Extracranial Active Carotid Plaque

Luigi Giusto Spagnoli and Alessandro Mauriello

Carotid atherosclerosis is the underline cause of a relevant proportion of ischemic strokes

Pathologic studies : Carotid atherosclerotic disease in 50% patients died of cerebrovascular ischemia.

(Yates PO and Hutchinson EC: Cerebral infarction: the role of stenosis of extracranial cerebral arteries. Med. Res. Council Spec. Rep. (London) 300:1_95, 1961)

Angiographic evidence: Carotid atherosclerosis in 67,9% of 4748 patients with symptoms of cerebrovascular ischemic disease and in 74,7% of 380 patients enrolled in the Cooperative stroke sudy.

(Hass W.H. et al: Joint study of extracranial arterial occlusion. II Arteriography, tecniques, sites and complications. JAMA 203,; 961, 1968)
(Fisher, C.M.:Clinical syndromes in cerebral arteries occlusion. In Fields WS: Pathogenesis and treatment of cerebrovascular disease. Springfield , Ill, 1961, Charles C. Thomas Publisher, p. 151)

Ultrasonographic evidence: increases of IMT is associated with increased risk of myocardial infarct and stroke in older adults
(O'Leary DH et al: N Engl J Med 1999;340:14-22)

Large multicentric trials: NASCET, ECST, ACAS endarterectomy reduces the risk of stroke

- degree of stenosis in symptomatic and asymptomatic individuals has been considered the most important predictor for clinical cerebrovascular events.

However

1) Low risk of stroke in near-occlusion carotid stenosis (Rothwell SA et Al Stroke; 2003;34:514-523)

2) Number of Patients Needed to Treat: it is necessary to treat 9 symptomatics and 38 asymtomatics with high angiographic carotid stenosis, in order to prevent one ipsilateral stroke in the following 5 yrs. (NASCET and ACAS Trials)

3) The degree of stenosis does not help to select patients at risk in the lower grades of carotid stenosis

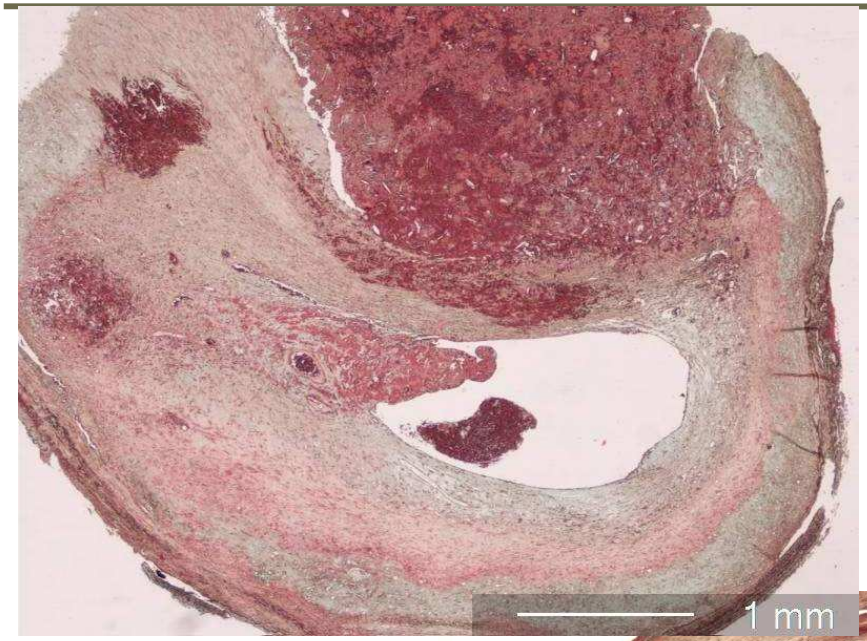
4) Potentially life threatening events have been reported in insignificant stenosis. (Wassermann BA et al.Stroke 2005;36:2504-13)

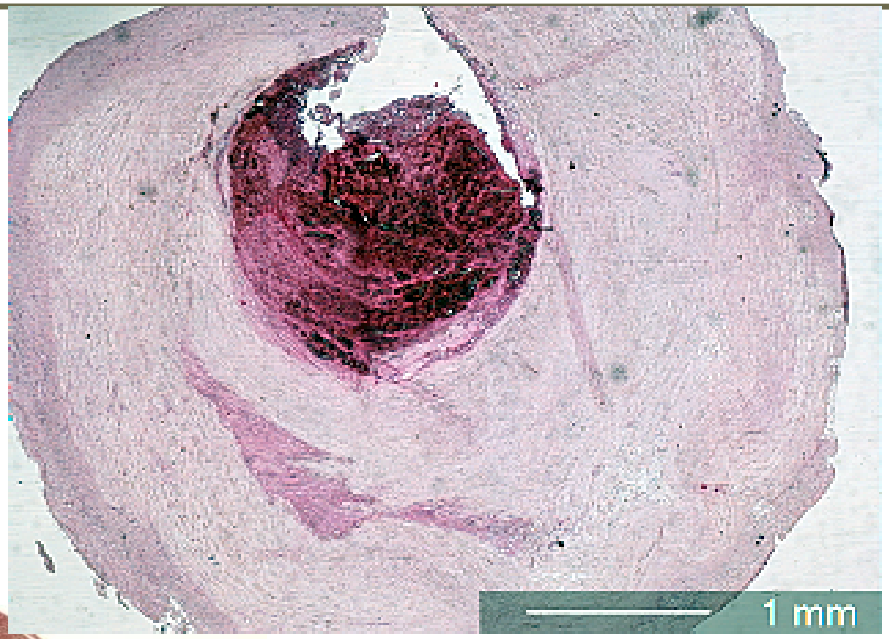
Markers related to the Pathogenesis of stroke are needed

