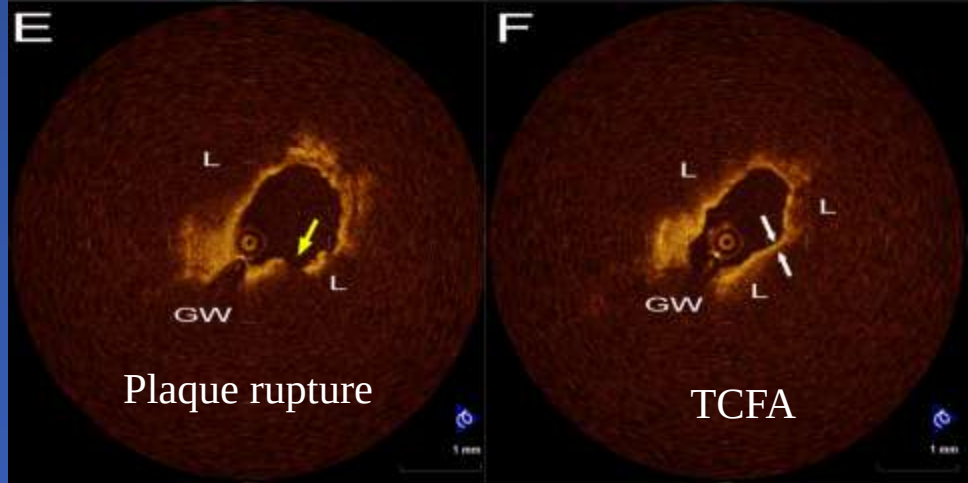
Non-culprit lipid-rich plaque with thick cap

Napkin ring – significant lesion



Red thrombus

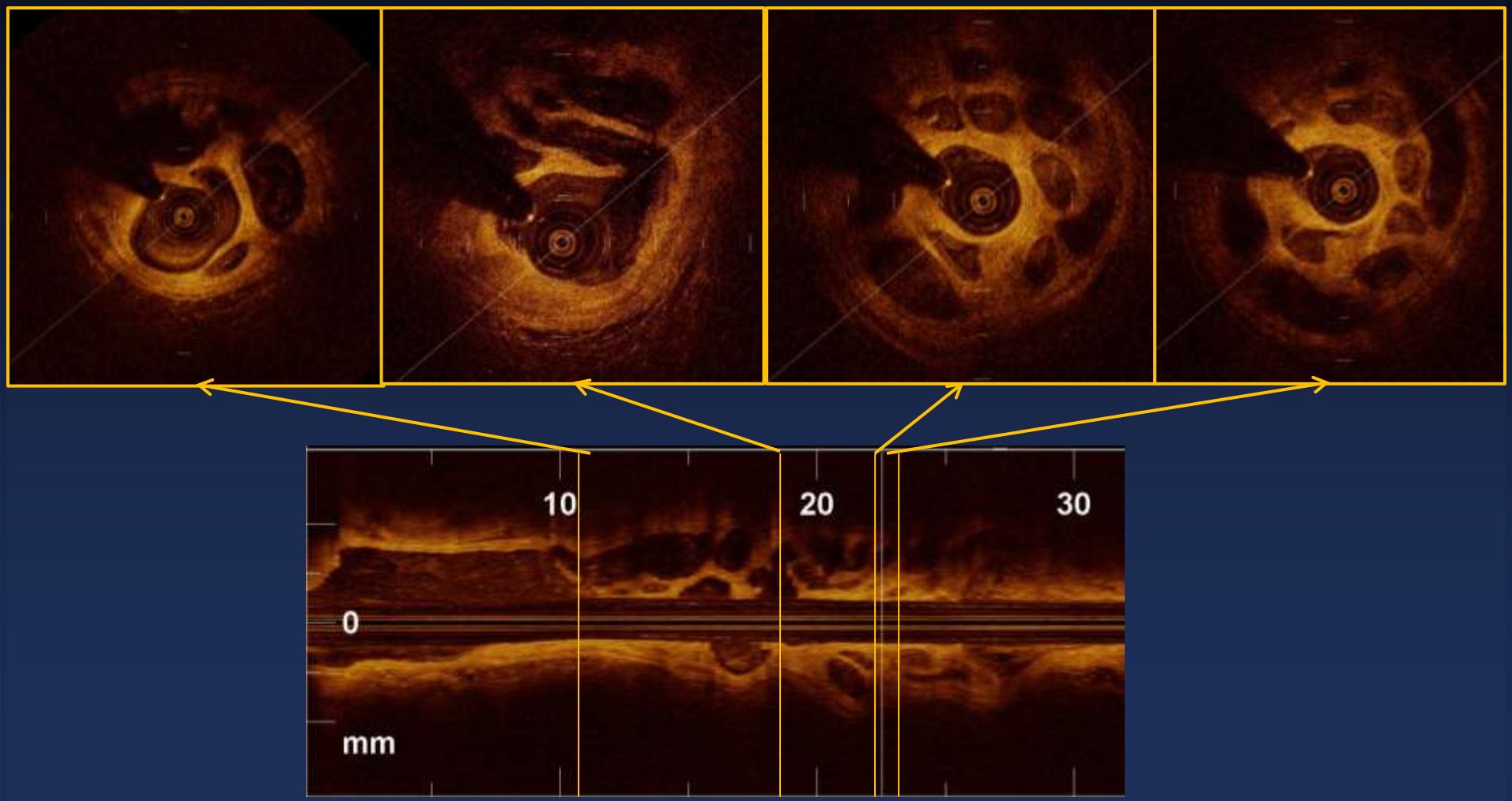
MLS - white thrombus



Plaque rupture

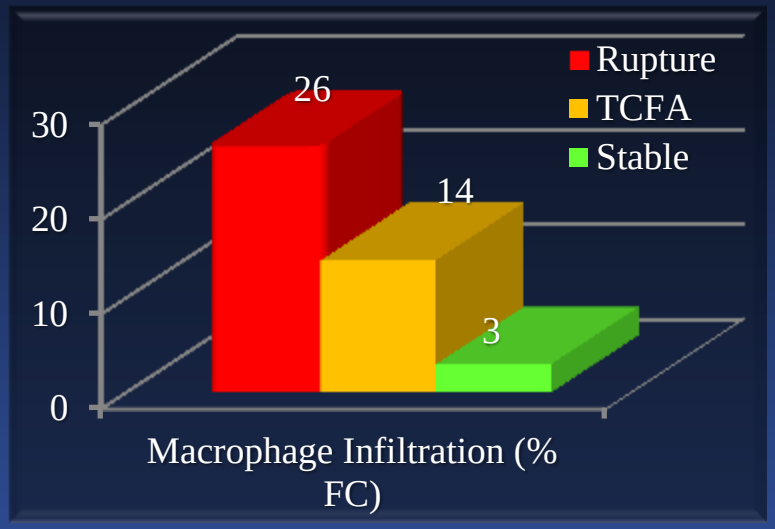
TCFA

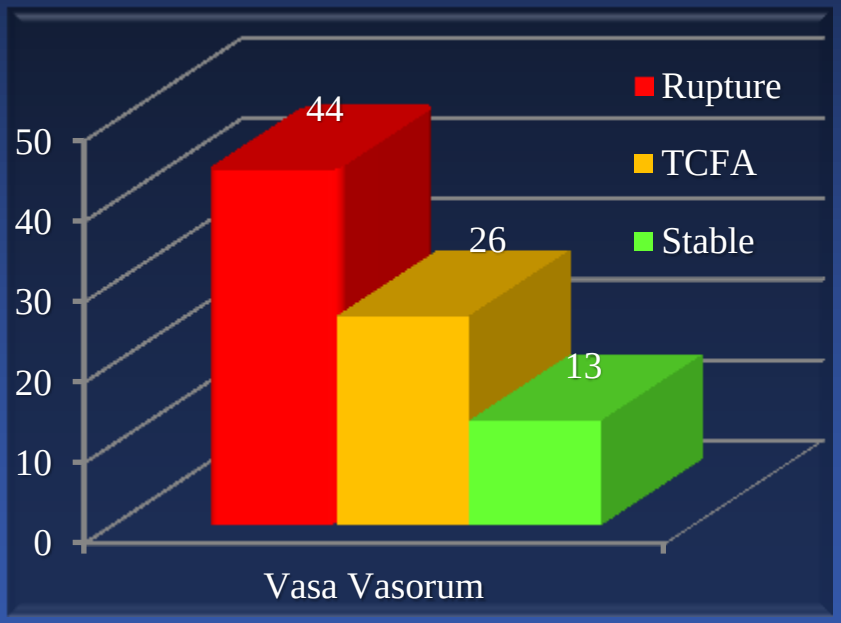
Recanalized Thrombus

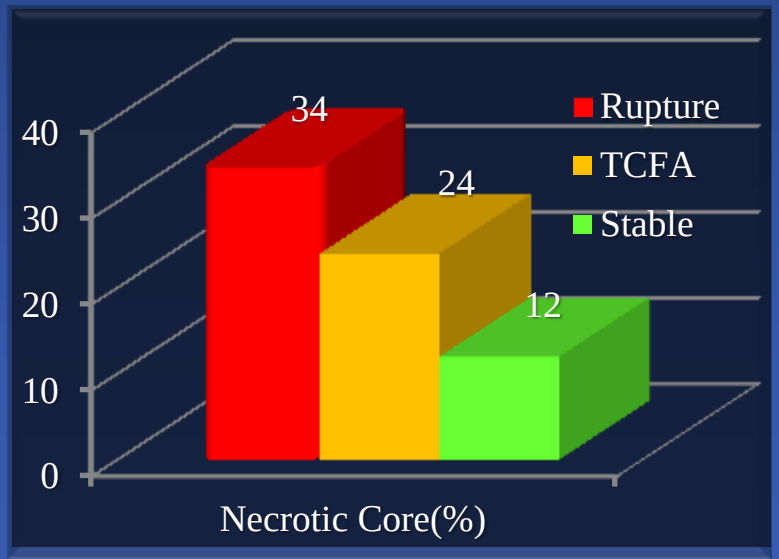


Toutouzas et al, submitted

Stable vs TCFA vs Ruptured Plaque

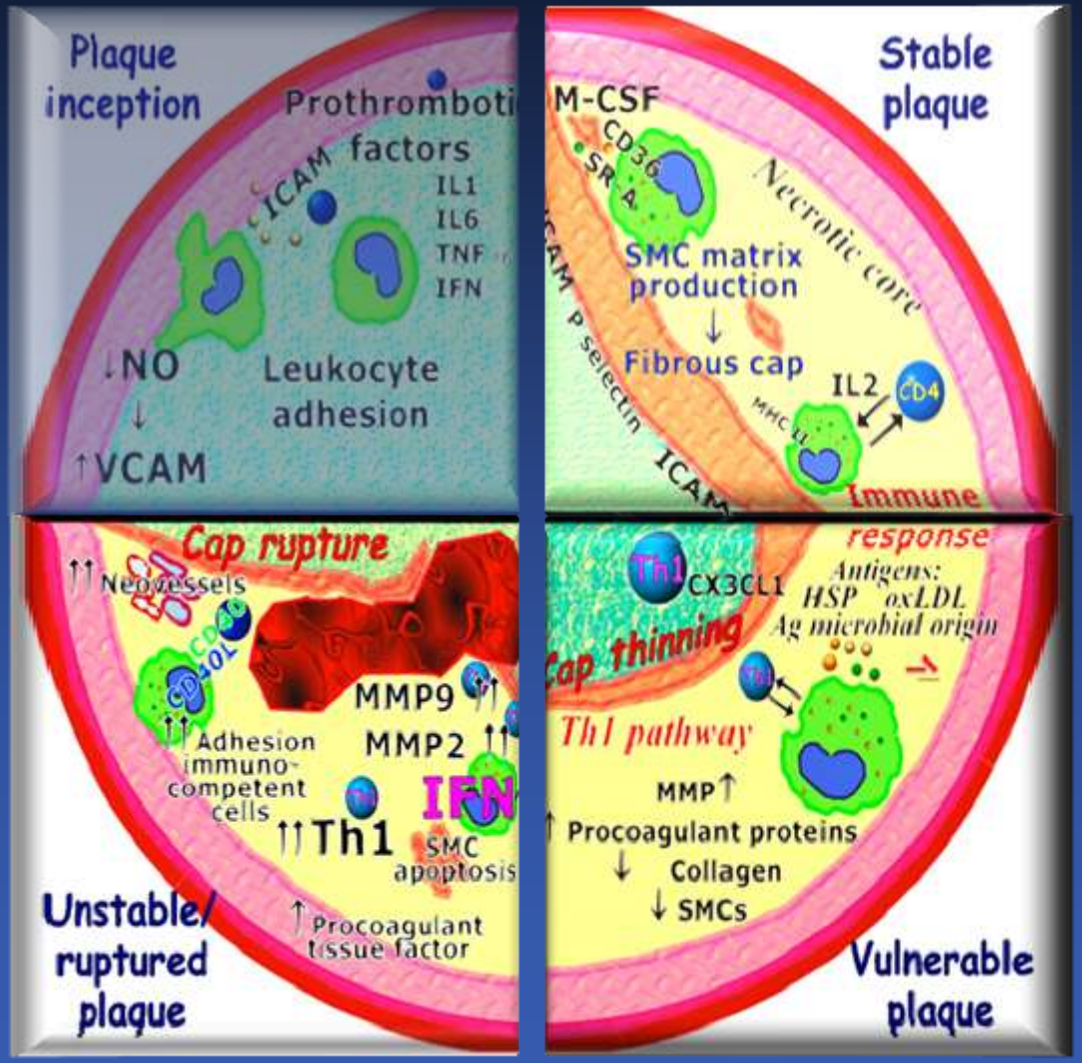




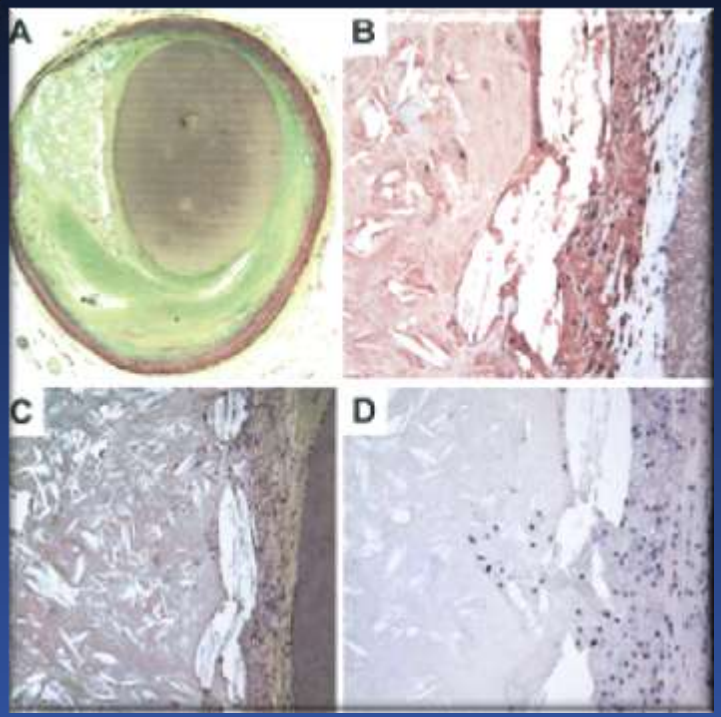


Virmani R, et al., JACC 2006;47:C13–8

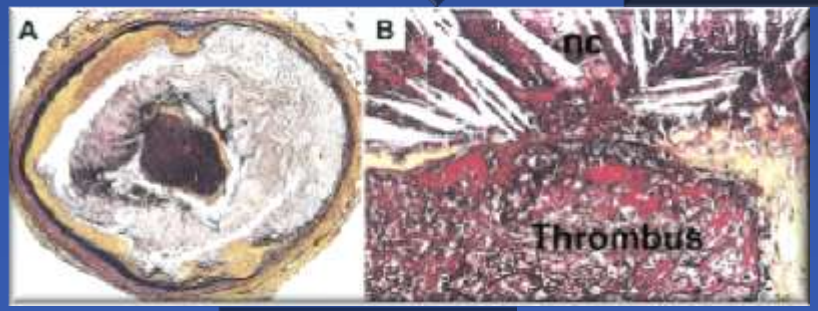
What is a "vulnerable plaque"?



Vulnerable Plaque Components



Rupture



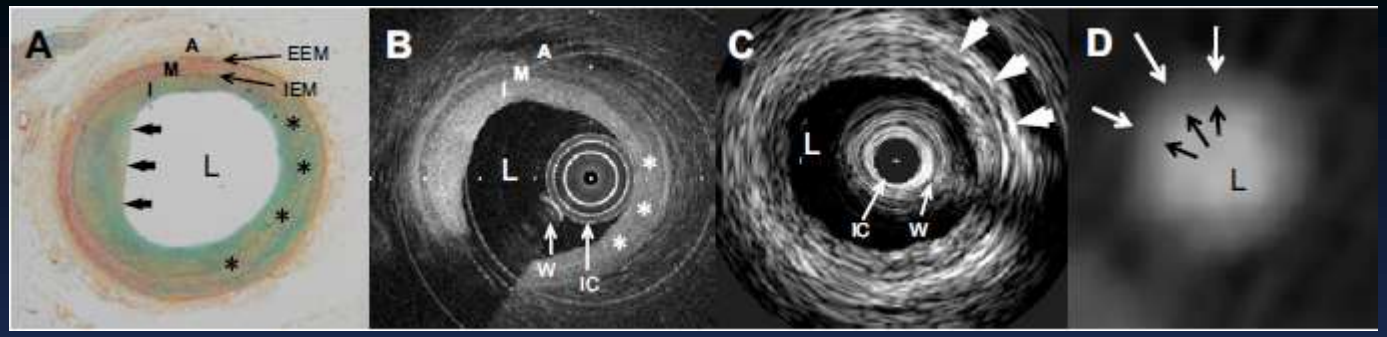
Thrombosis

- **Increased Plaque size**
  - ***Positive remodeling***
- **Increased Necrotic core**
  - **~34% of plaque area**
  - **~3.8 mm^2 & ~9 mm long**
- **Fibrous cap**
  - **Reduced Thickness, *~23 μm (95% <65 μm)***
  - **Increased Macrophage Density, *~26% of cap***
  - ***Reduced Smooth Muscle Cells***
- **Increased Angiogenesis**
  - **Intraplaque hemorrhage**
- **Perivascular inflammation**
- **Reduced Calcification & *Spotty***

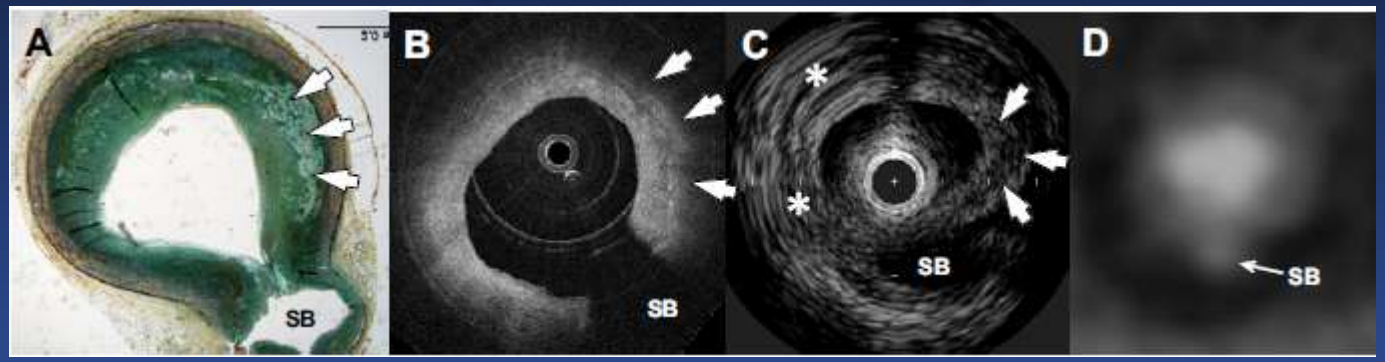
Virmani R, et al., JACC 2006;47:C13–8

Vulnerable plaque

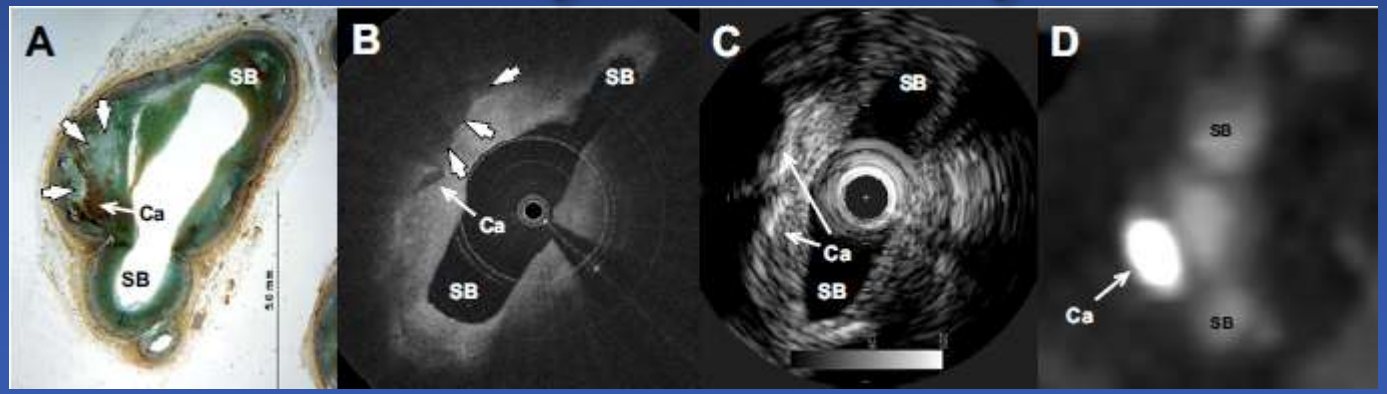
- From ruptured plaque to vulnerable plaque
- Tools for VP imaging
- Research applications of VP imaging
- Clinical perspective of VP imaging
- Potential for treatment