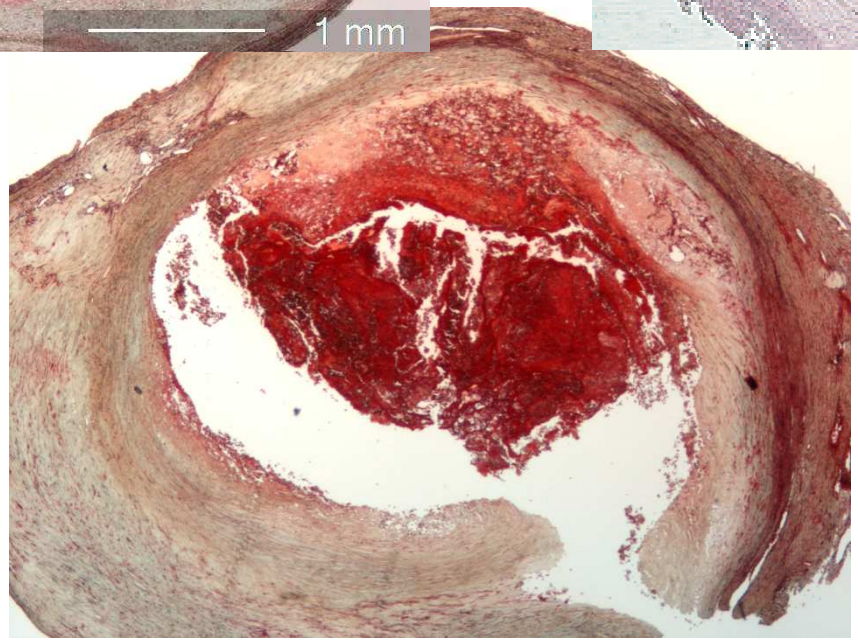
Issues to be addressed

TAP	• morphology of the Thrombotically Active Plaque (TAP) and its role in the pathogenesis of stroke and in the natural history of carotid disease
TFCA	• Features of the Thin Fibrous Cap Atheromas (TFCA) and their distribution by the degree of luminal stenosis
Healed PlaqueRupture	• Do carotid plaques, similarly to coronary plaques progress through repeated silent ruptures?

The Thrombotically Active Plaque (TAP): Acute Thrombosis often overlying an organizing or organized thrombus. *Spagnoli LG et al JAMA 2004; 292:1845-1852)*







Thrombotically Active Plaques (TAP) in patients with stroke

Months after stroke	
TAP	7 (53.8%)
Organized thrombus	
No thrombosis	

Although
the pathology of intracranial vessells in symptomatic carotid atherosclerosis
is not completely aknowledged

all carotids removed early (0-2 mo) after stroke showed a Thrombotically Active Plaque (TAP)

Early cerebral angiography : 80% of stroke Pts had intracranial vessels embolism (Fieschi C et al J neurol Sci 1989;91:311-322)

Transcranial Doppler Ultrasound studies :
-the rate of HITS is higher in symptomatic patients with 70-95% carotid stenosis than in asymptomatics;
-the rate of HITS correlates with **plaque ulceration** and **lumen thrombosis**
(Sitzer M et al Stroke 1995;26:1231-3)

-plaque atherothrombosis is the ground for artery-to-artery embolization of intracranial vessells *(Ringelstein et al. Stroke 1983; 14: 867-875)* ;

-TAP is likely the major dominant cause of large vessell brain infarction;

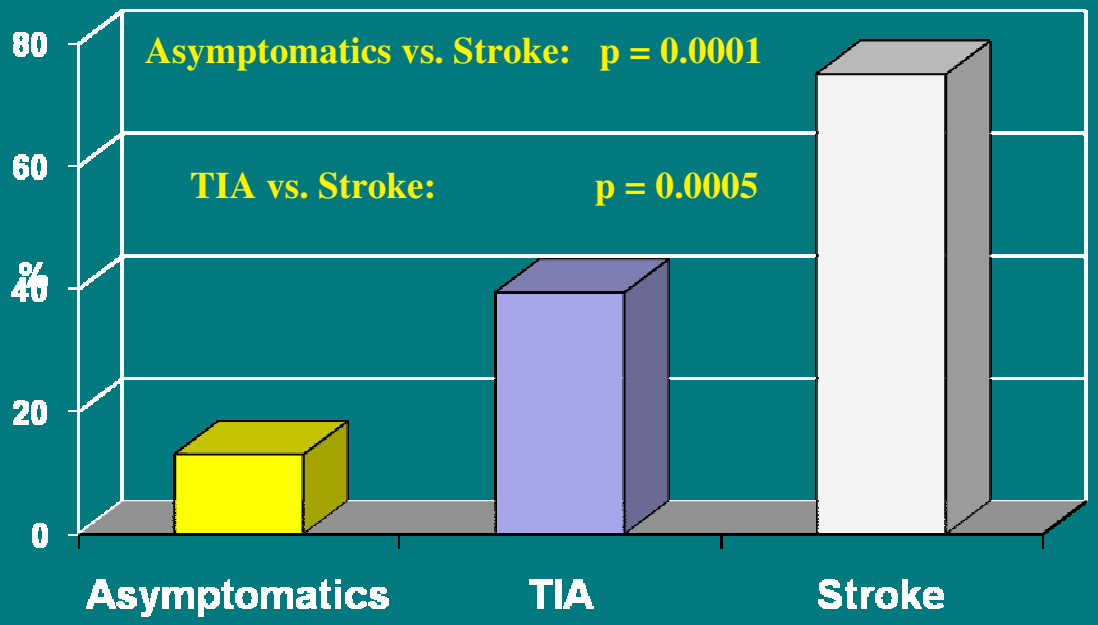
long term persistent TAP

finding

TAP in 54% of carotids removed > 24 m after symptoms onset

may reasonably explain:

-recurrent strokes affecting about 10% of patients included in this study.



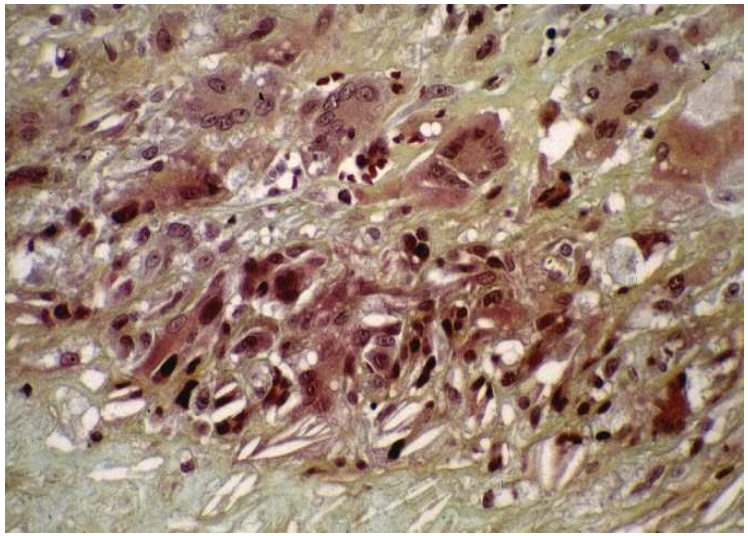
Clinically Silent TAP

	No. of Plaques		
	Patients with Major Ipsilateral Stroke (N=96)	Patients with TIA (N=91)	Asymptomatic (N=82)
Angiographic stenosis (%)			
Ipsilateral carotid	**86.1**	**79.5**	**84.6**
Controlateral Carotid	60.9	64.2	57.5
Thrombotically active plaque (n,%)	**71 (74.0)**	**32 (35.2)**	**12 (14.6)**
Cap Rupture	64 (66.7)	21 (23.1)	11 (13.4)
Cap Erosion	7 (7.3)	11 (12.1)	1 (1.2)