Adaptive intimal thickening

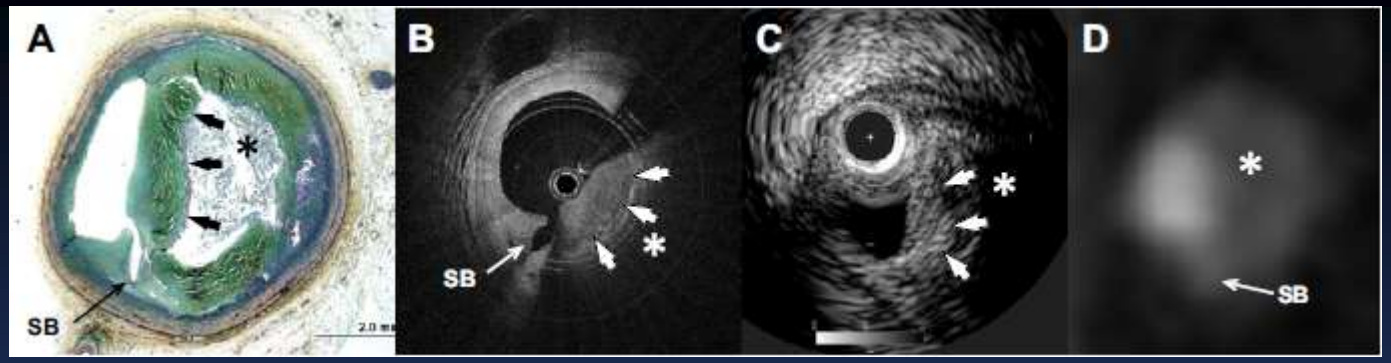


Pathologic intimal thickening

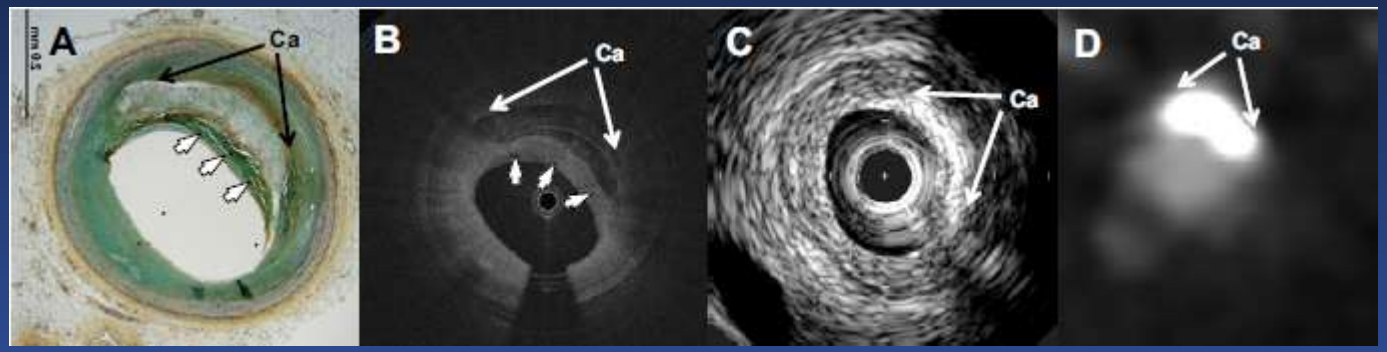


Pathologic intimal thickening with calcification

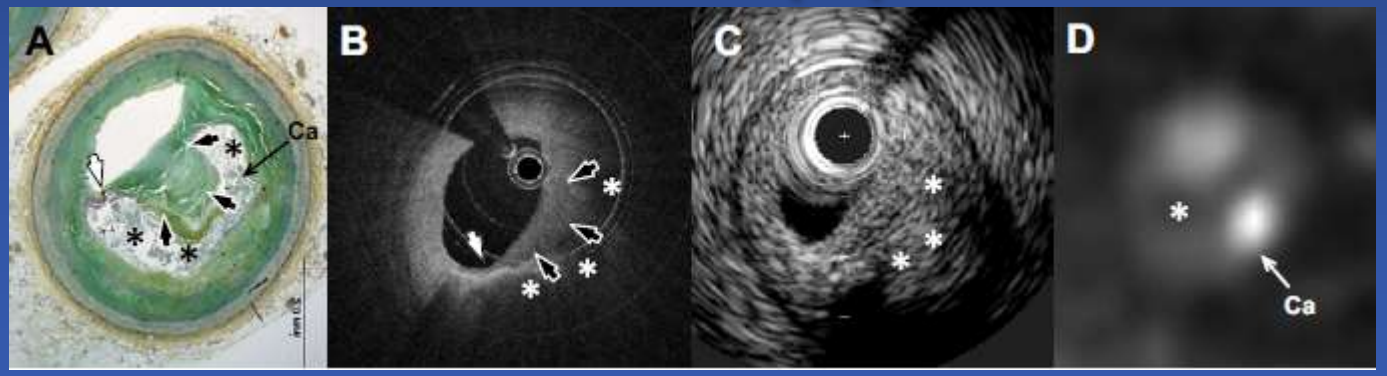
Donelly et al., JACC Cardiovasc Img 2010; 3(8): 876-80



Late fibroatheroma



Fibrocalcific plaque

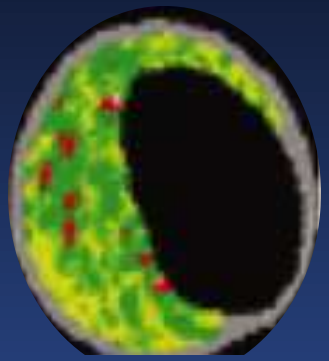


Thin cap fibroatheroma with spotty calcification

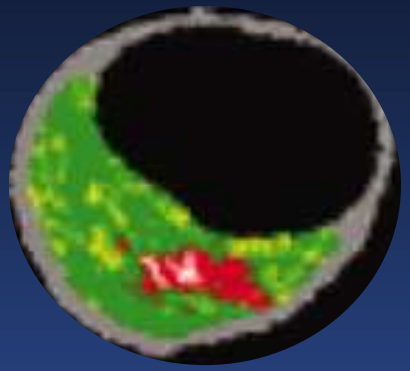
Donelly et al., JACC Cardiovasc Img 2010; 3(8): 876-80

Plaque characterization with IVUS-VH

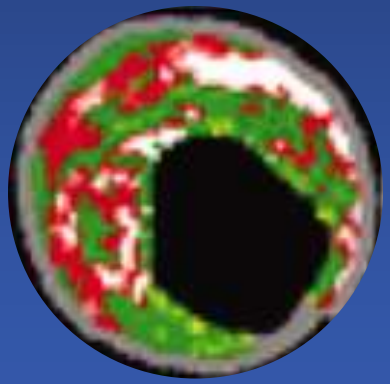
Fibrotic



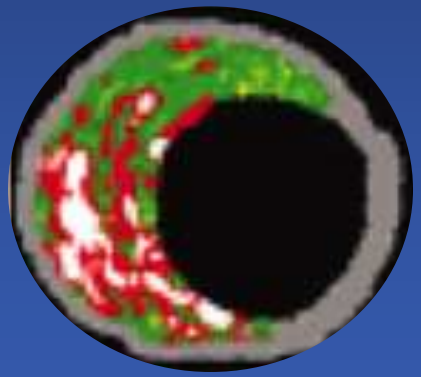
Pathologic intimal thickening



Fibroatheroma



Calcified FA



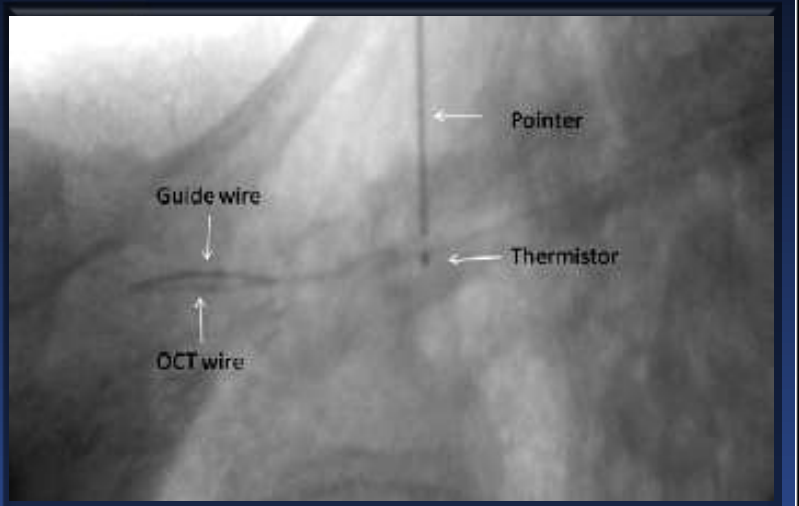
TCFA

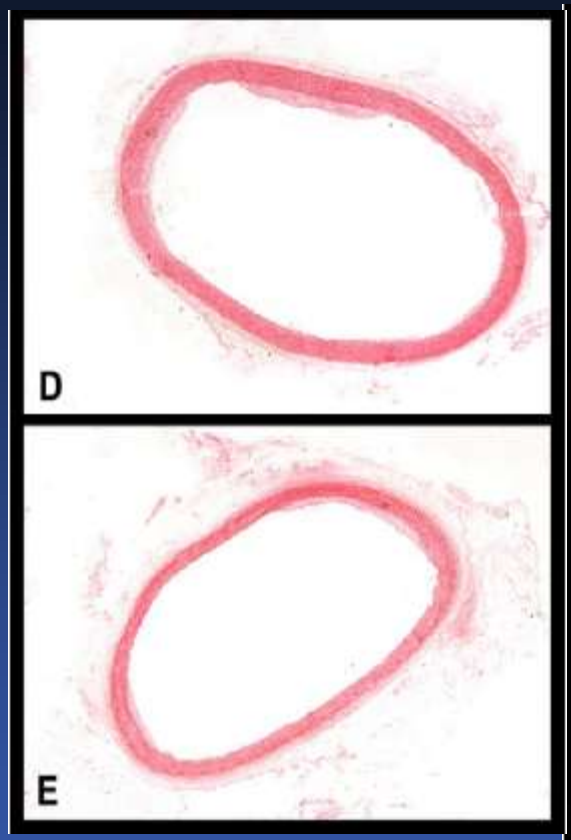
TCFA with previous ruptures

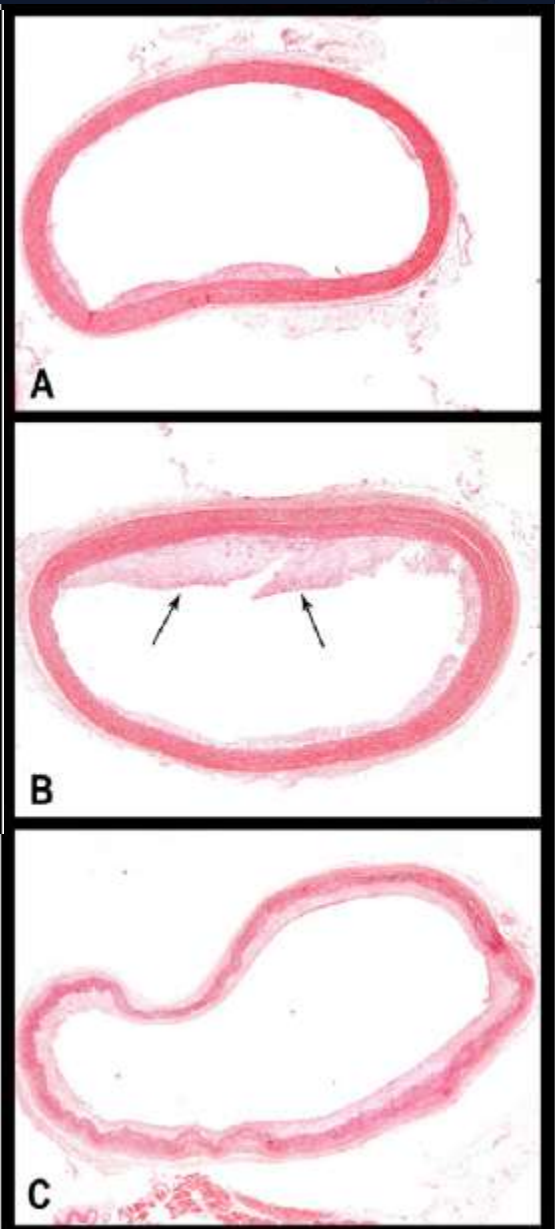
Fibrocalcific

Sangiorgi GM et al, Cath Cardiov Interv 70:203–210 (2007)

Microwave Radiometry



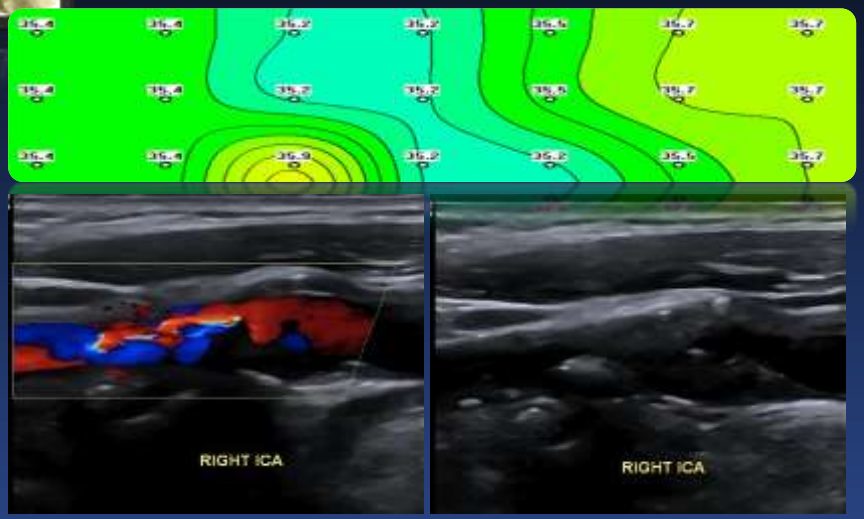




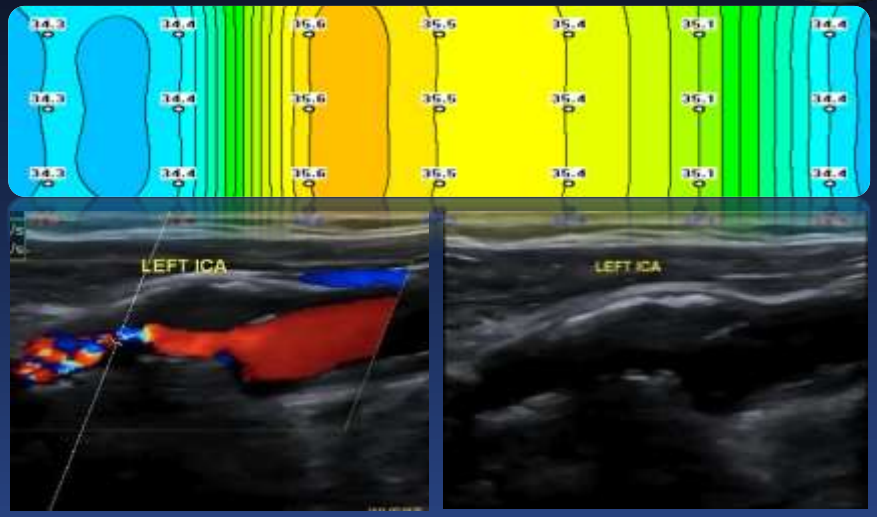
Detection of thermal heterogeneity in atheromatic rabbit aortas

Toutouzas K et al., Atherosclerosis 215 (2011) 82–89

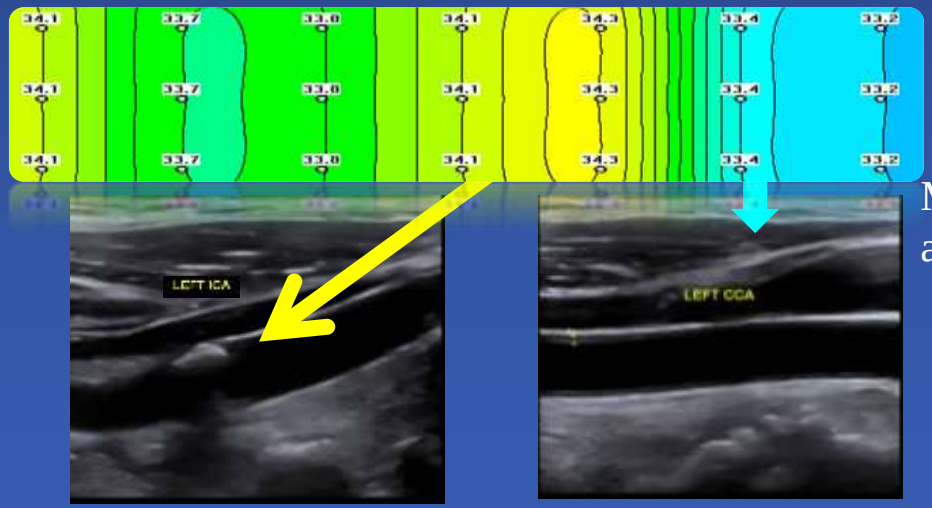
Carotid plaque morphology and inflammation



Calcified plaque with 85% stenosis ΔT:0,5°C



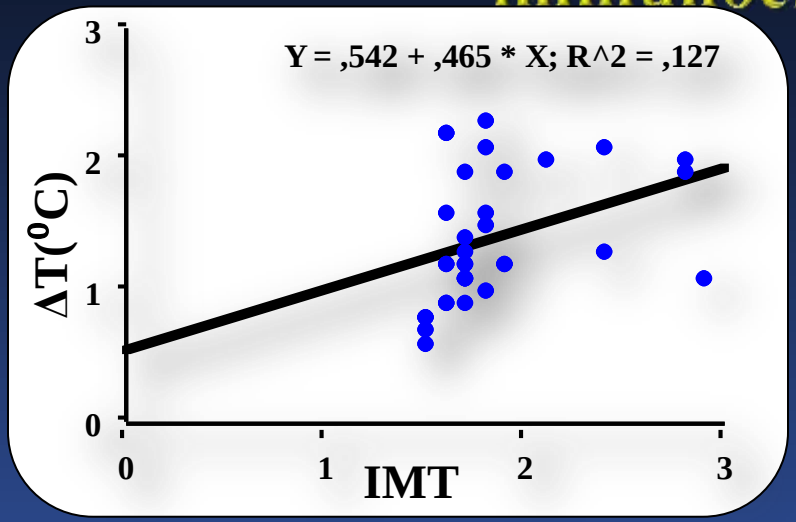
Fatty plaque with low echogenicity, causing 80% stenosis at the right carotid artery. ΔT : 1,3°C

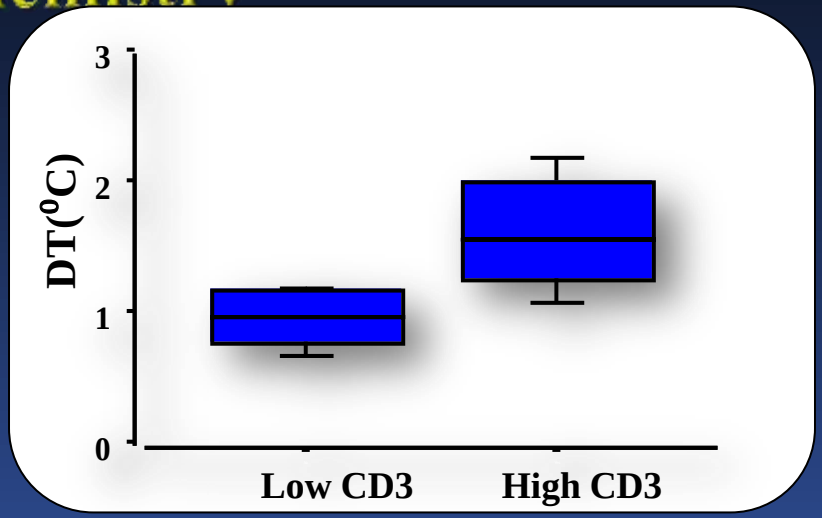


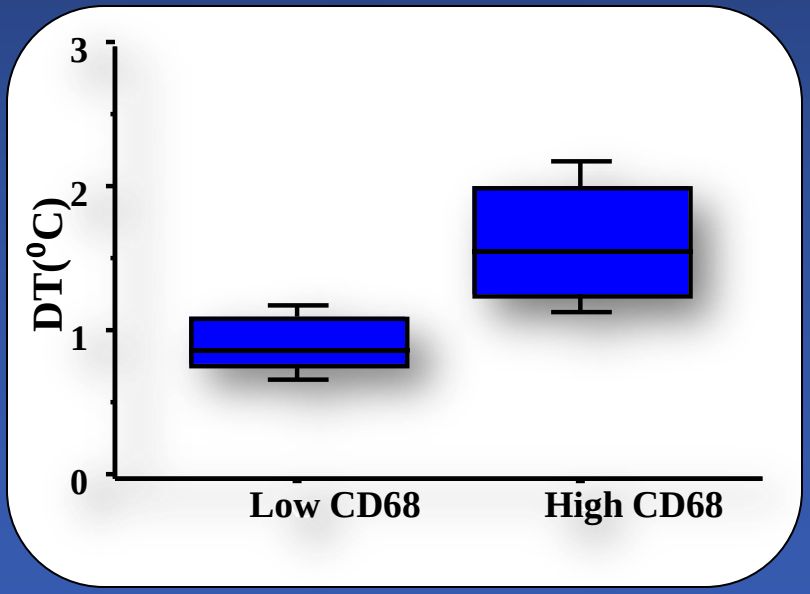
Mixed atheromatic plaque causing 75-80% stenosis at the left carotid artery. ΔT : 1,2°C.

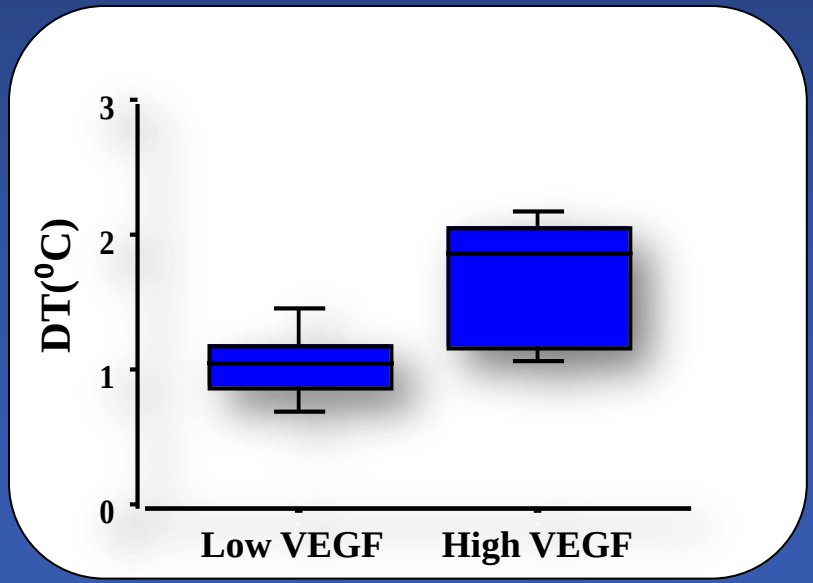
Toutouzas K et al, submitted

Microwave radiometry at human carotid arteries: Correlation with IMT and immunochemistry



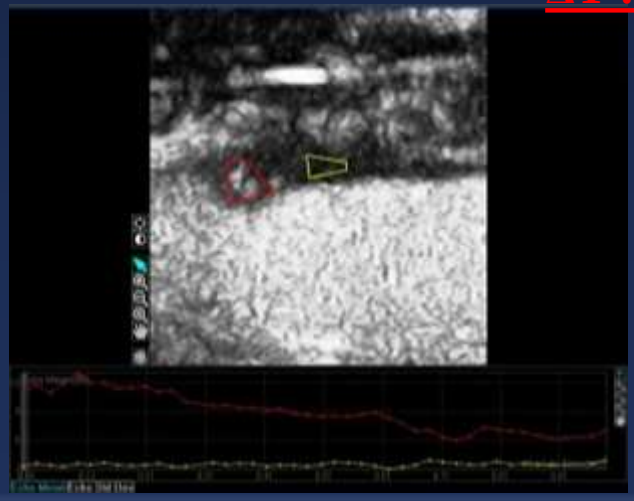




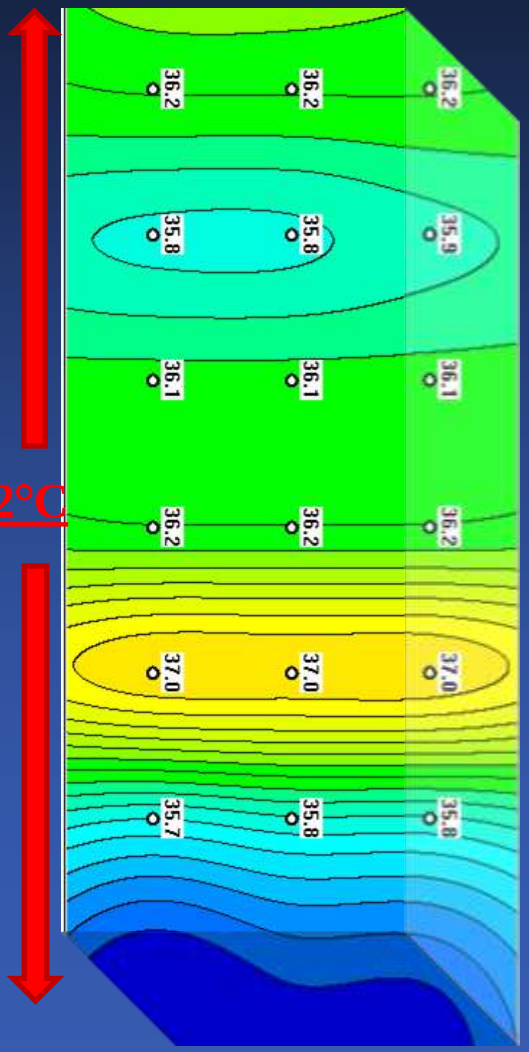


Toutouzas K et al, submitted

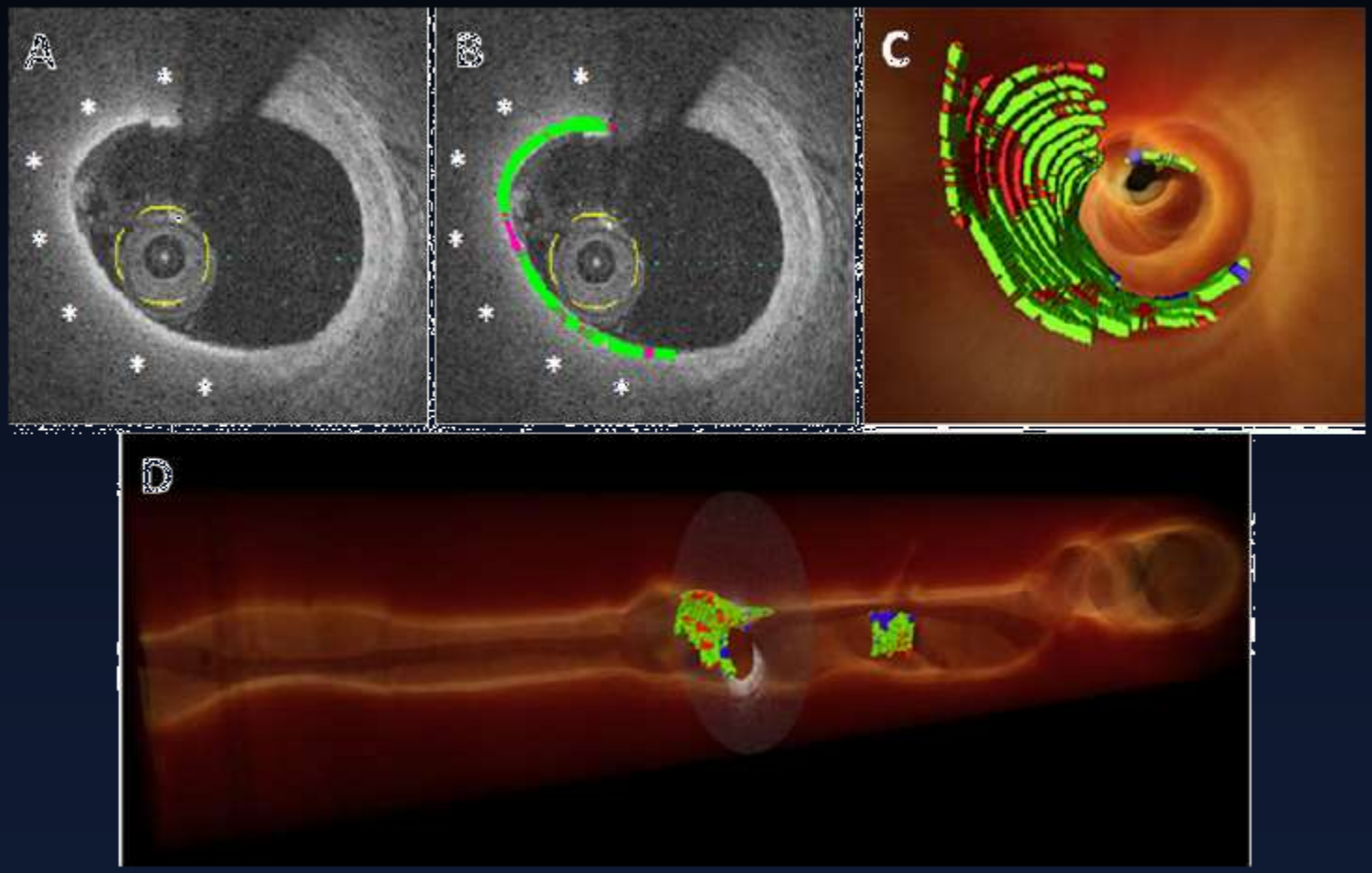
Prognostic value of carotid thermal heterogeneity



ΔT : 1,2°C



Volumetric assessment of TCFA

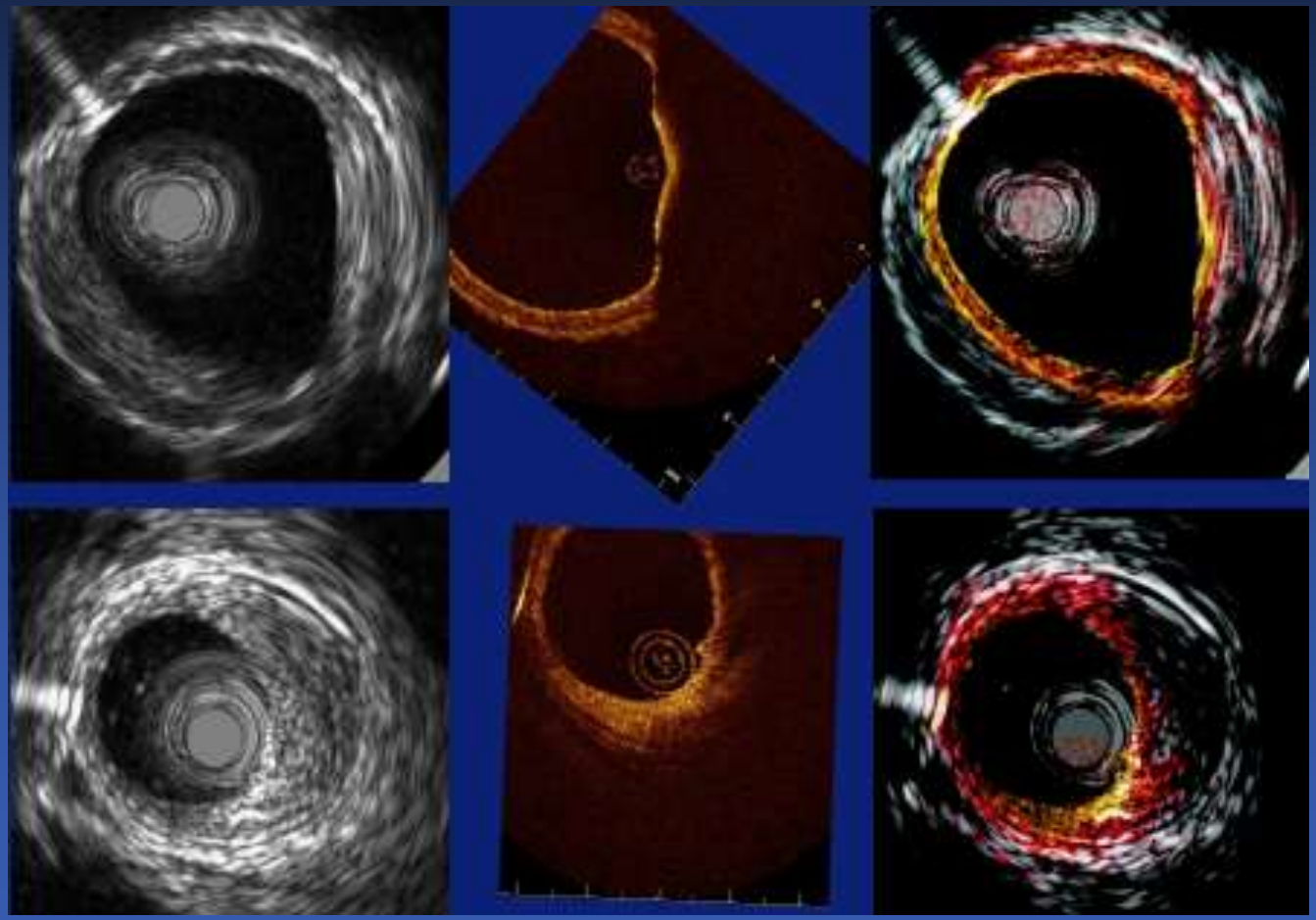


3D reconstruction for measurement of the area of the thin fibrous cap

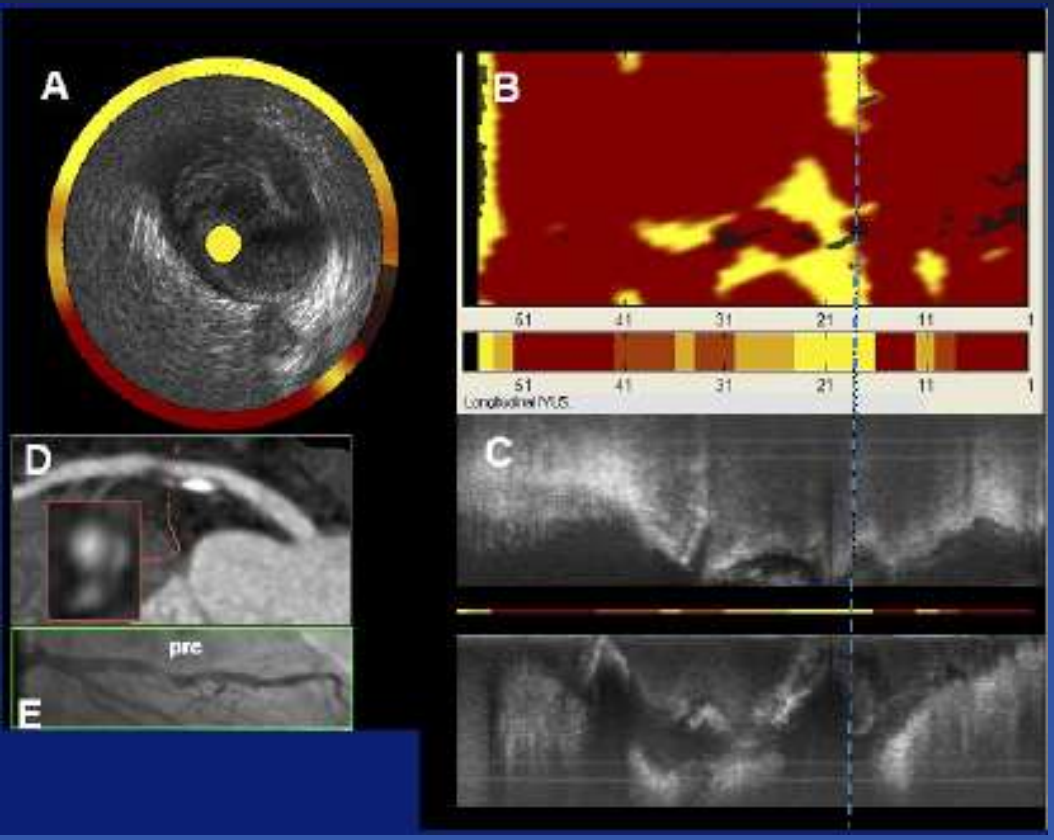
Chamie D et al, Curr Cardiovasc Imaging Rep (2011) 4:276–283