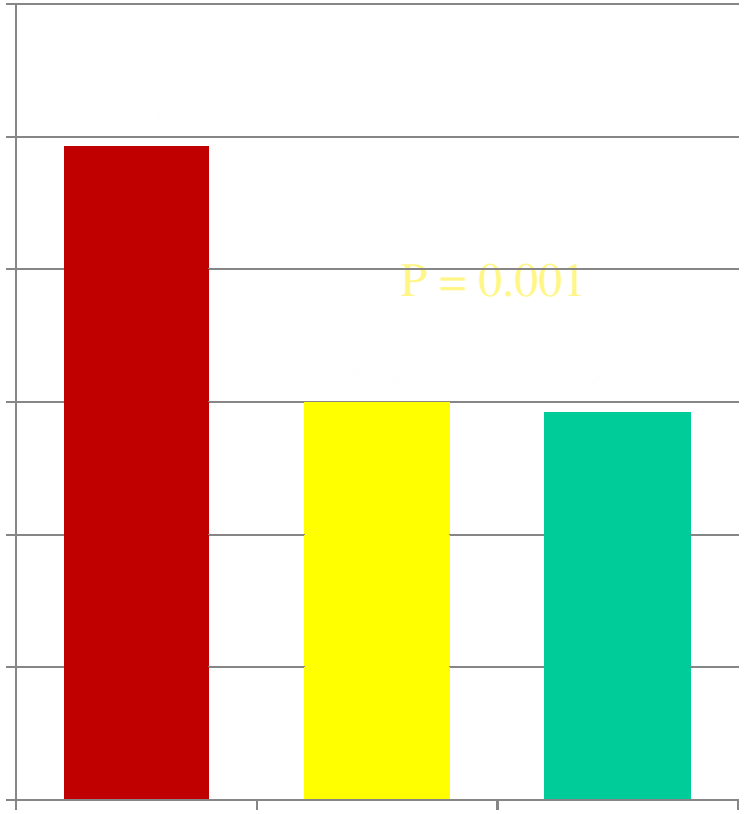
Spagnoli LG, Mauriello A et al, JAMA 2004; 292:1845-1852

Is there any morphological difference between silent TAP and symptomatic TAP?

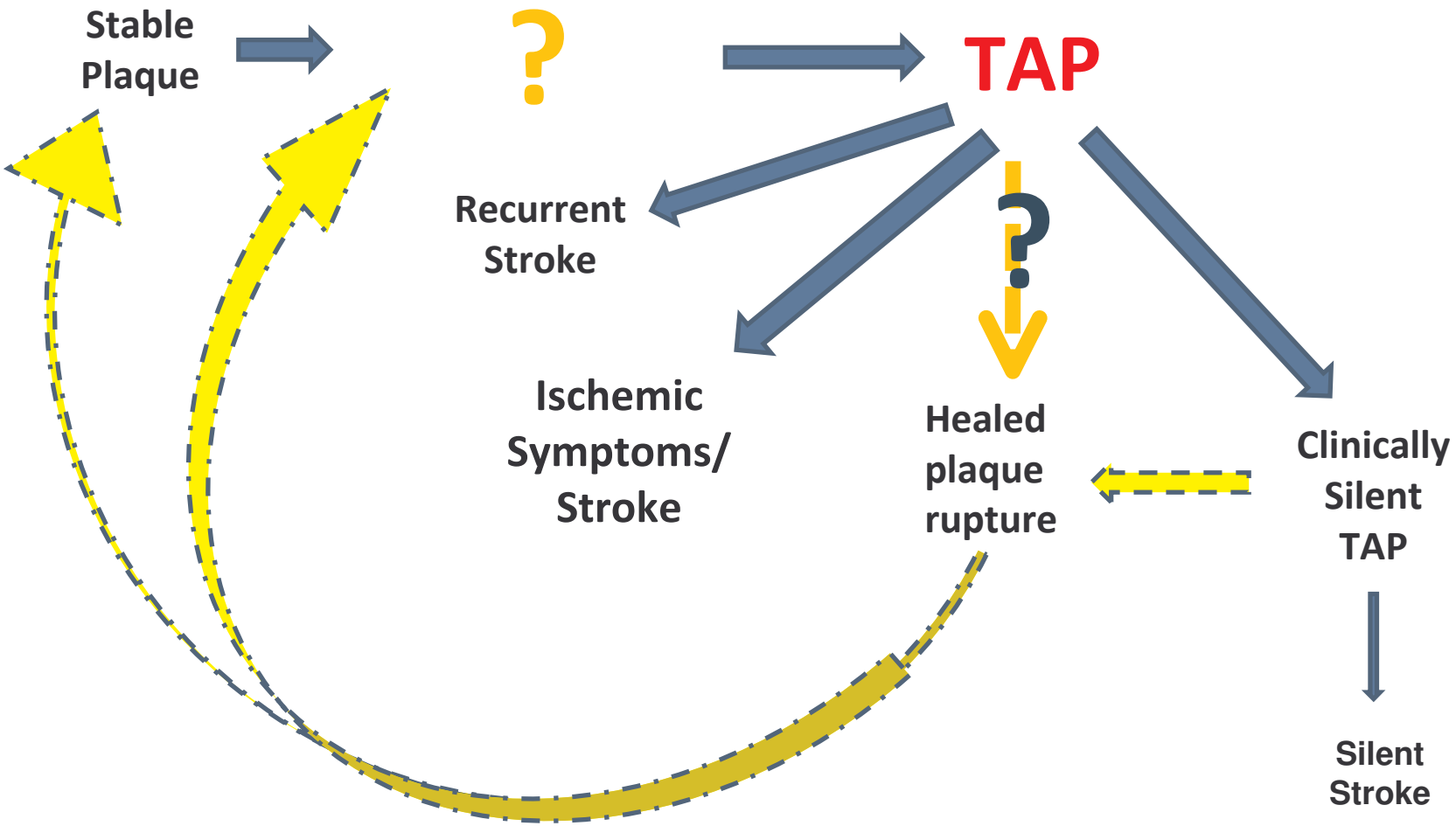
correlates with symptoms



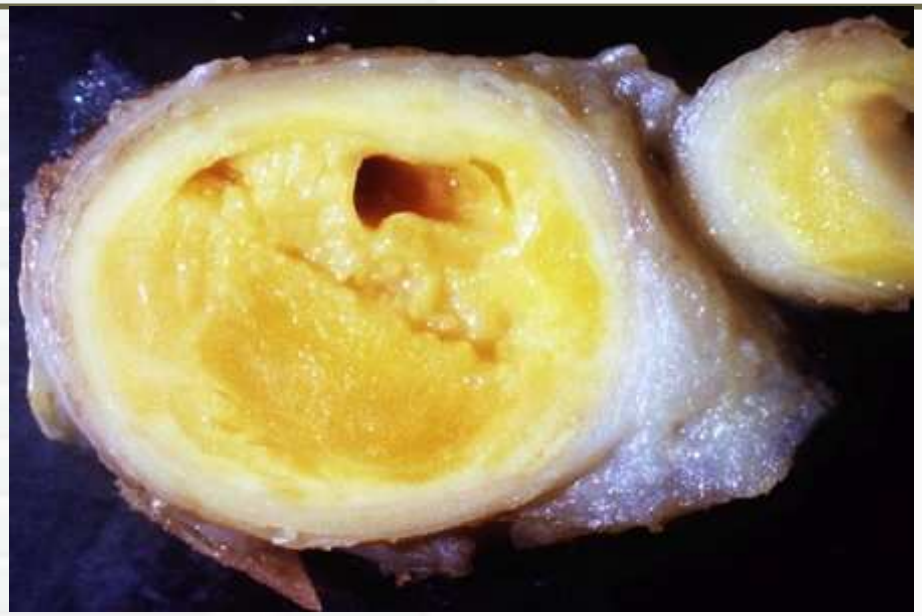
Cap Inflammation
(macrophages and
T-lymphocytes)



Has TAP a role in natural history of carotid disease?



CAROTID VULNERABLE PLAQUES: HISTOPATHOLOGICAL STUDY Mauriello, Sangiorgi et al. (JACC, submited)



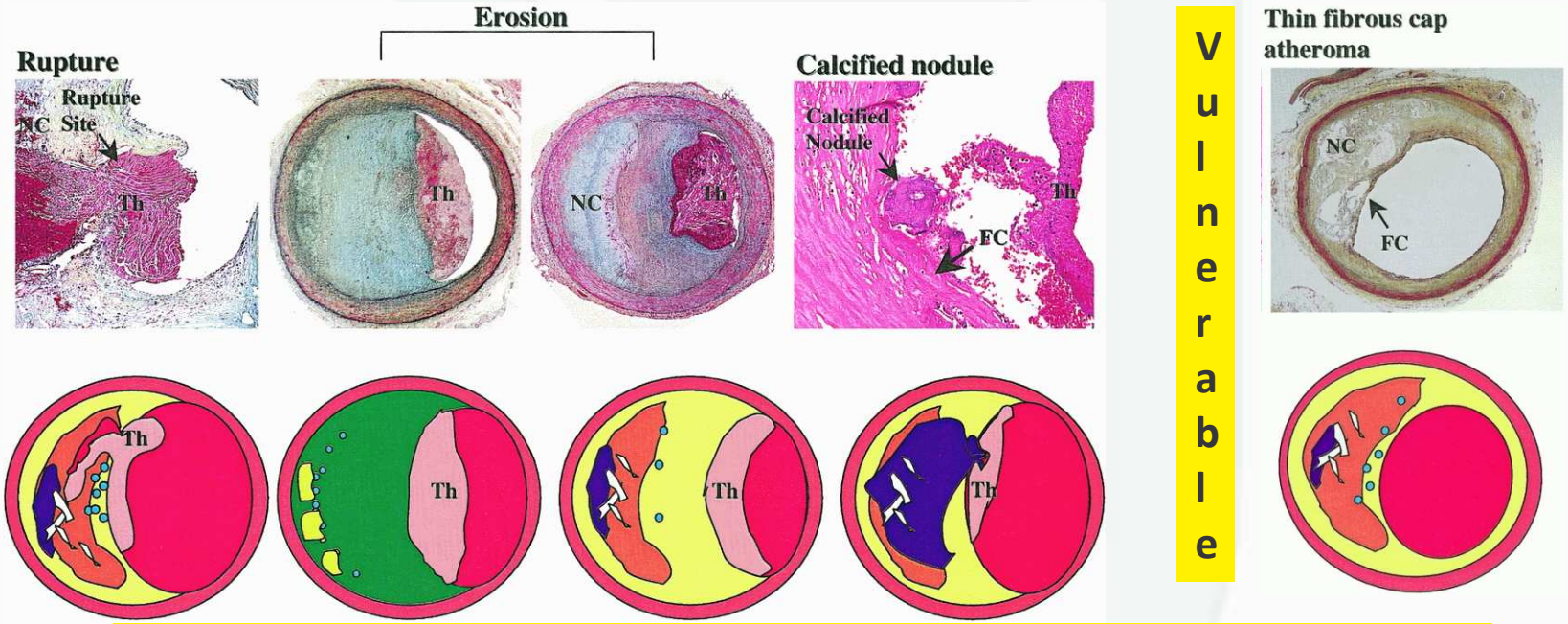
To better understand the natural history of carotid disease…

….we studied all **plaques types** in 209 endarteriectomies by patients presenting clinical symptoms

Plaque types observed in carotids according to the **modified AHA Classification**
(Virmani R. et al Arterioscl Thromb Vasc Biol 2000 ;20:1262

TAP subtypes

Vulnerable



STABLE PLAQUES

A . Mauriello, Sangiorgi G. et al. (JACC, submited)