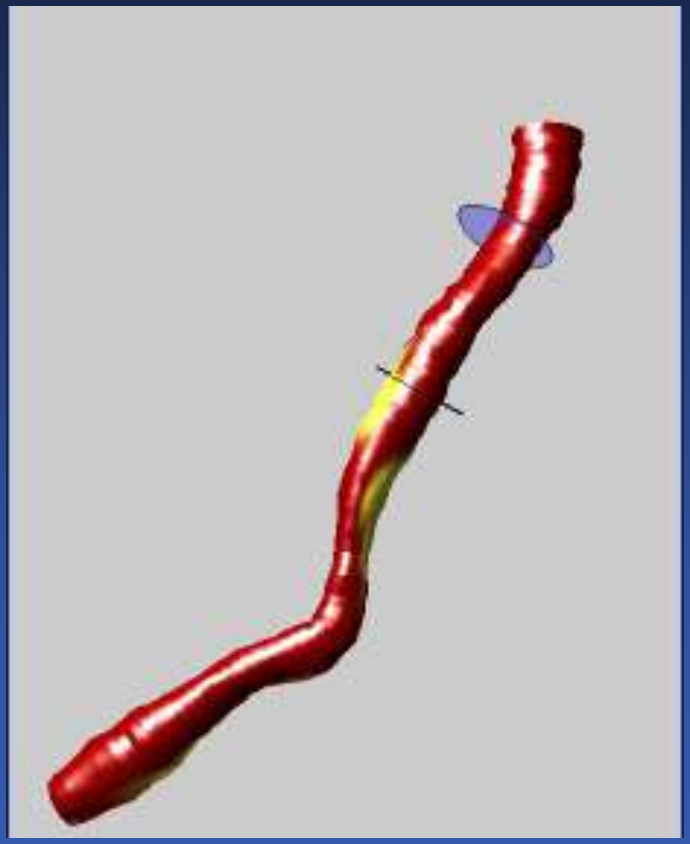
Ενσωμάτωση απεικονιστικών τεχνικών

OCT-IVUS



Συνδυασμός NIR και IVUS – Τρισδιάστατη αναπαράσταση αγγείου



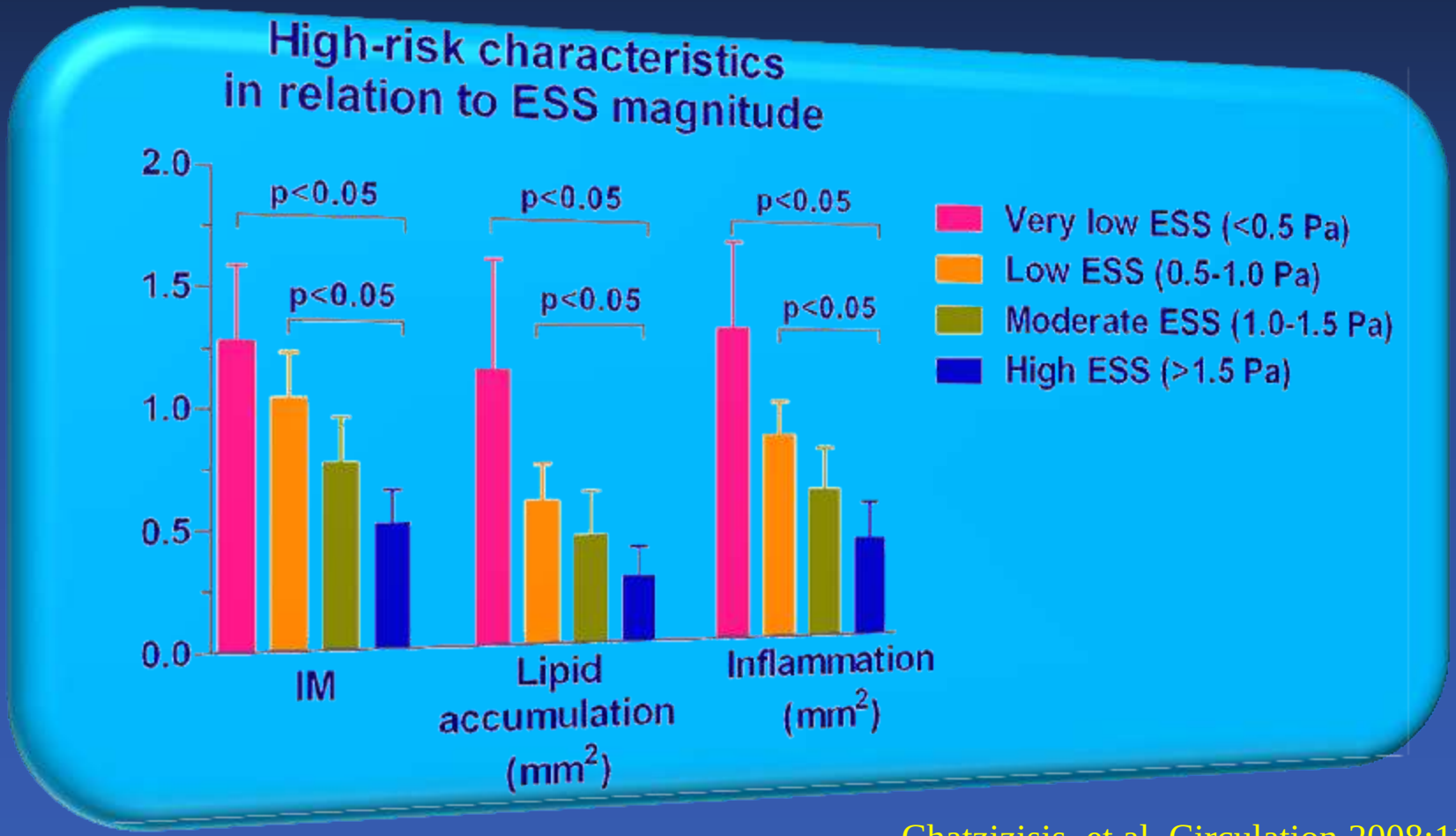


Schultz et al, JACC 2010

Wentzel et al, Circ Cardiovasc Imaging. 2010 Nov 1;3(6):e6-7

Correlation Between Magnitude of Low ESS and Severity of CAD

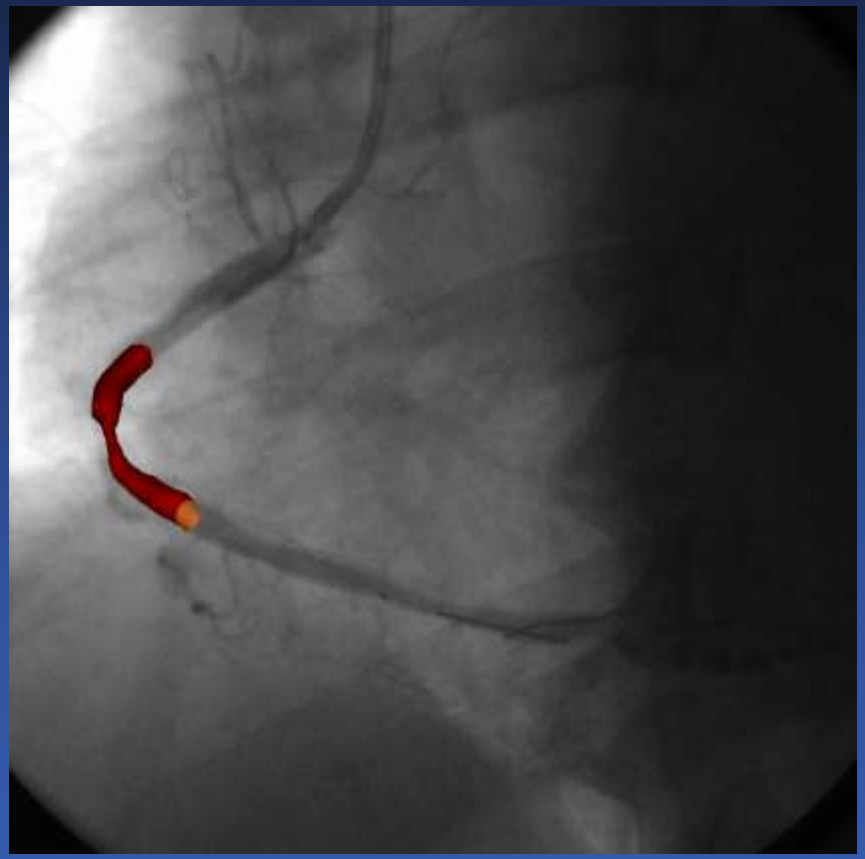
"Dose-Response" Relationship between Magnitude of Low ESS And Severity of Plaque Pathology

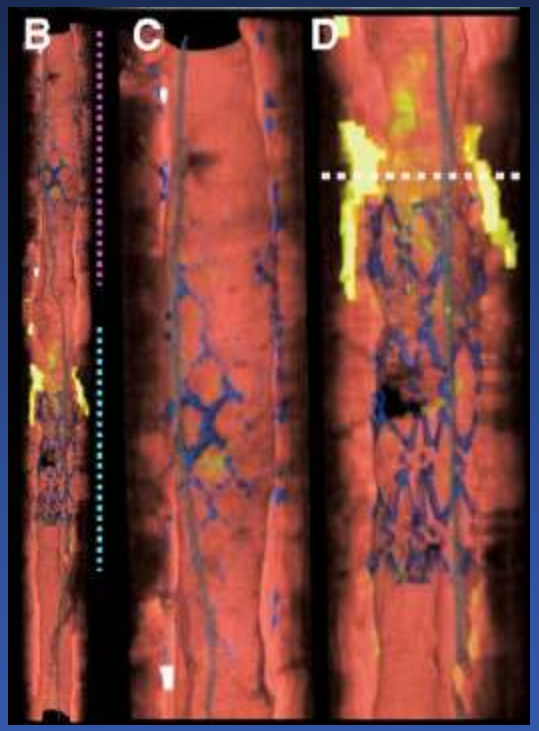


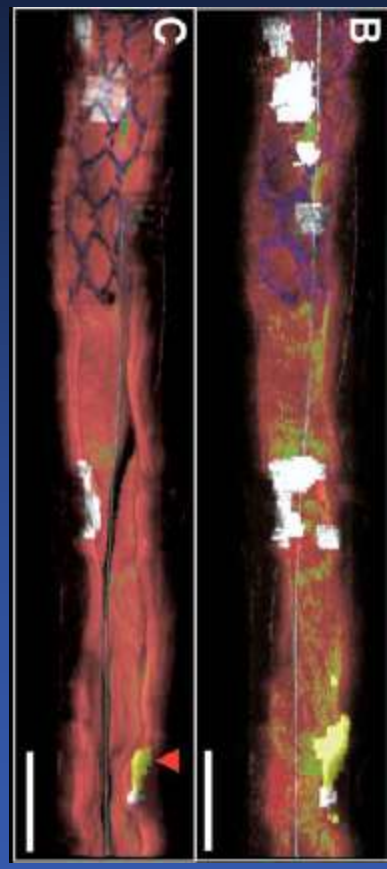
Chatzizisis, et al. Circulation 2008;117:993

New advances in imaging

Τρισδιάστατη απεικόνιση με OCT







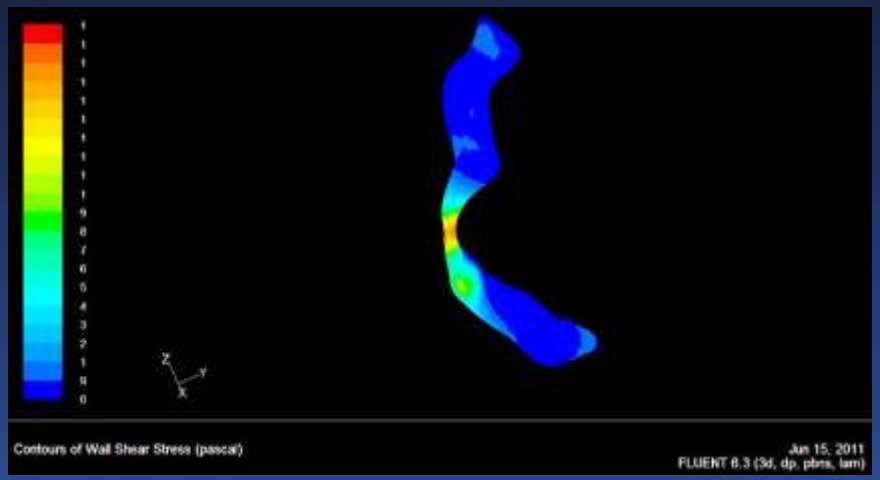
Tearney et al,
J. Am. Coll. Cardiol. Img. 2008;1;752-761

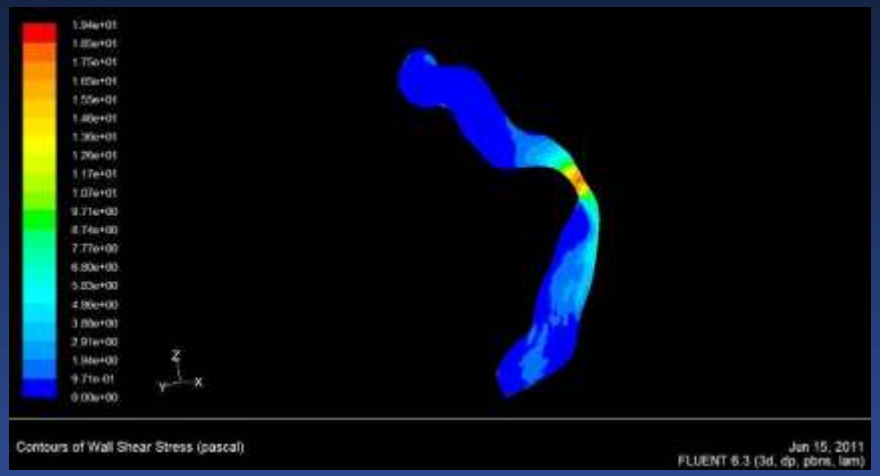
3D OCT

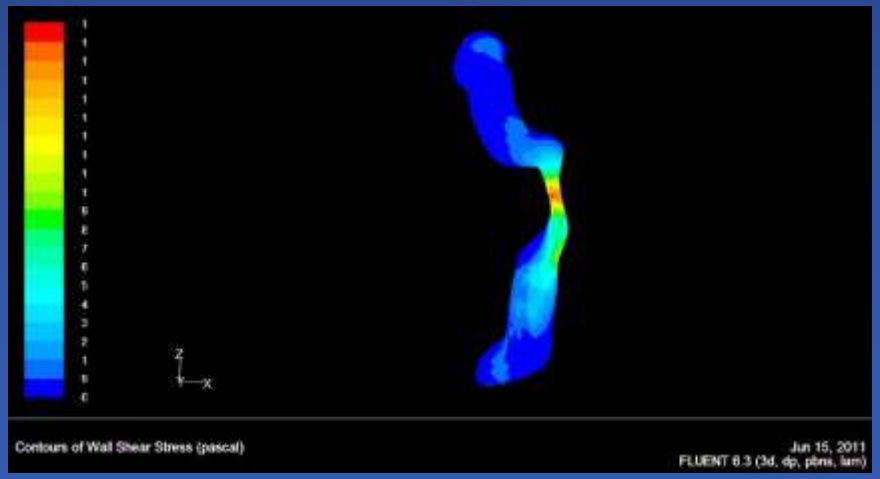
Fusion of Angiography and OCT

3D Reconstructed RCA

Shear Stress Map of the Reconstructed RCA



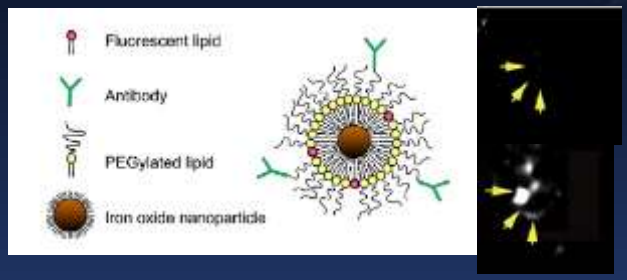




Future tools for imaging

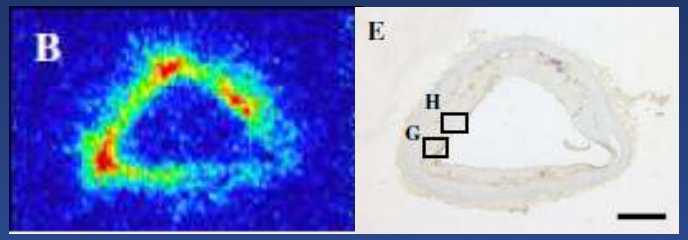
Iron oxide particles targeted to oxidation-specific epitopes for enhancement of MRI imaging

Briley-Saebo KC et al. J Am Coll Cardiol 2011;57:337–47



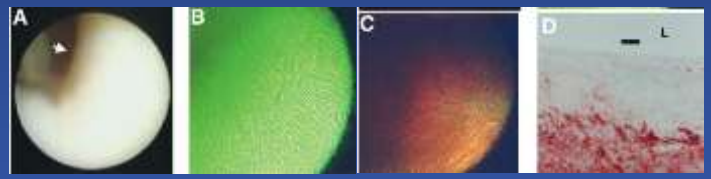
99mTc-labelled anti-MMP abs for imaging atherosclerosis

Kuge Y et al, Eur J Nucl Med Mol Imaging (2010) 37:2093–2104



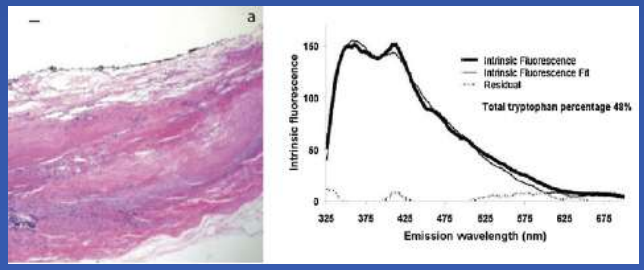
Color fluorescent angioscopy for oxidized LDL imaging

Uchida Y et al, J Am Coll Cardiol Img 2010;3:398–408



Fluorescent spectroscopy for detection of superficial proteoglycans and foam cells

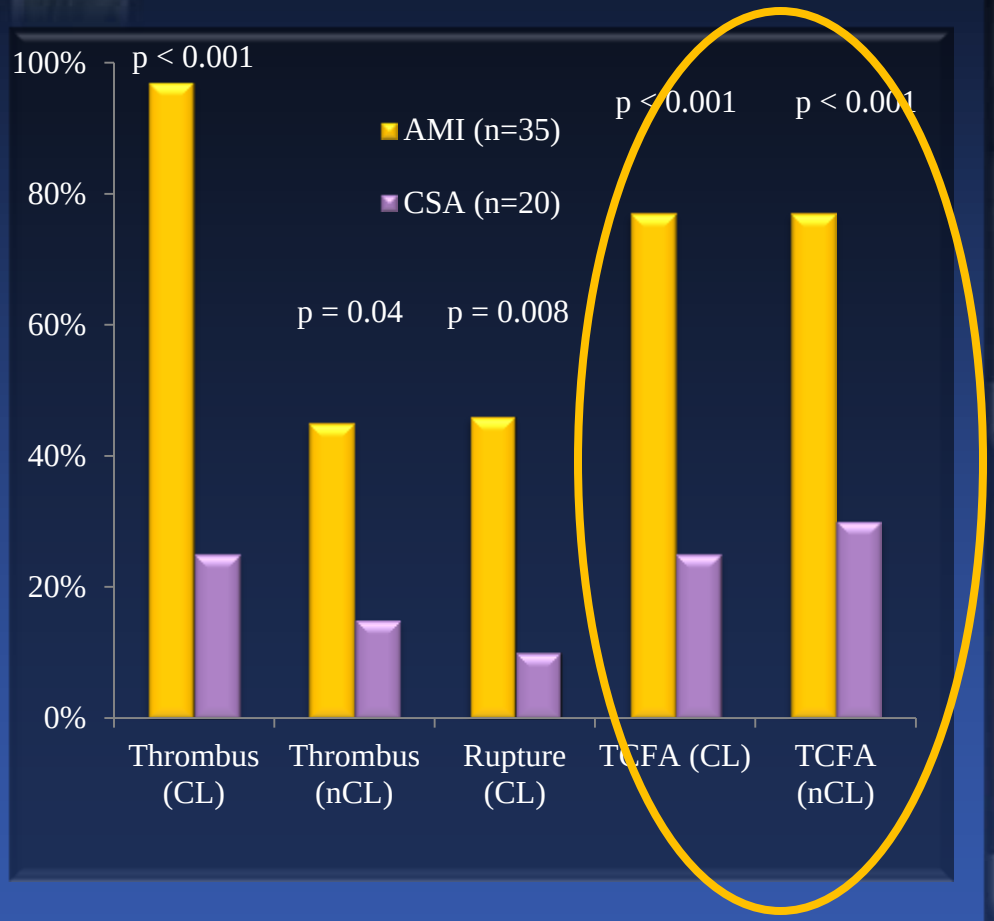
Angheloiou GO et al, Atherosclerosis (2011), doi:10.1016/j.atherosclerosis.2010.11.020



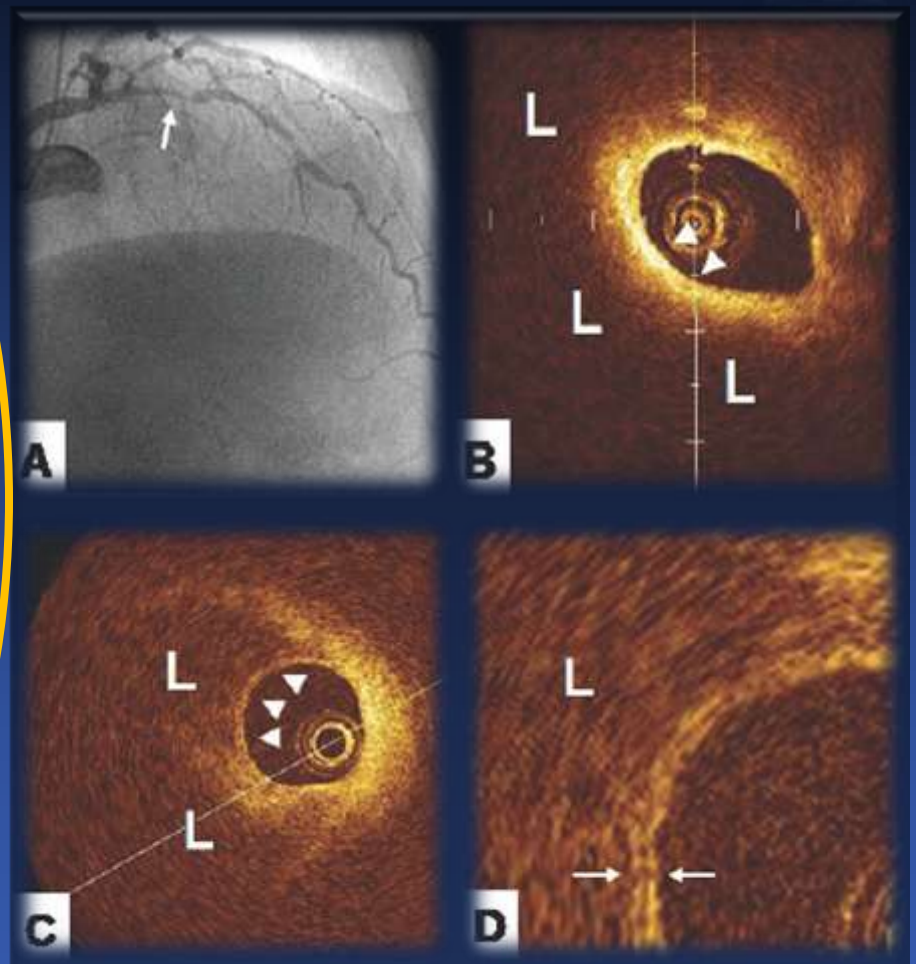
Vulnerable plaque

- From ruptured plaque to vulnerable plaque
- Tools for VP imaging
- Research applications of VP imaging
- Clinical perspective of VP imaging
- Potential for treatment

TCFA in SA vs AMI



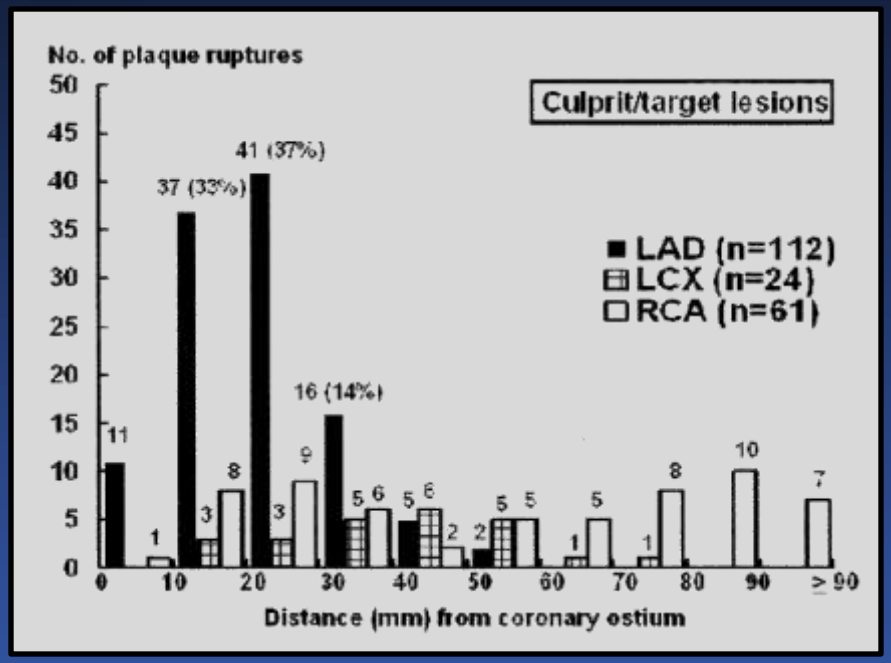
Patients with AMI present more often with thrombus and TCFA in CL and nCL and ruptured plaques in CL