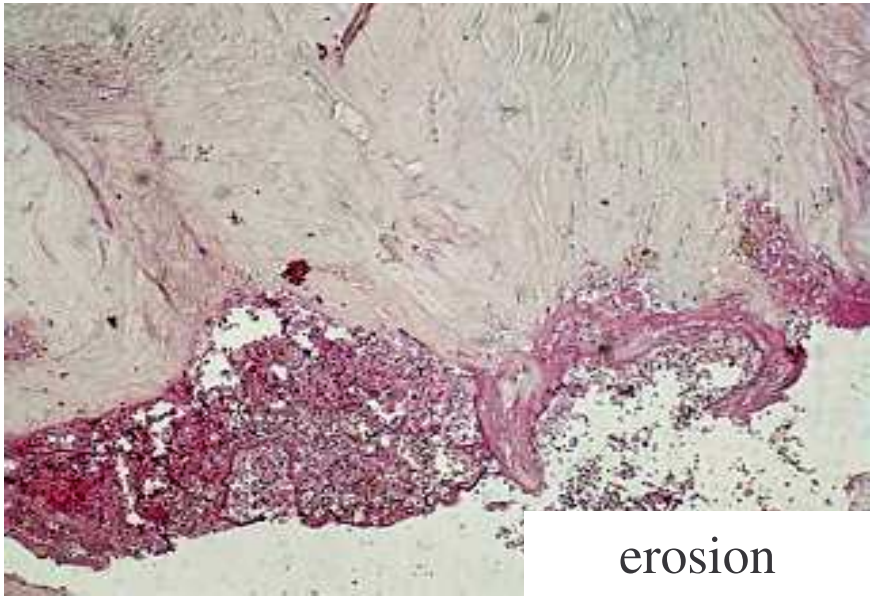
Histologic features of carotid plaques associated with symptomatic v/s asymptomatic disease in **209 Carotid Endoarterectomies**

Plaque types	(I) Stroke (N=63)	(II) TIA (N=69)	(III) Asymptomatics (N=77)	Total Cases (209)	P -value		
					I/II	I/III	II/III
Thrombotically Active Plaques n(%)	51 (81.0)	18 (26.1)	16 (20.8)	85 (40.7)	.001	.001	.45
Plaque rupture	39 (61.9)	10 (55.6)	10 (62.5)	59 (64.4)			
Organizing thrombus	10 (15.9)	5 (27.8)	3 (18.8)	18 (21)			
Erosion	0	3 (16.7)	3 (12.5)	5 (5.9)			
Calcific nodule	2 (3.2)	0	1 (6.2)	3 (3.5)			
Healed Plaque rupture, n(%)	8 (12.7)	22 (31.9)	35 (45.5)	65 (31.1)	.009	.001	.09
Stable Plaque n (%)	4 (6.3)	29 (42.0)	26 (33.8)	59 (28.2)	.001	.001	.030

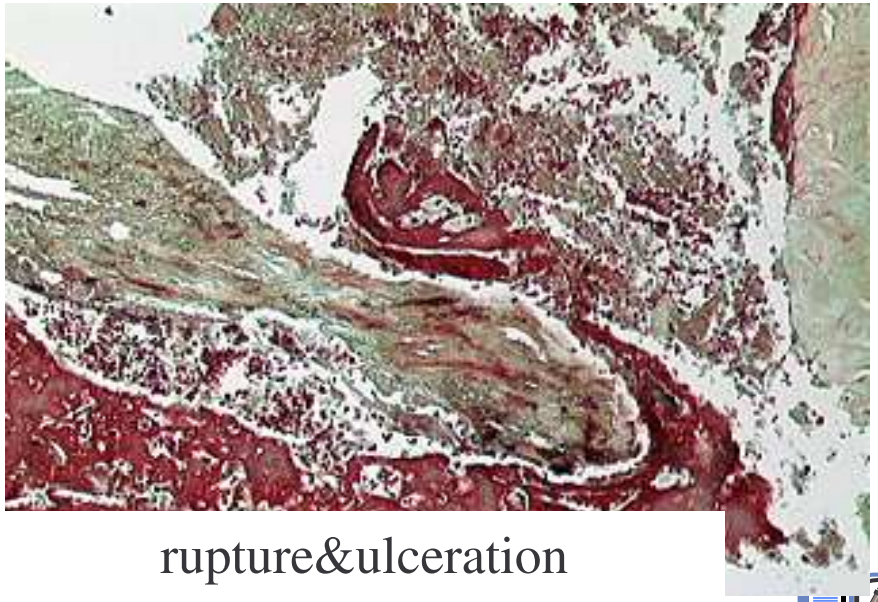
A . Mauriello, Sangiorgi G. et al. (JACC, submited)