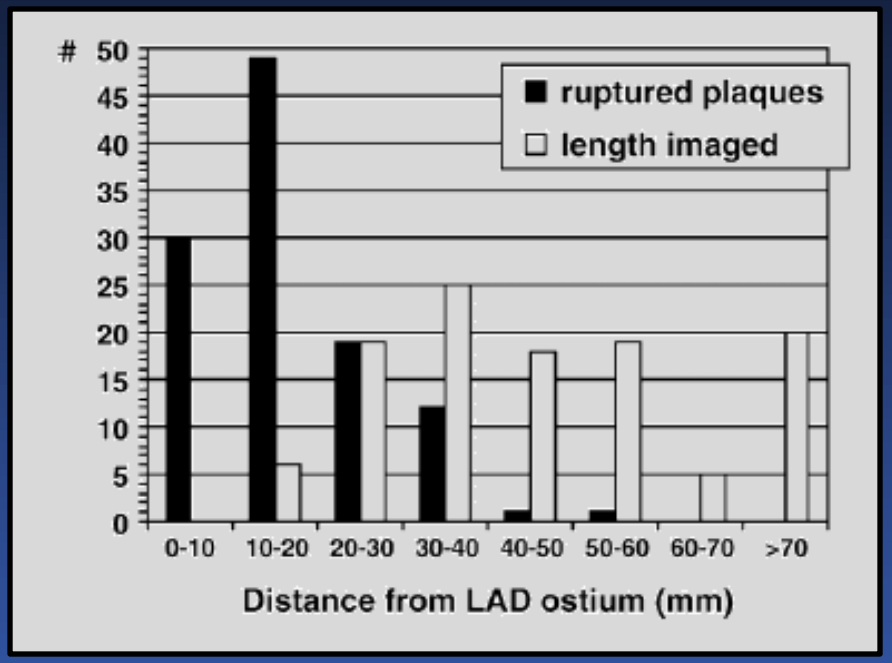


OCT examination of CL (A,B) and nCL (C,D) of patient with SA reveal TCFA

Fujii et al, JACC 2008

Increased incidence of IVUS-detected plaque rupture in proximal lesions





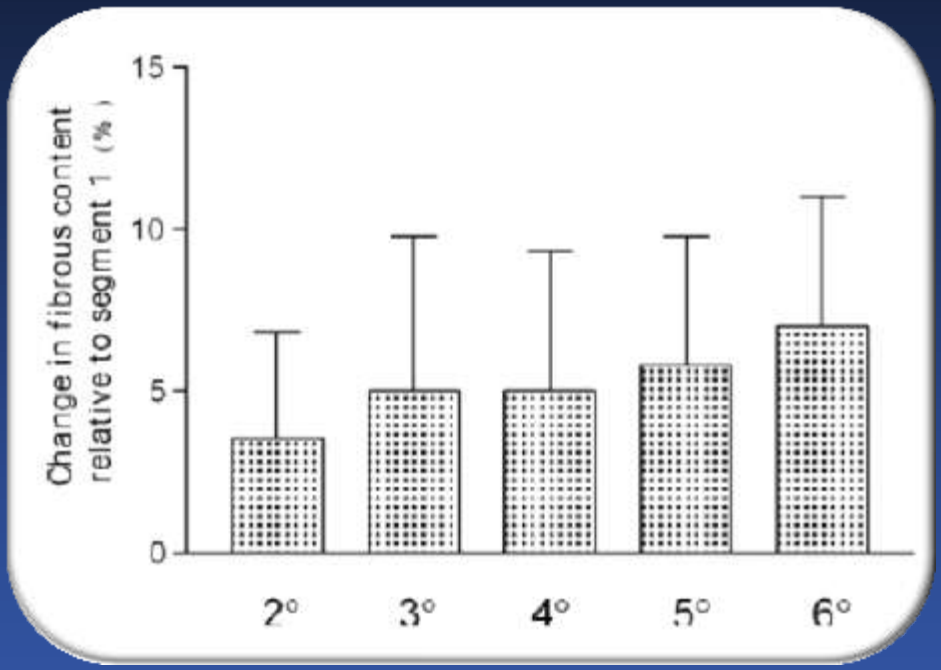
The majority of 197 plaque ruptures of the culprit lesion of patients with ACS/SA was located in proximal segments, especially in the case of LAD

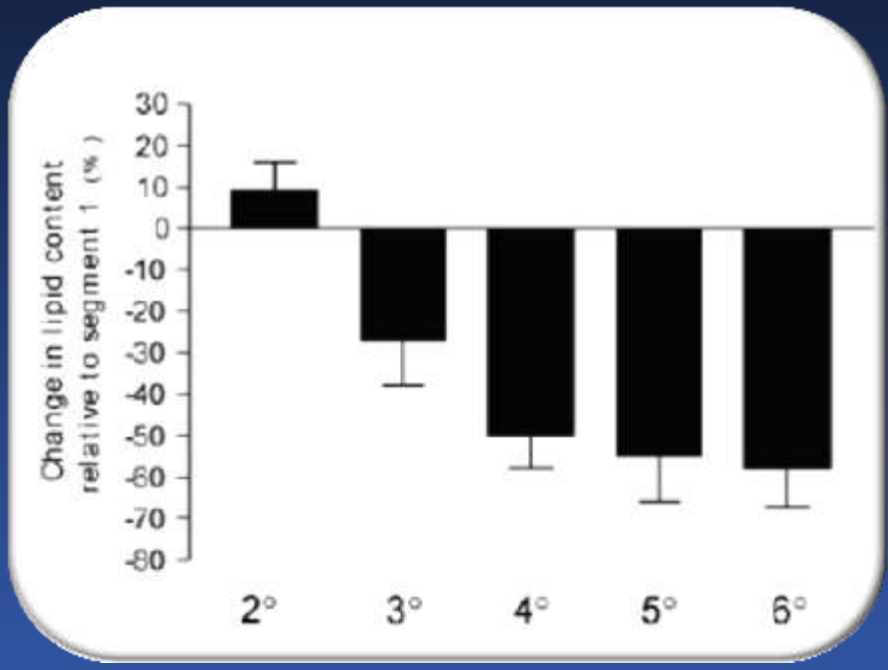
88% of 160 plaque ruptures in the LAD were located in the first 30 mm.

Hong MK. et al, J Am Coll Cardiol 2005;46:261–5

Pregowski J. et al, Am Heart J 2006; 151:898-901

Change in plaque composition with respect to the distance from the ostium

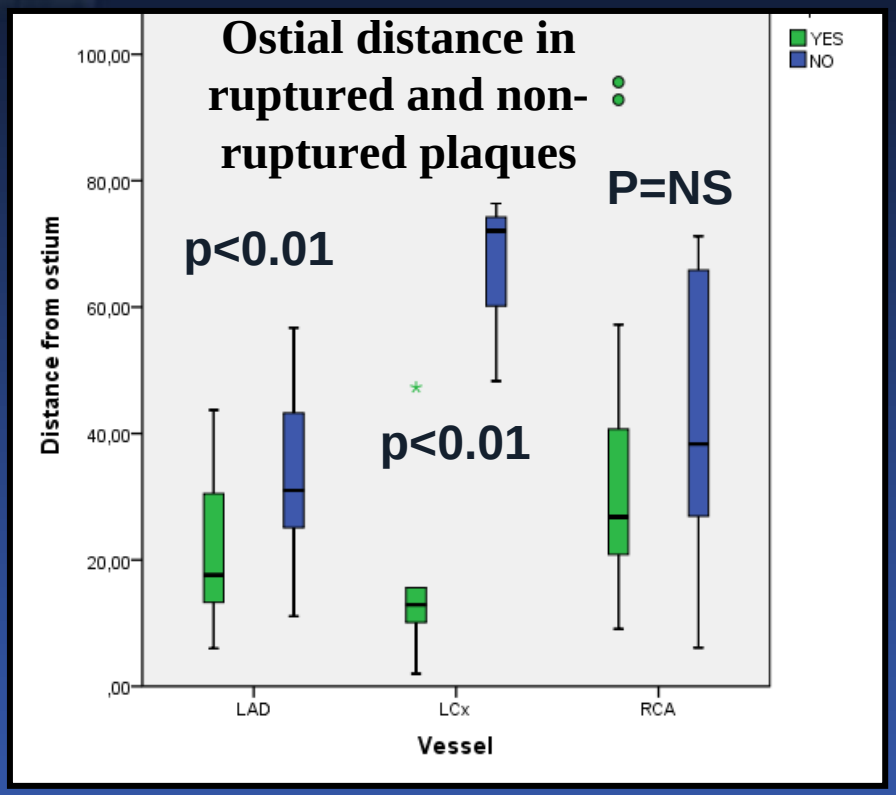


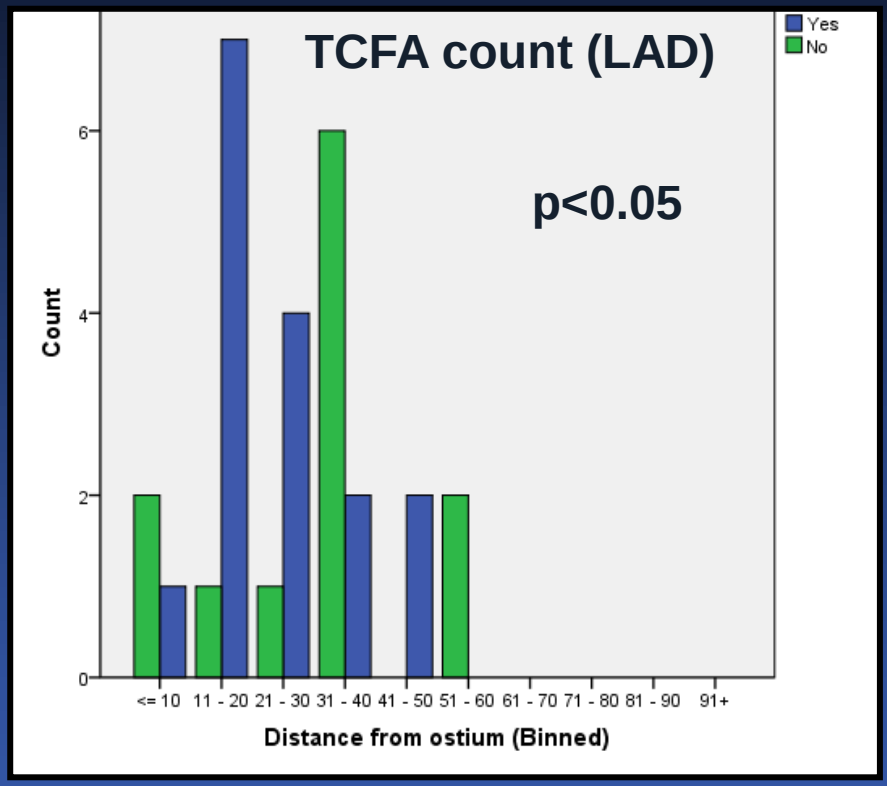


A study with IVUS-VH revealed that distal lesions were characterized by increased fibrous content and decreased lipid content

Vaglimigli M. et al, European Heart Journal (2006) 27, 655–663

Spatial distribution of rupture and TCFA by OCT



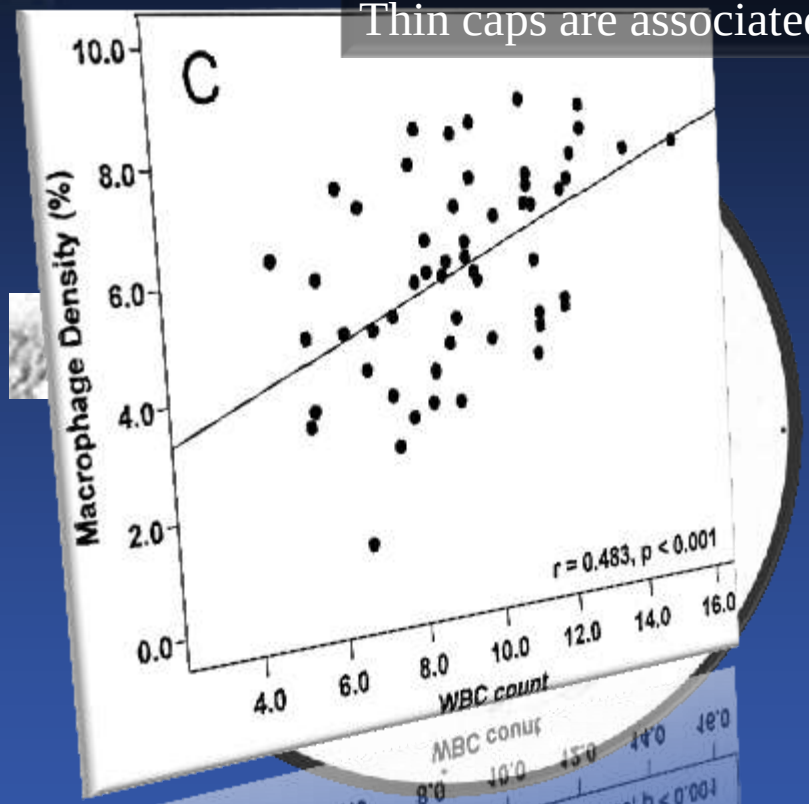


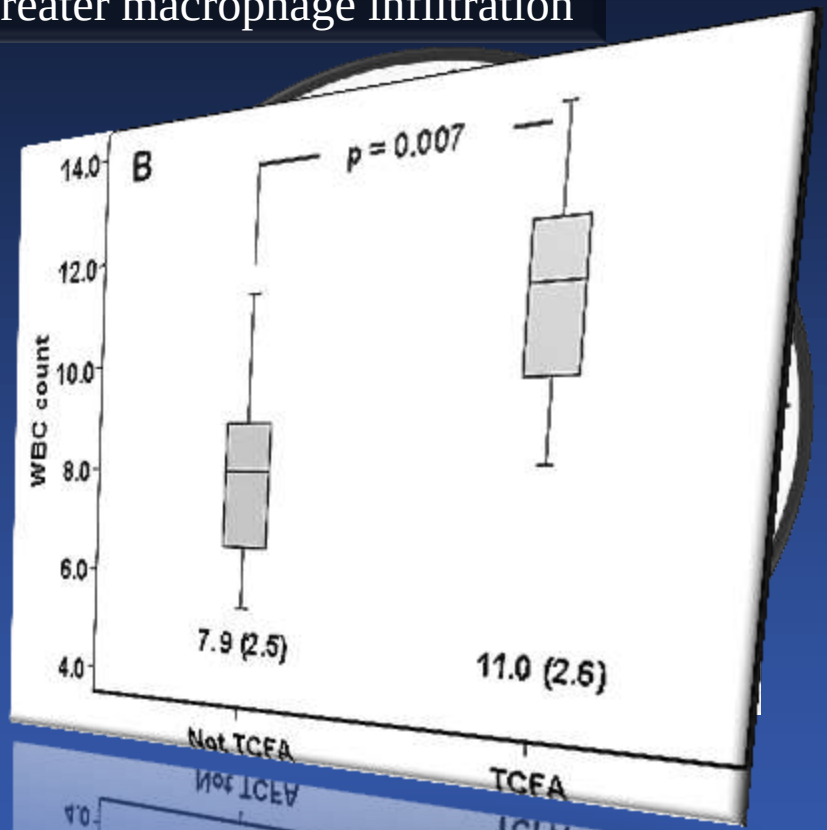
Difference in the morphological characteristics of distal and proximal culprit lesions in ACS

Toutouzas K et al, AHA 2011

OCT - Inflammation

Thin caps are associated with greater macrophage infiltration





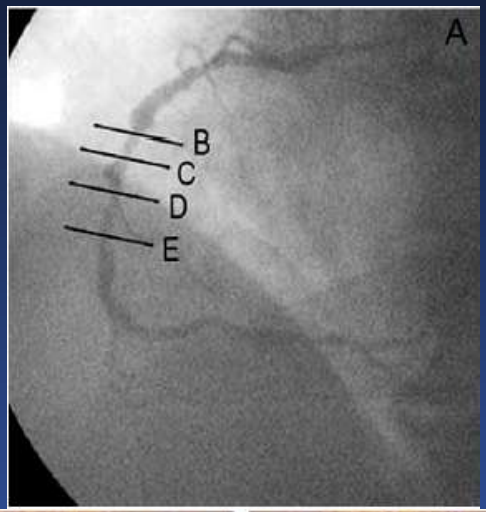
Patients with CL that present with TCFA or thin caps with great macrophage infiltration have greater WBC count

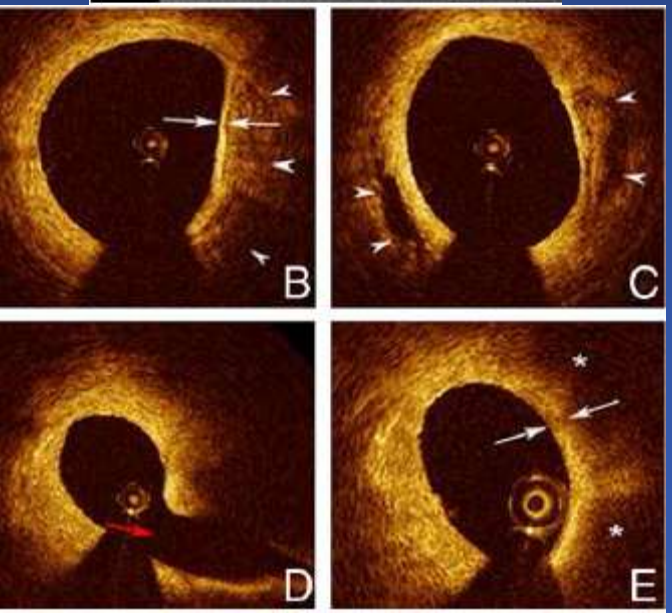
Cap thickness:43 µm
NSD (macrophage density): 6%
White Blood Cells: 9K

Cap thickness: > 500 µm
NSD (macrophage density) : 3%
White Blood Cells: 5,4K

Raffel, O. C. et al. Arterioscler Thromb Vasc Biol 2007

Relationship of plaque morphology with serum biomarkers in ACS and SA



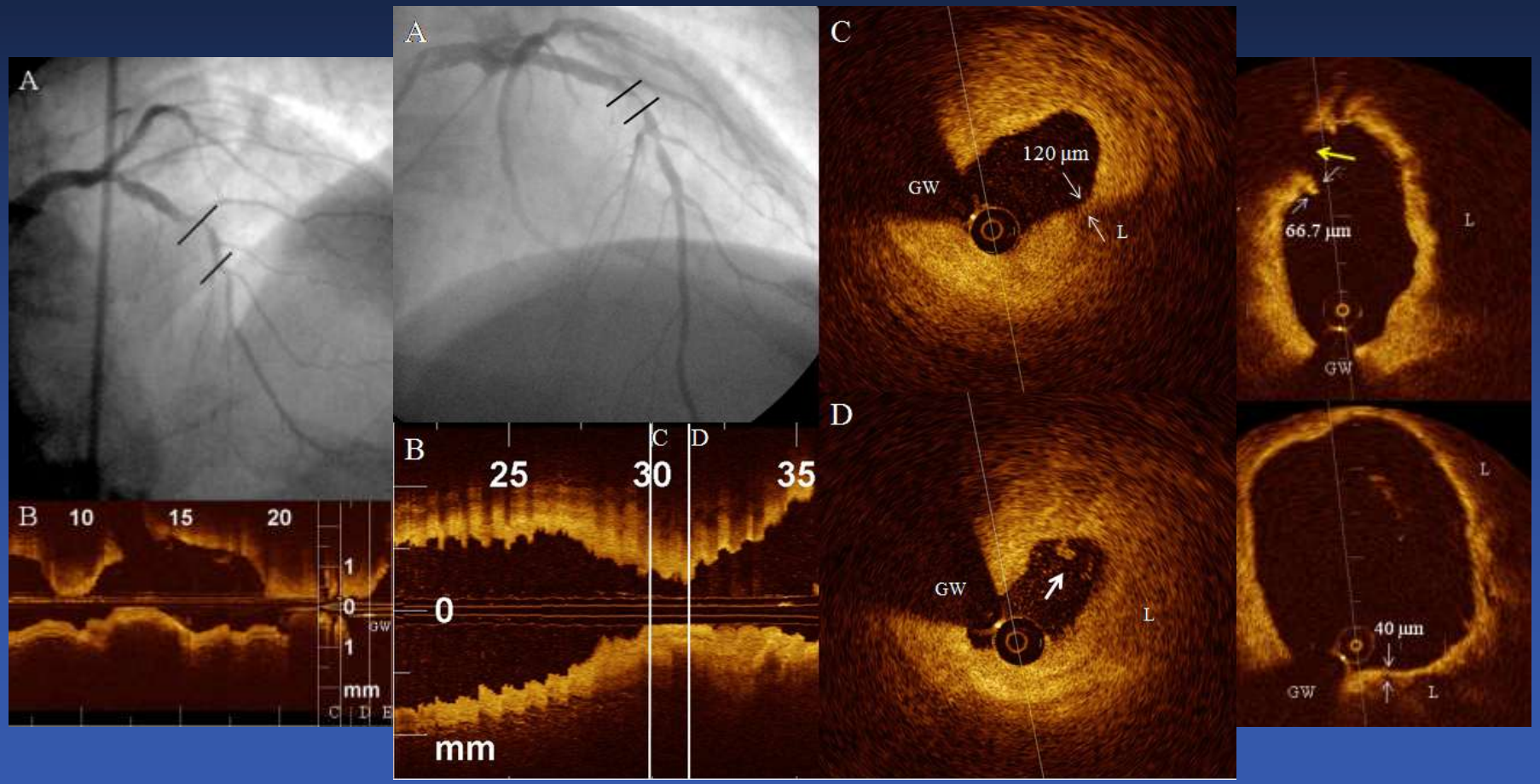


		Number n = 42	hs-CRP (mg/L)	p value	IL-18 (pg/ml)	p value
TCFA	Yes	28	15.2 (0.5–70.4)	0.004	209.0 (123.0–370.0)	0.03
	No	14	1.6 (0.7–63.6)		153.2 (99.4–259.0)	
RUPTURE	Yes	24	19.2 (0.5–70.4)	<0.001	219.5 (143.0–370.0)	0.001
	No	18	1.6 (0.7–17.8)		127.5 (99.4–259.0)	
THROMBUS	Yes	17	10.1 (0.5–54.8)	0.3	216.0 (143.0–306.0)	0.1
	No	25	2.9 (0.7–70.4)		193.0 (99.4–370.0)	
CALCIUM	Yes	22	6.0 (0.7–33.7)	0.2	132.0 (99.4–370.0)	0.002
	No	20	12.5 (0.5–70.4)		216.0 (164.0–306.0)	