Occlusive thrombosis

Subocccclusive thrombosis

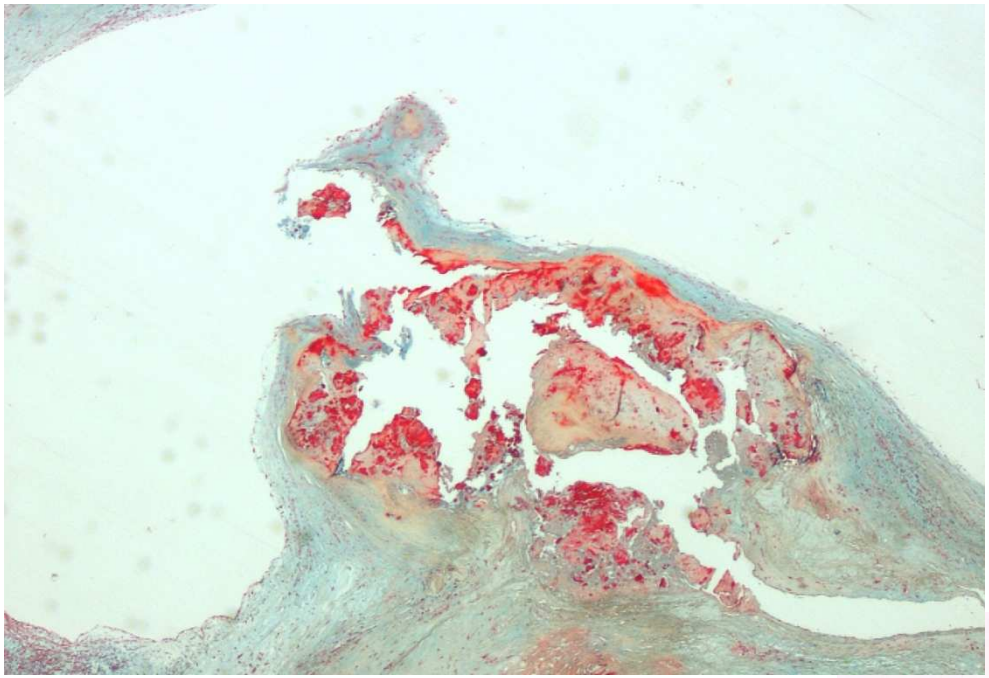


erosion



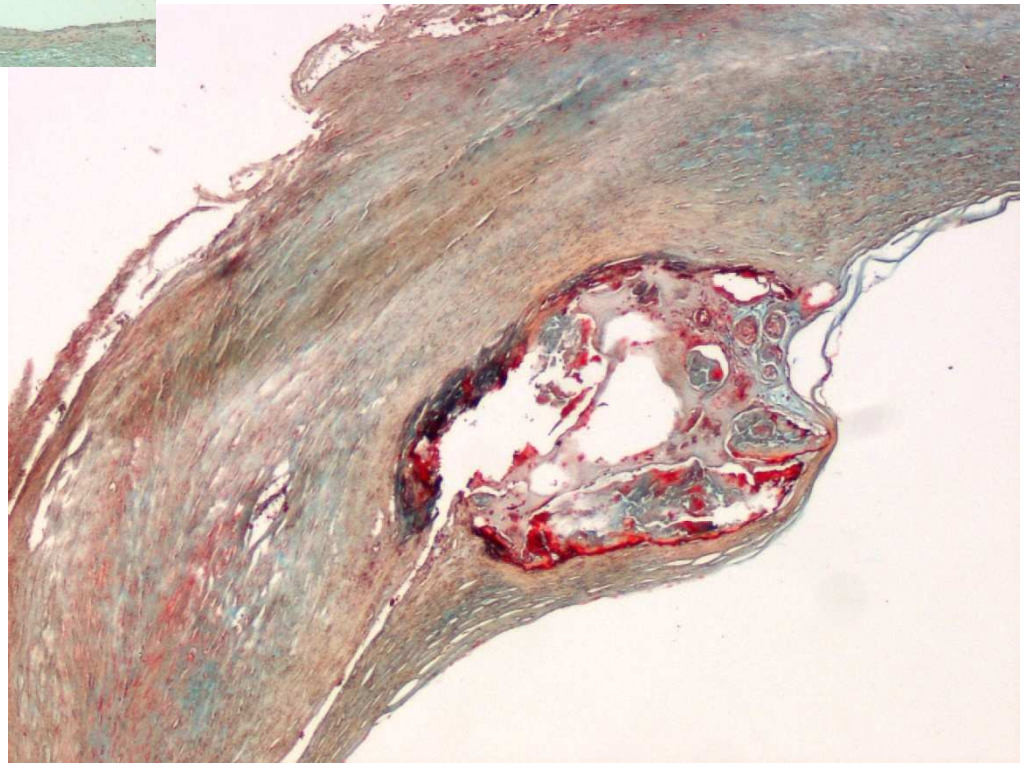
rupture&ulceration

Carotid TAPs: morphologic subtypes



Calcific nodule

… a special type of carotid TAP



The Vulnerable Plaque (TCFA) : definitions

"… which lesions are likely to rupture"
(Muller et al., 1992)

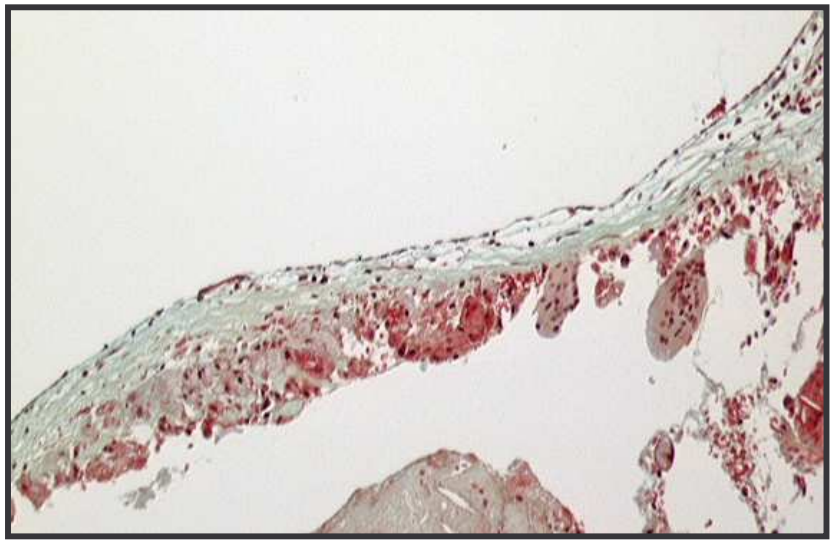
"lesions composed of a lipid-rich core in the central portion of an eccentric plaque, with a thin, friable fibrous cap"
(Libby et al, 1994)

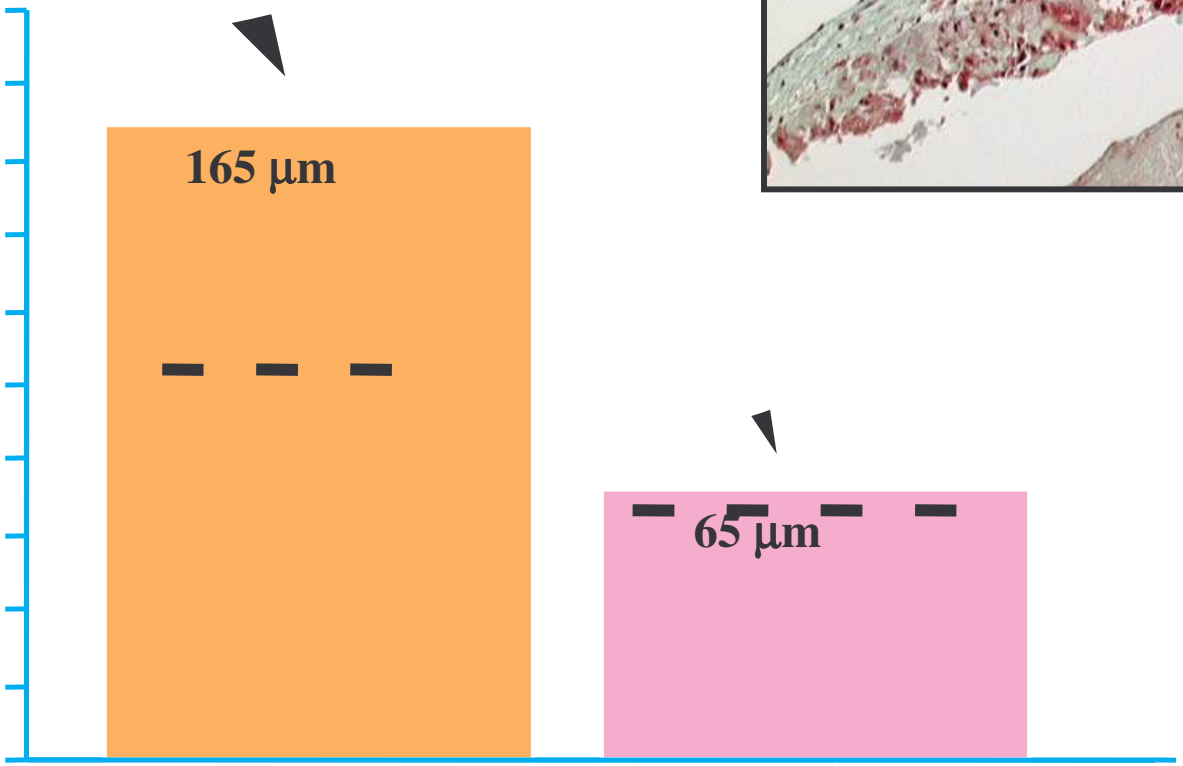
"lesion with a fibrous cap < 65 µm thick and infiltrated by macrophages (>25 cells per 0.3 mm diameter field)"

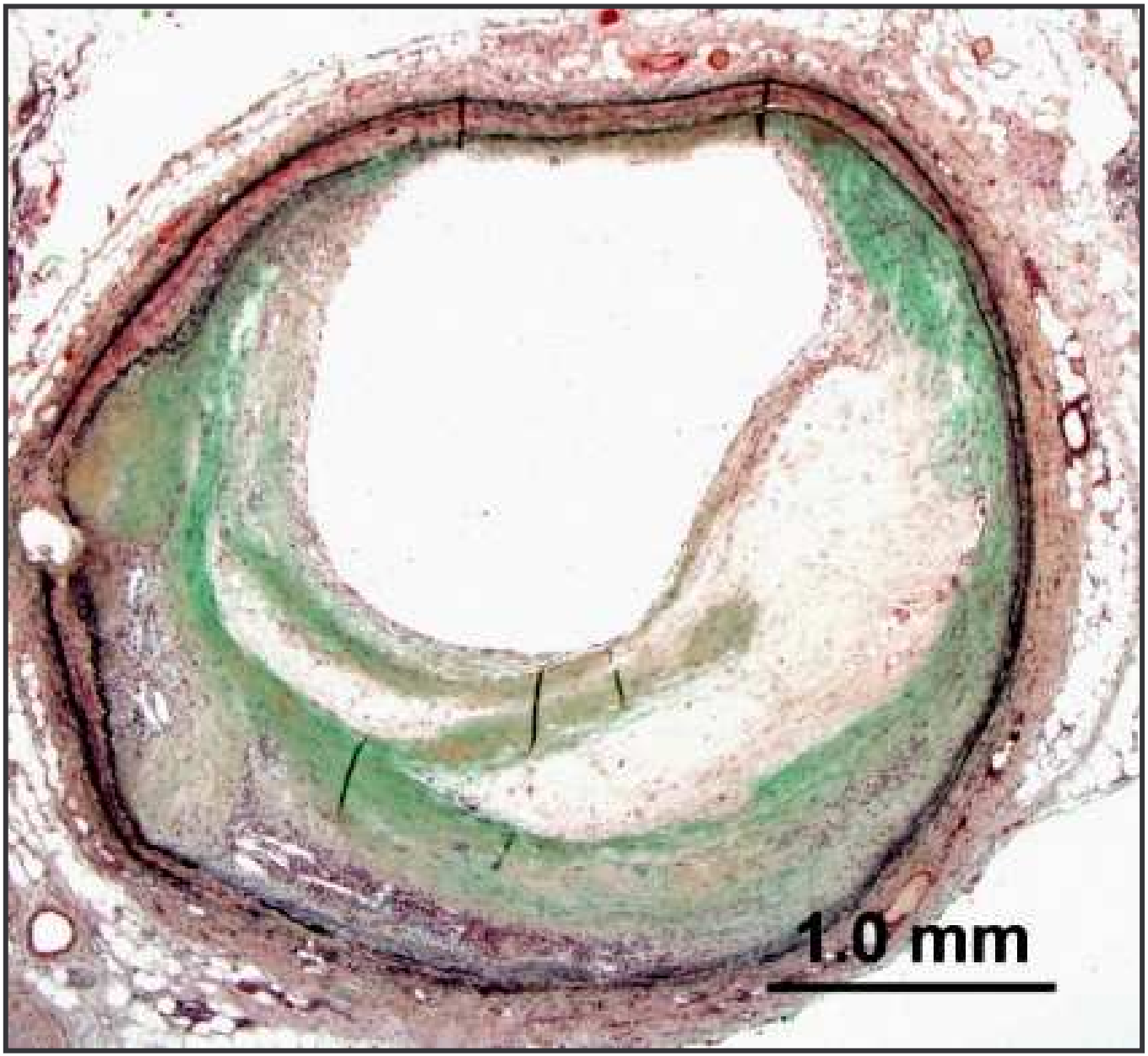
(Burke et al, 1997 – in coronaries)