Increased levels of CRP and IL-18 in SA and ACS patients with TCFA and rupture

Bouki et al, Int J Cardiol 2010

Vulnerable plaque characteristics are associated with thrombolysis failure

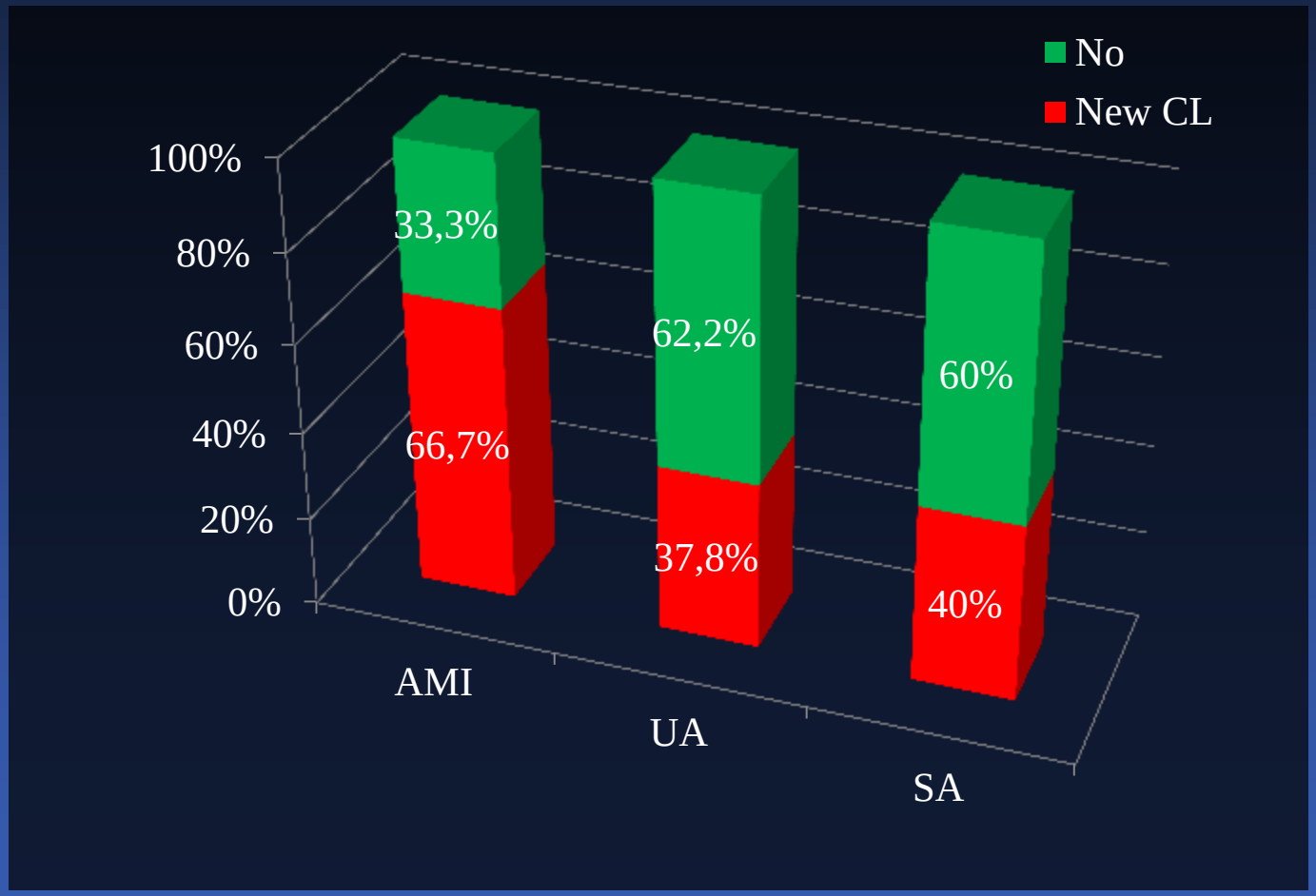


Toutouzas K, Tsiamis E, Karanasos A, Drakopoulou M, Synetos A, Tsioufis C, Tousoulis D, Davlouros P, Alexopoulos D, Bouki K, Apostolou T, Stefanadis C. JACC Cardiovasc Interv. 2010 May;3(5):507-14

Vulnerable plaque

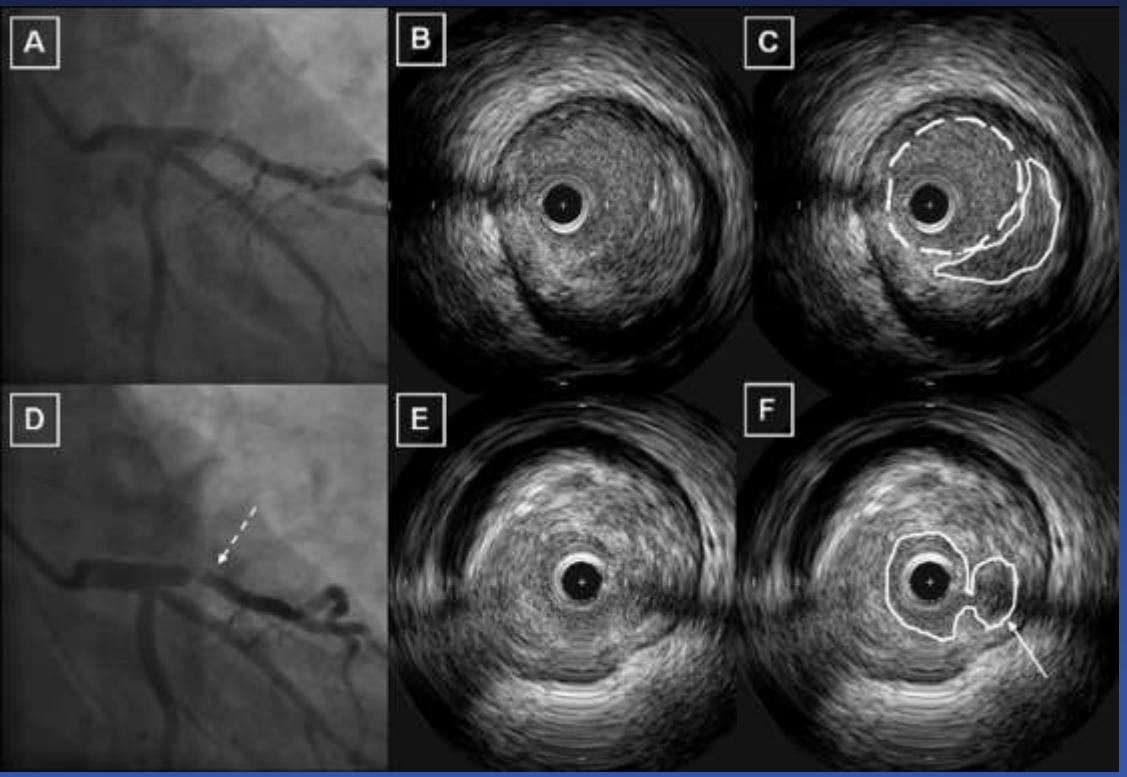
- From ruptured plaque to vulnerable plaque
- Tools for VP imaging
- Research applications of VP imaging
- Clinical perspective of VP imaging
- Potential for treatment

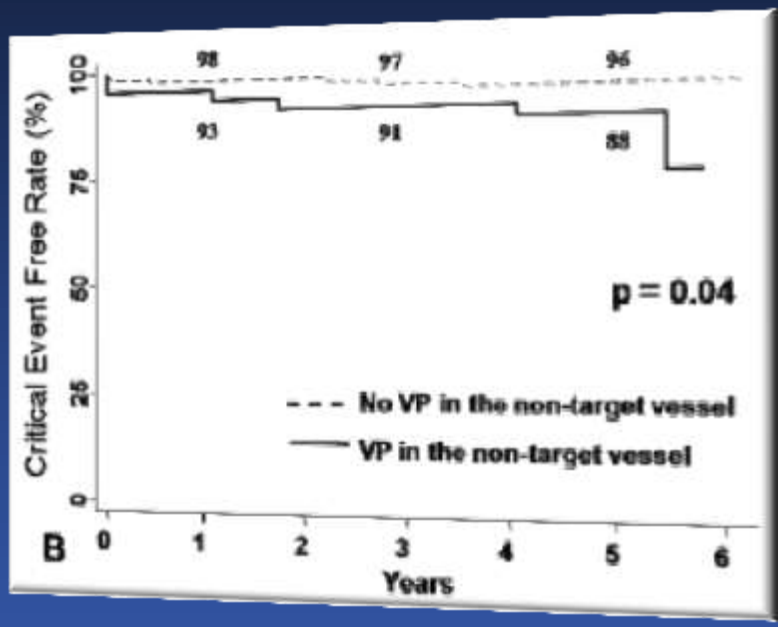
MI patients develop a new culprit lesion more often!



Tsiamis E, Toutouzas K et al, Int J Cardiol 2009

Plaques with "vulnerable" morphology associated with adverse outcomes

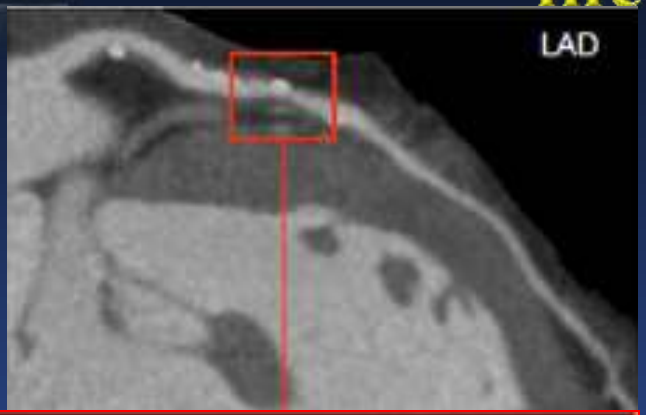


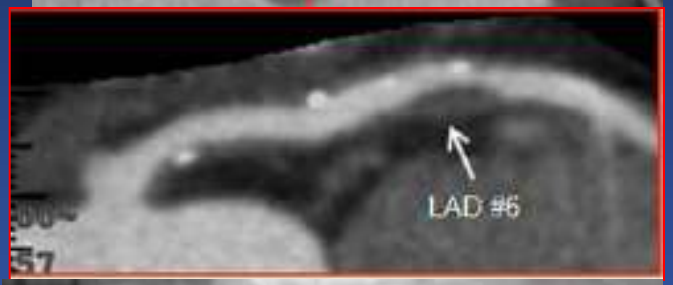


The multiplicity of vulnerable plaque in the nontarget vessels was the only indepedent predictor of long-term critical events (HR 2.2, 95% CI 1.4 to 3.4, p <0.001).

Kim SH et al , Am J Cardiol 2009;103:1221–1226

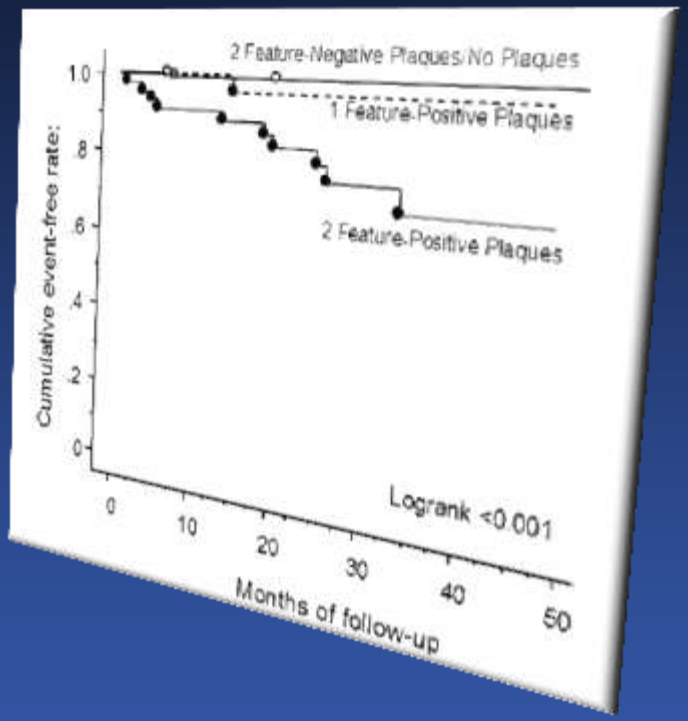
Presence of positive remodelling and low-attenuation plaque associated with increased MACE





LAP with PR

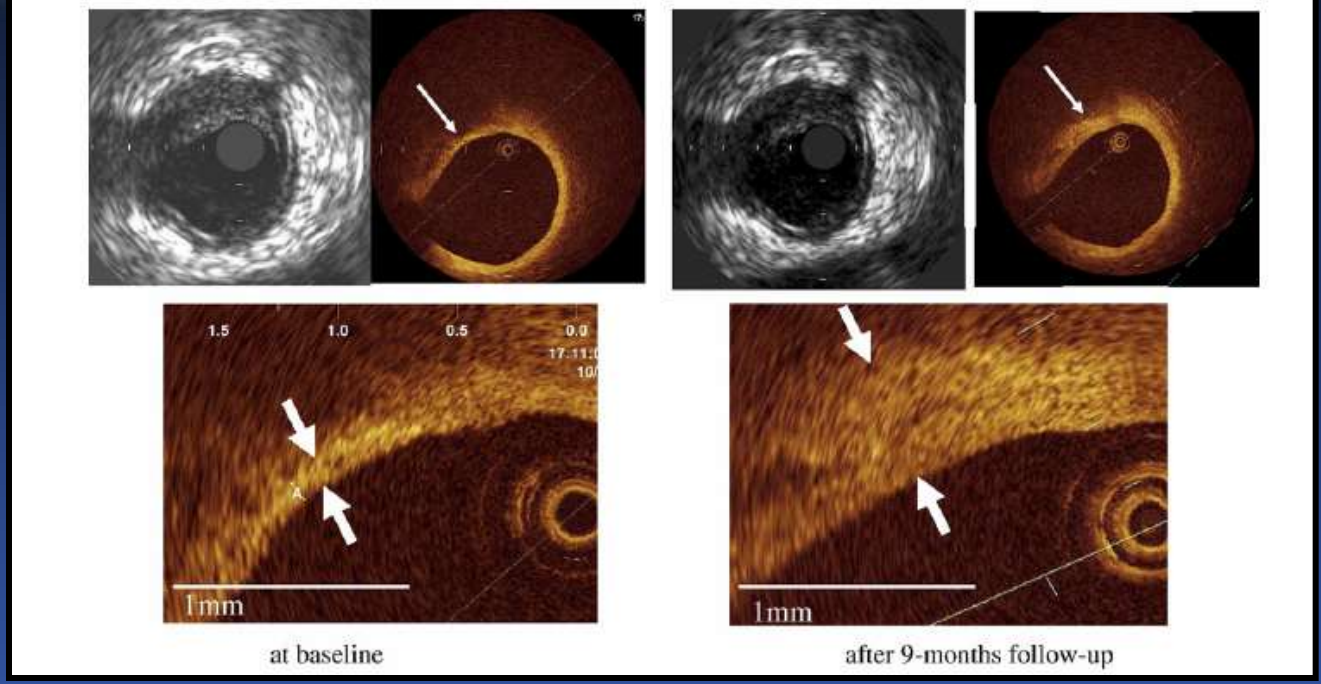
AMI 6m



ACS was independently predicted by PR and/or LAP (hazard ratio: 22.8, 95% confidence interval: 6.9 to 75.2, p <0.001)

Motoyama S et al, J Am Coll Cardiol 2009;54:49–57

Evaluation of progression of non-culprit plaques in ACS



at baseline

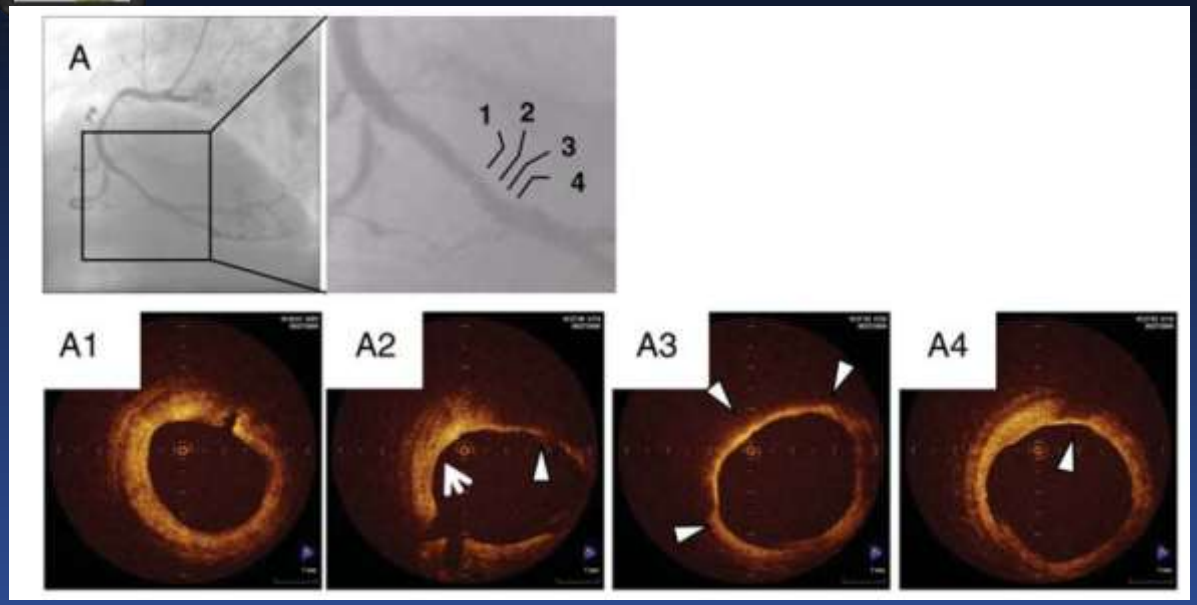
after 9-months follow-up

	Baseline	Follow-Up	Percentage Change	p Value
LDL (mg/dl)	122 ± 38	103 ± 21	−16 ± 4	<0.010
HDL (mg/dl)	44 ± 10	45 ± 11	2.0 ± 0.8	0.087
LDL/HDL	2.6 ± 0.8	2.1 ± 0.8	−12 ± 20	0.032
hs-CRP (mg/dl)	0.72 ± 2.64	0.60 ± 2.52	−16 ± 24	0.010
Total atheroma volume (mm^3)	74 ± 44	76 ± 45	3.1 ± 11	0.120
Fibrous cap thickness (μm)	95 ± 32	112 ± 45	15 ± 17	<0.001

82 patients underwent OCT & IVUS study of a non-culprit lesion in ACS at baseline and at 9 months

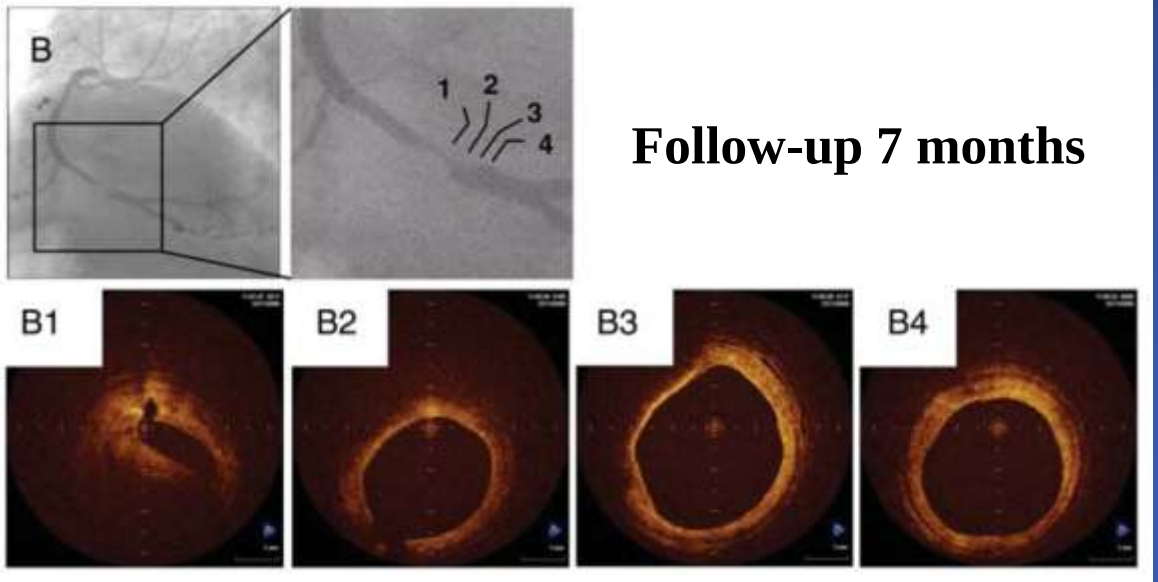
Takarada S et al., J. Am. Coll. Cardiol. Intv. 2010;3;766-772

Evaluation of progression with OCT



Plaque progression was observed more often in plaques with ‘vulnerable’ characteristics

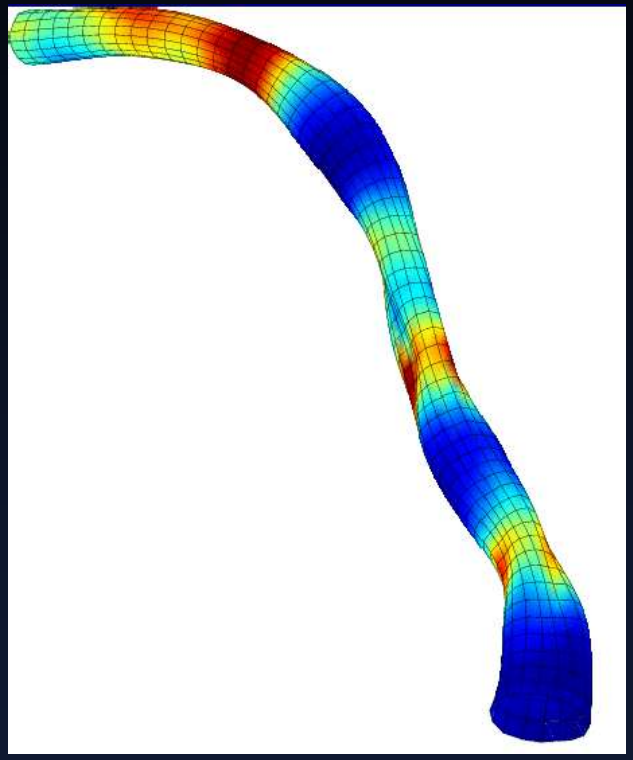
Microvessels **I** **M**
plac

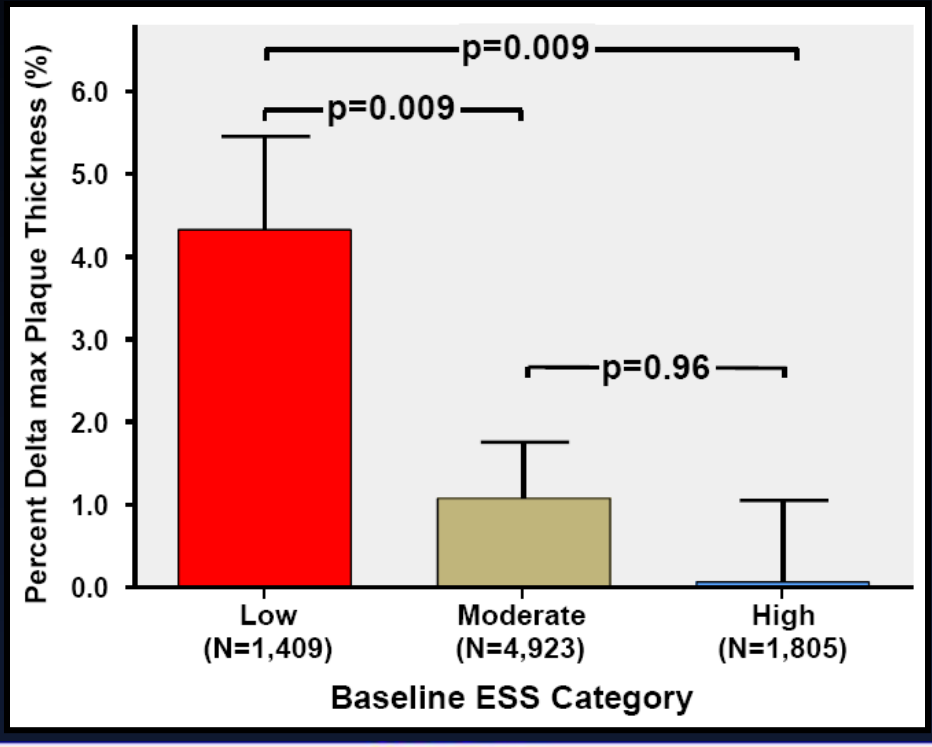


Follow-up 7 months

Uemura et al, Eur Heart J, doi:10.1093/eurheartj/ehr284

Μελέτη PREDICTION:
Συσχέτιση shear stress με μελλοντικά συμβάματα





Το χαμηλό shear stress ήταν ανεξάρτητος προγνωστικός παράγοντας για εξέλιξη βλάβης

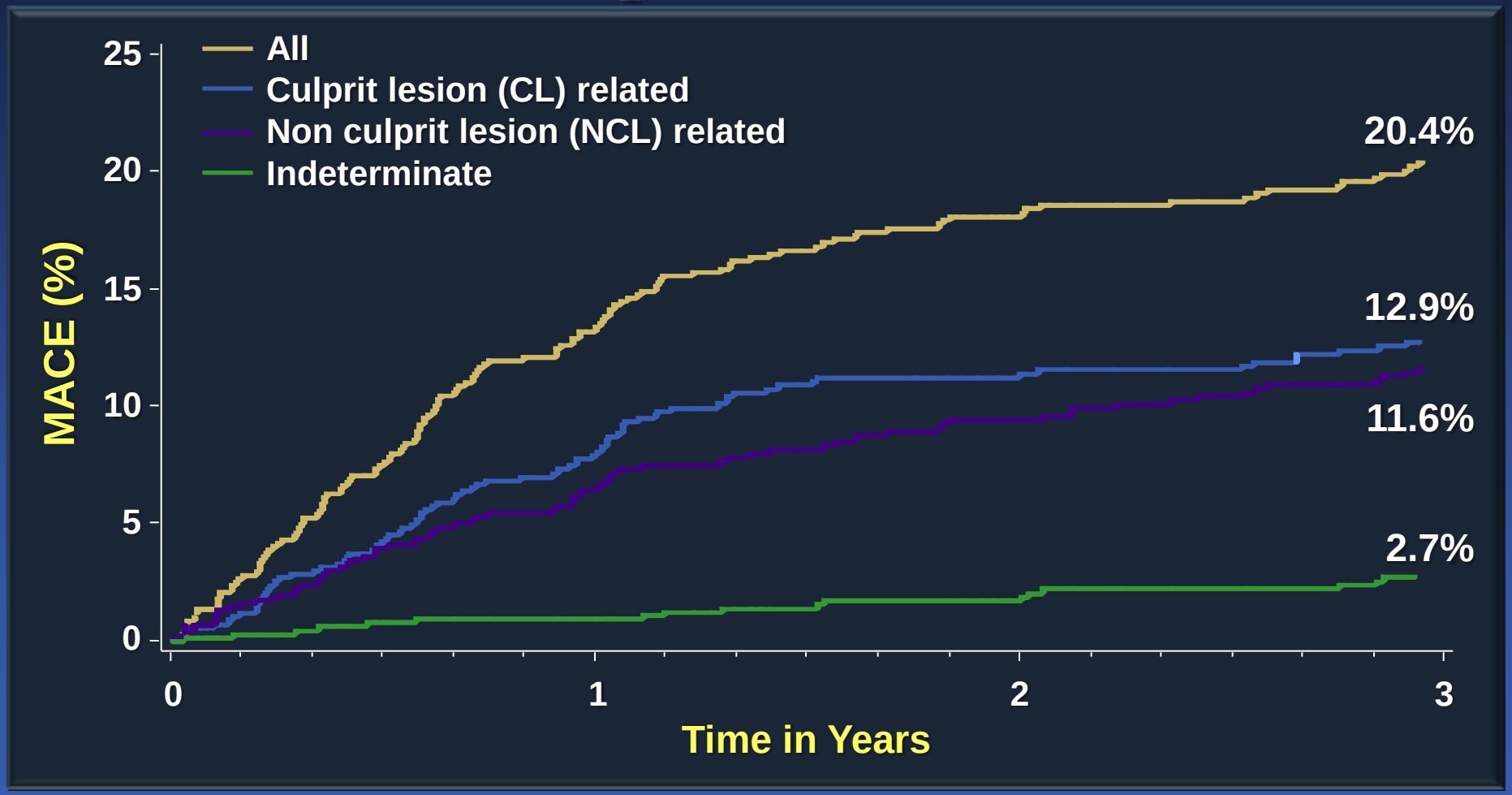
Predictor at Baseline	Odds Ratio (95% CI)	p value
Plaque Burden > 60% (at Throat)	5.26 (2.04-13.57)	0.001
Low ESS (distal to Throat)	2.64 (1.11-6.26)	0.028

1 2 5 10

Stone P, TCT 2010

PROSPECT trial:

The significance of evaluation of non-culprit lesions



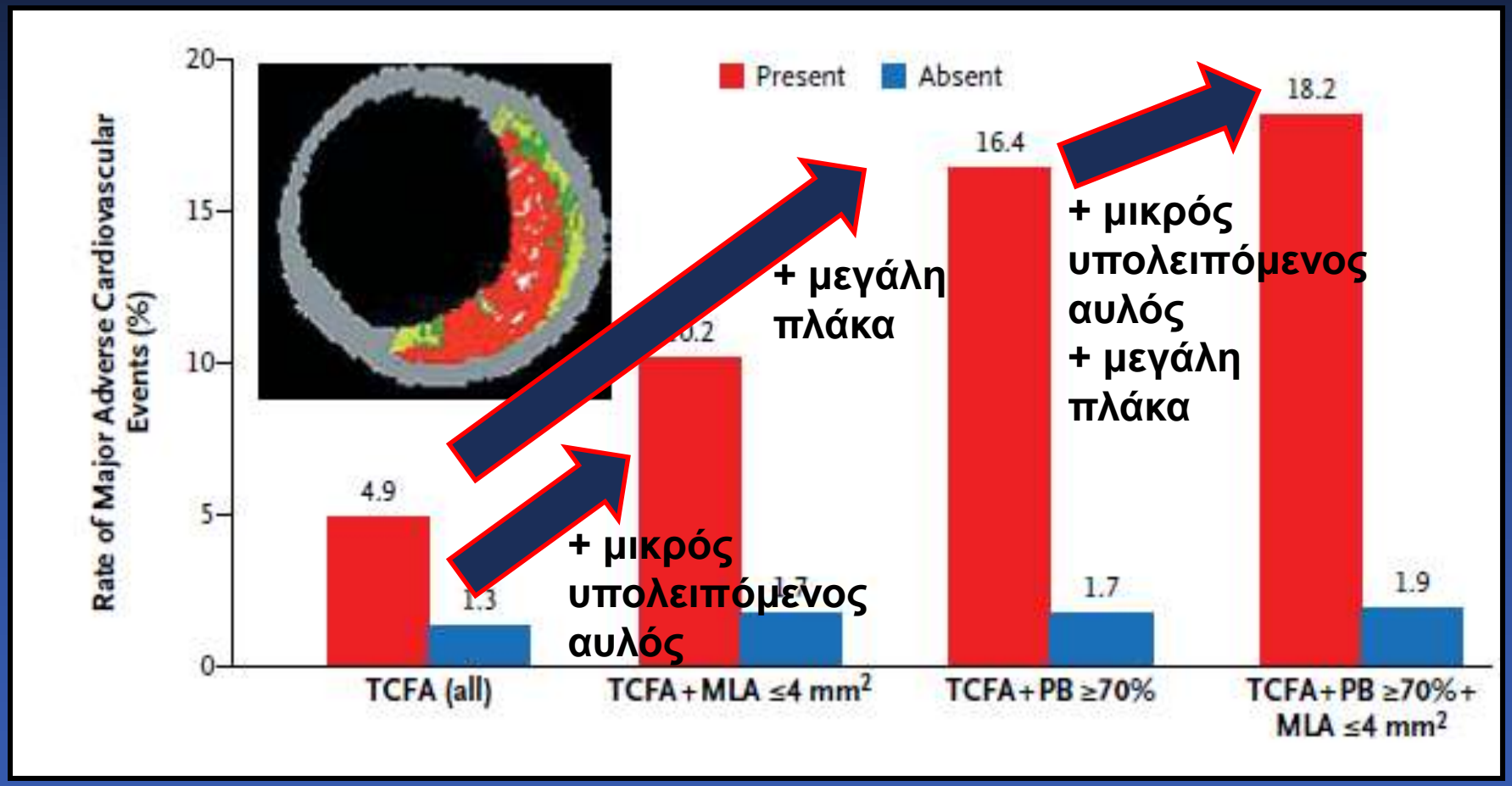
Stone GW et al., N Engl J Med 2011;364:226-35.

PROSPECT: Independent predictors of patient and lesion level events by logistic regression analysis

Correlates	Hazard Ratio (95% CI)	P Value
Predictors of patient-level events†		
Insulin-requiring diabetes	3.32 (1.43–7.72)	0.005
Previous percutaneous coronary intervention	2.03 (1.15–3.59)	0.02
Predictors of events at individual lesion sites‡		
Plaque burden ≥70%	5.03 (2.51–10.11)	<0.001
Thin-cap fibroatheroma	3.35 (1.77–6.36)	<0.001
MLA ≤4.0 mm^2	3.21 (1.61–6.42)	0.001

Stone GW et al., N Engl J Med 2011;364:226-35.

Μελέτη PROSPECT: VH-TCFA ως προγνωστικός δείκτης σε επίπεδο βλάβης



Stone GW et al., N Engl J Med 2011;364:226-35.

Vulnerable plaque

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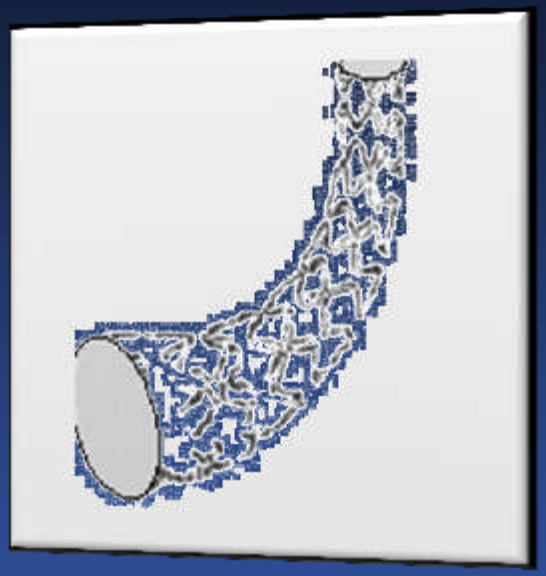
Proposed Regional Methods to Stabilize Vulnerable Plaque

- Angioplasty
- Drug-Eluting Stent
- Change of rheologic characteristics
- New dedicated stents (Inhibition of Neovascularization)
- PhotoDynamic Therapy
- Red-light Therapy
- Intravascular Sonotherapy
- Cryodestruction
- Local Drug Injection

Special geometry stents

Cylindrical stent

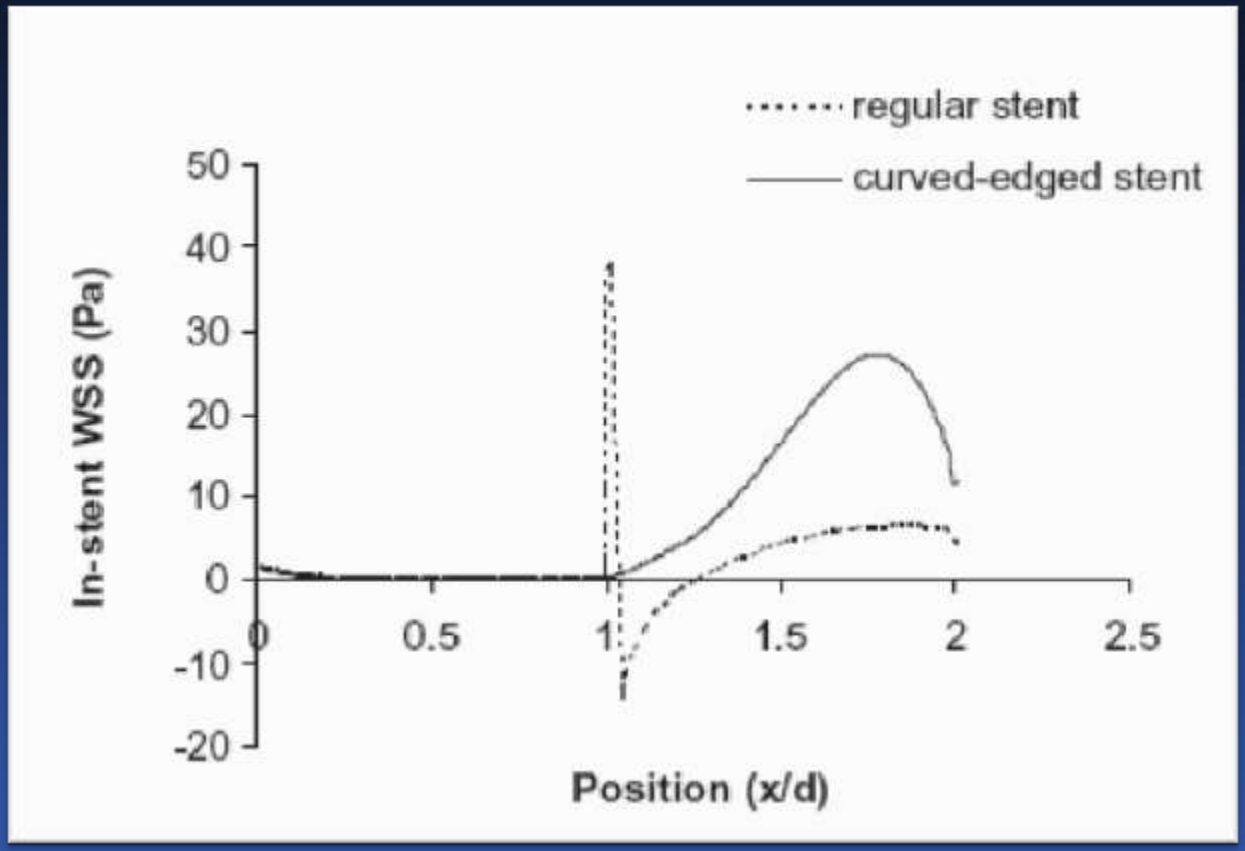


Non-cylindrical stent

- Increase of flow velocity
- Increase of shear stress forces
- Normalization of local rheologic characteristics

Papaioannou TG, ..Stefanadis C, Artificial Organs Vol.30;2007

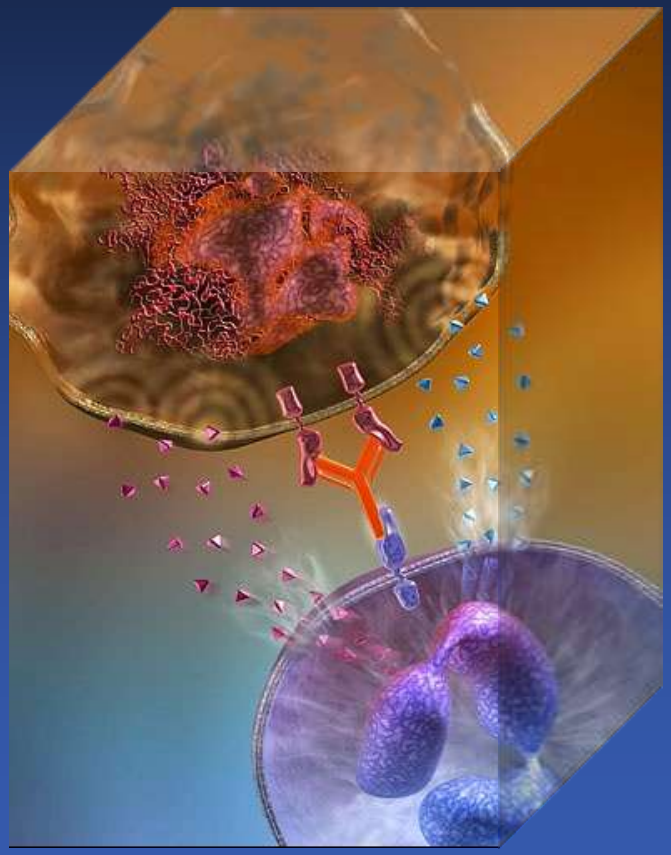
Special geometry stents



The non-cylindrical stent had higher values of wall shear stress than the regular stent

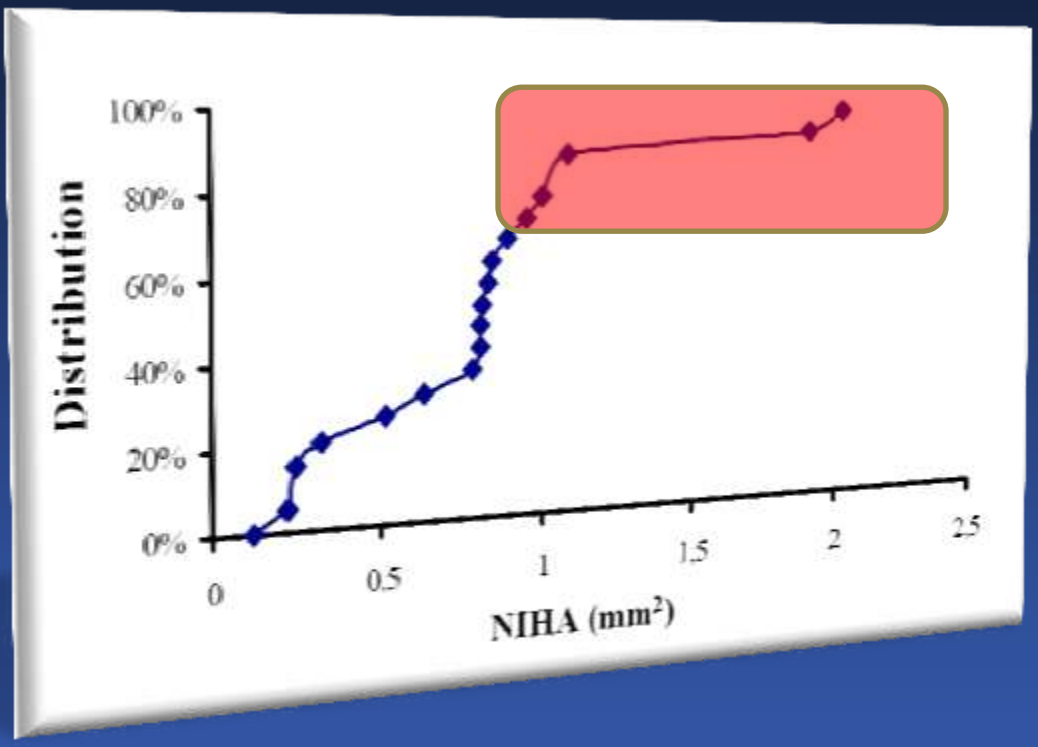
Papaioannou TG, ..Stefanadis C, Artificial Organs ***Vol. 31, No. 8, 2007***

Avastin (Bevacizumab)



Recombinant humanized monoclonal antibody that directly binds to VEGF and reduces microvascular growth

First-in-man Study
Avastin eluting BiodivYsio stent Follow-up

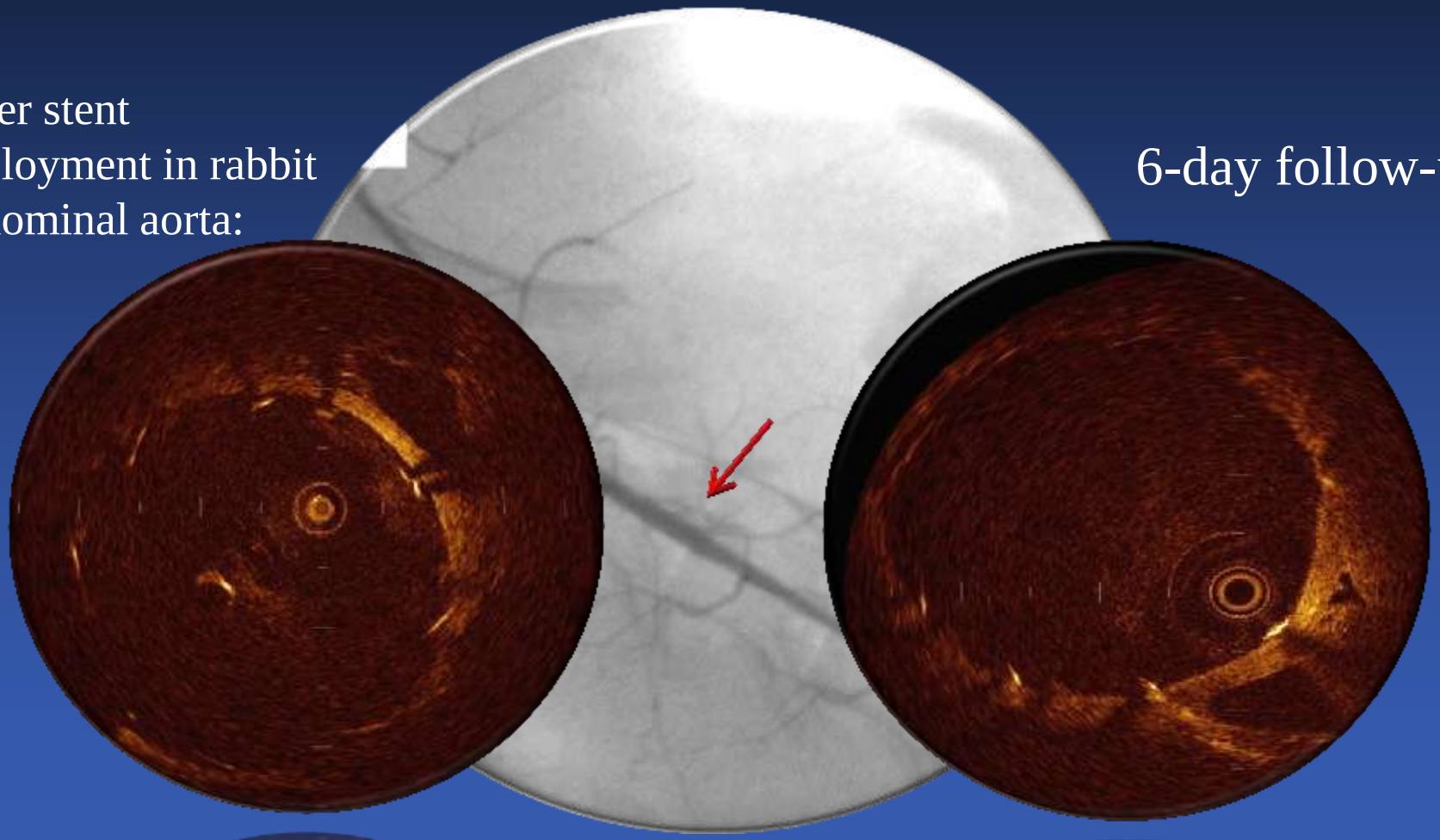


Cumulative distribution curves of neointimal hyperplasia area (NIHA) in Avastin-eluting stent treated patients at follow up. In only 4 patients the neointimal hyperplasia area was more than 15%.

Steganadis et al.,, Eurointervention 2007;3:460-464

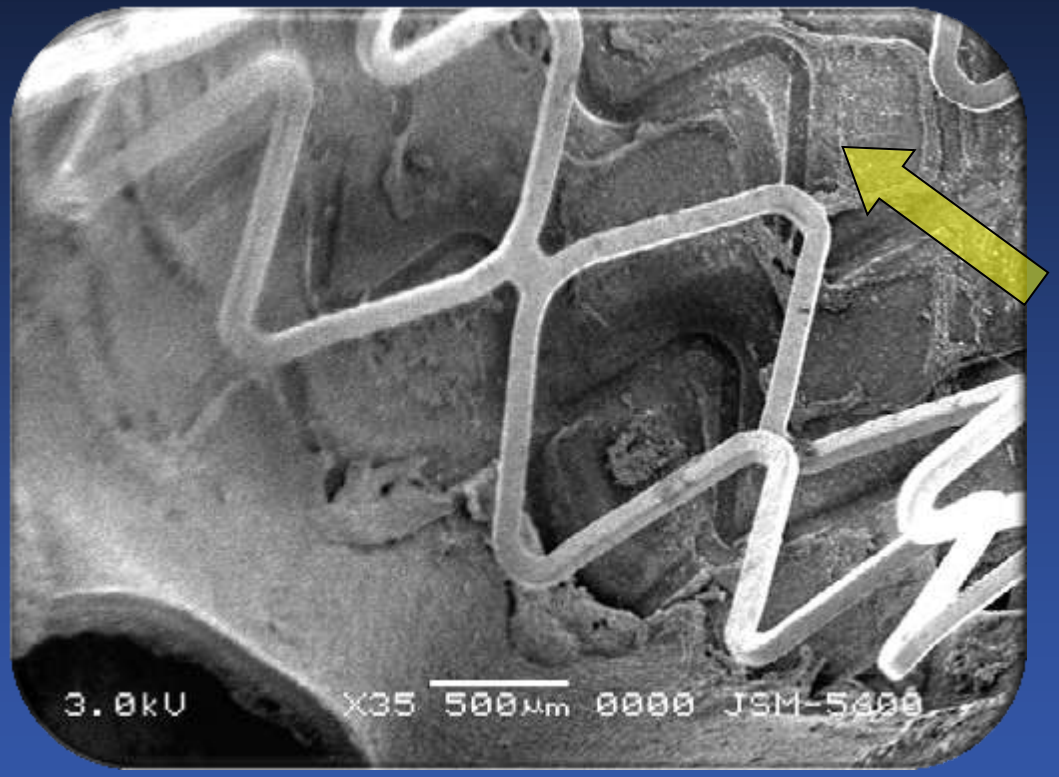
Angiographic – OCT images of stent post deployment

After stent deployment in rabbit abdominal aorta:



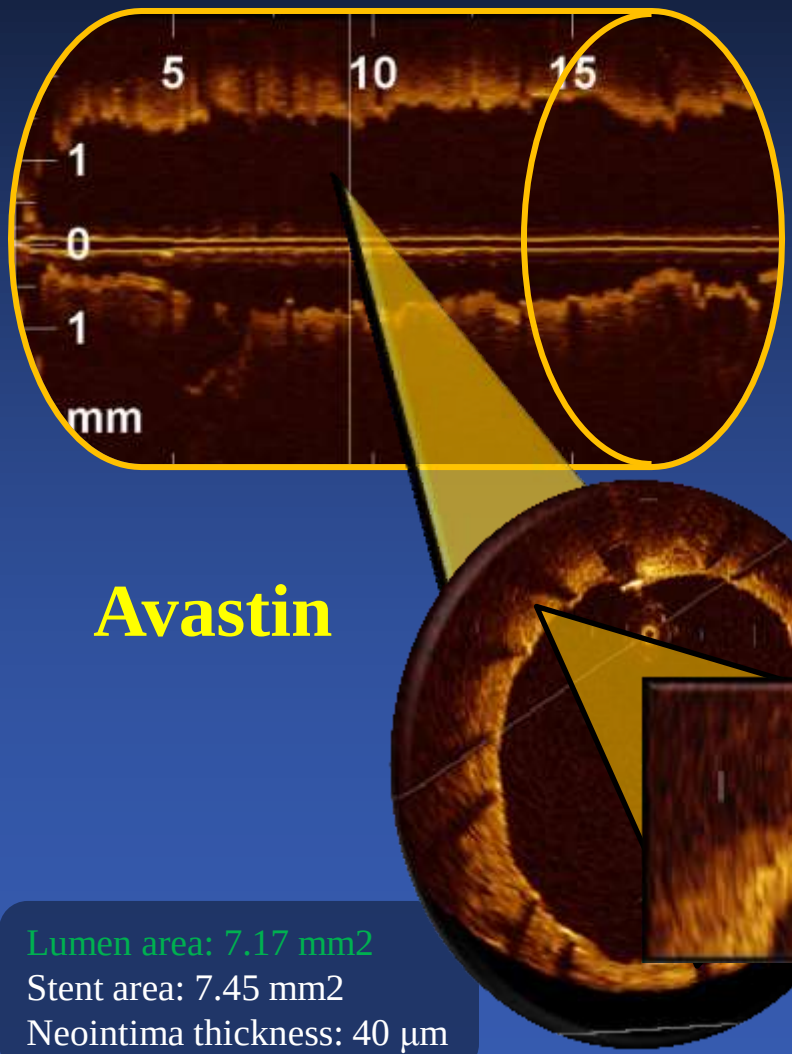
6-day follow-up:

Electronic microscopy images:
6 day follow-up



Initiation of endothelialization

OCT images
28 day follow-up



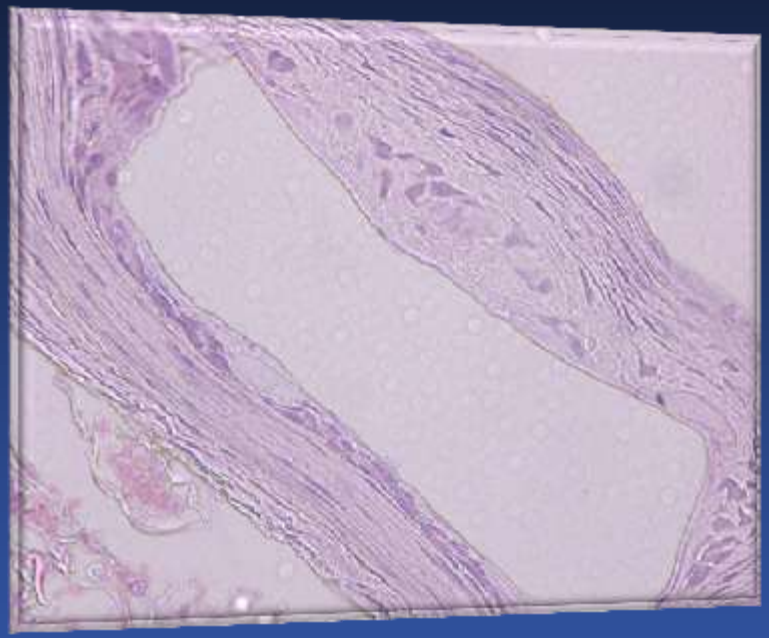
Avastin

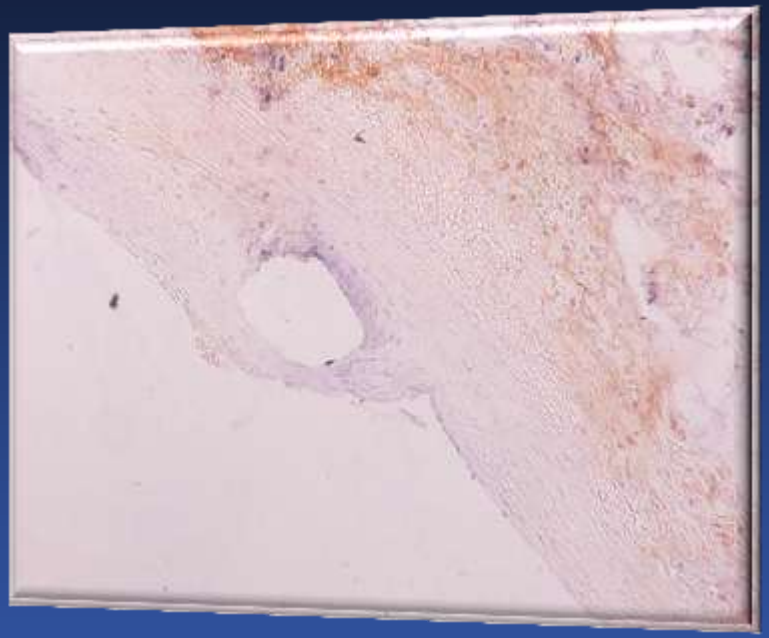
Lumen area: 7.17 mm2
Stent area: 7.45 mm2
Neointima thickness: 40 µm

Control

Lumen area: 6.19mm2
Stent area: 6.88 mm2
Neointima thickness: 80 µm

Histological Images
28 days follow-up





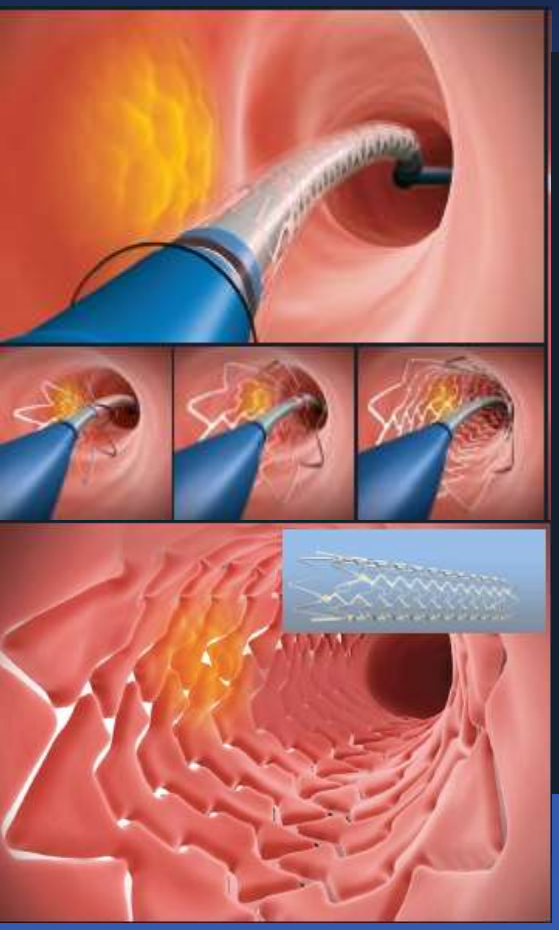
Avastin **Control**

VEGF staining in the Avastin and in the control groups. Avastin-treated groups demonstrated significantly decreased neovascularization compared to the control group.

First Dept. of Cardiology Athens Medical School, unpublished data

SECRITT-I trial:

First-in-man stenting of the "vulnerable plaque"



What is done now:

All-comers with stable or unstable angina → QCA

QCA → QCA>50% Or QCA 40-50% with FFR<0.75 → Stent implantation to treat the culprit lesion

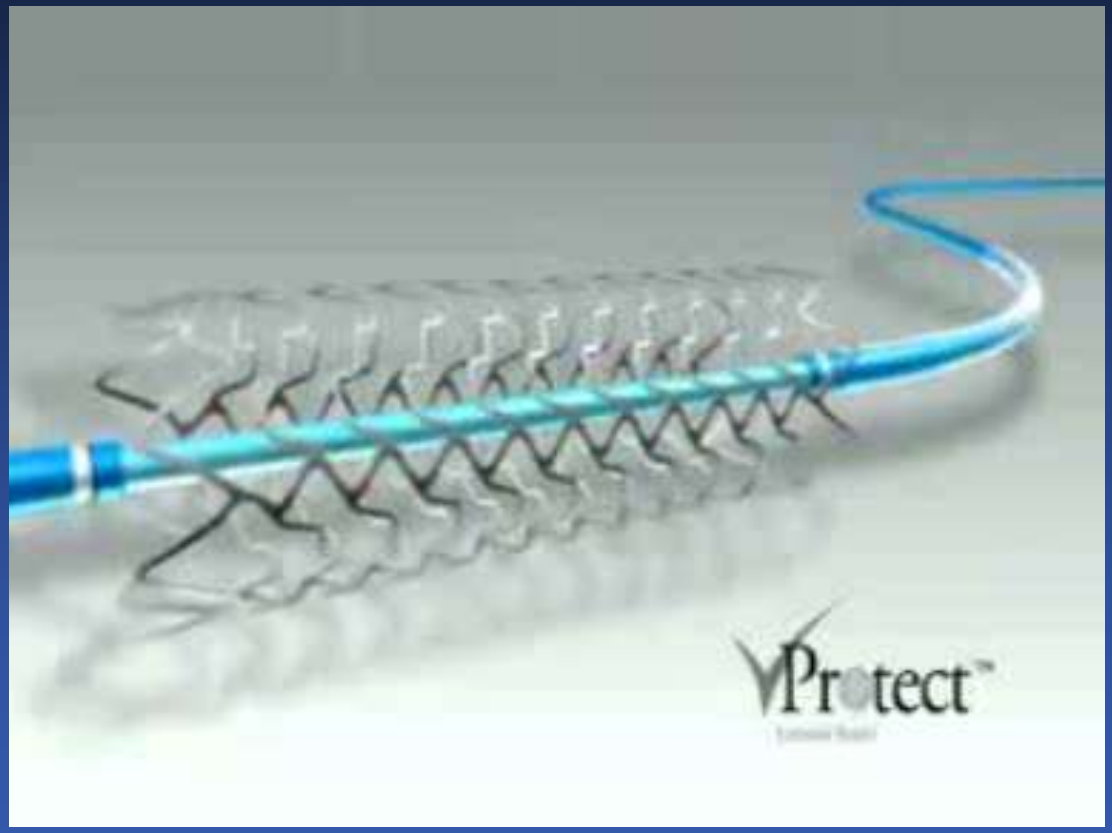
QCA → **SECRITT** → Intermediate 40-50% lesion → FFR> 0.75 Screen for SECRITT

RANDOMIZATION Based on on-line IVUS-VH TCFA

- **V-shield STENT N=15**
- **Medical therapy N=15**

IVUS-VH **Palpography and OCT**

Shield Stent



Conclusions

- Our knowledge regarding the pathology of the vulnerable plaque has increased
- Coronary plaque imaging can help in the better understanding of the pathophysiology and the natural history of the vulnerable plaque.
- There is evidence that vulnerable plaque morphology is associated with adverse outcomes
- Better understanding of the vulnerable plaque will help us in properly identifying it and stabilizing it prior to the occurrence of adverse events

Not all plaques are the same!