TCFA: Cap thickness in 209 Carotid Endoarterectomies

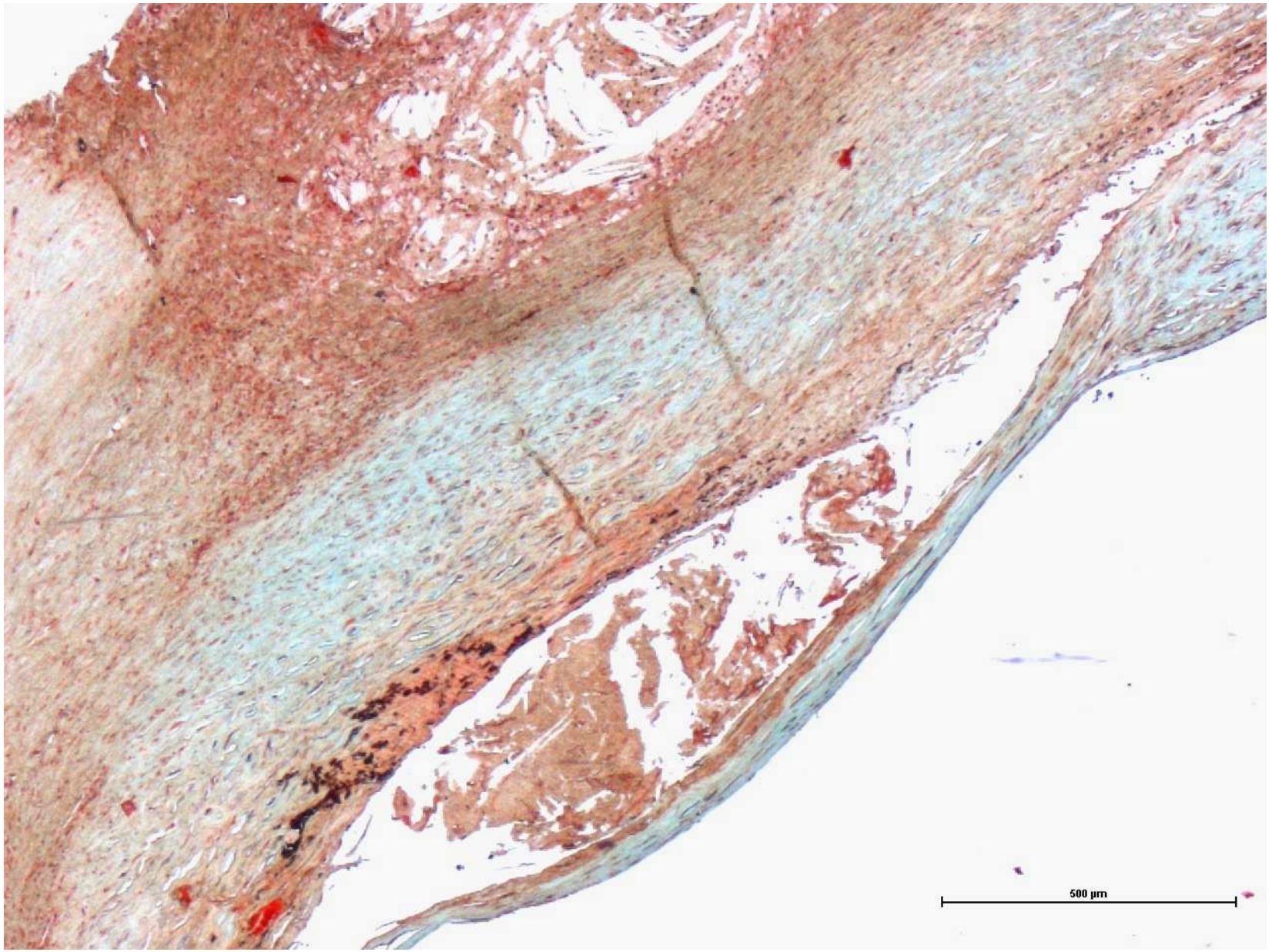
(Mauriello A, Sangiorgi G et al JACC in press)



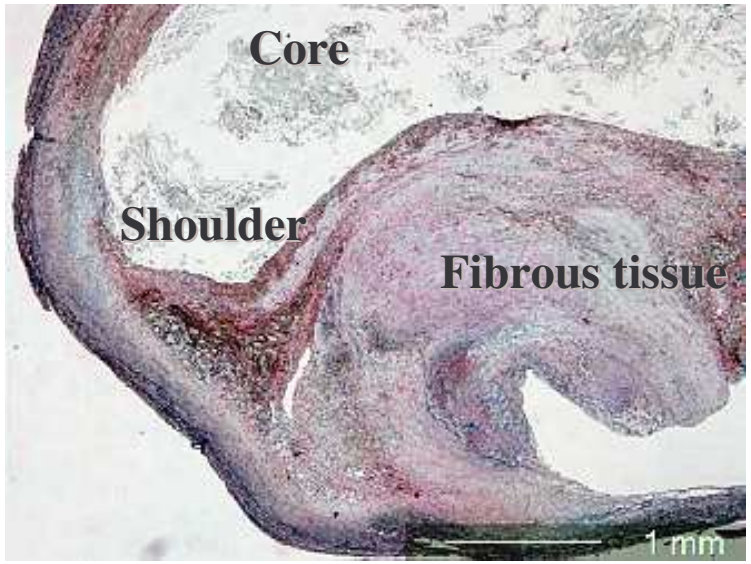


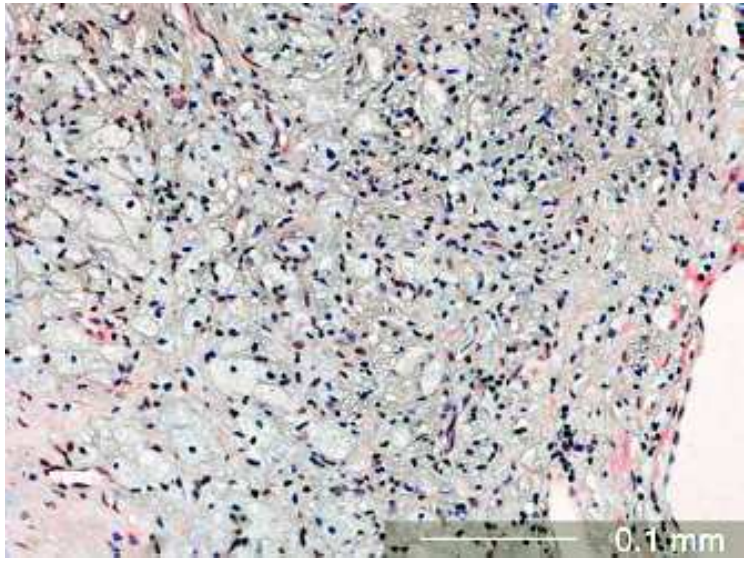


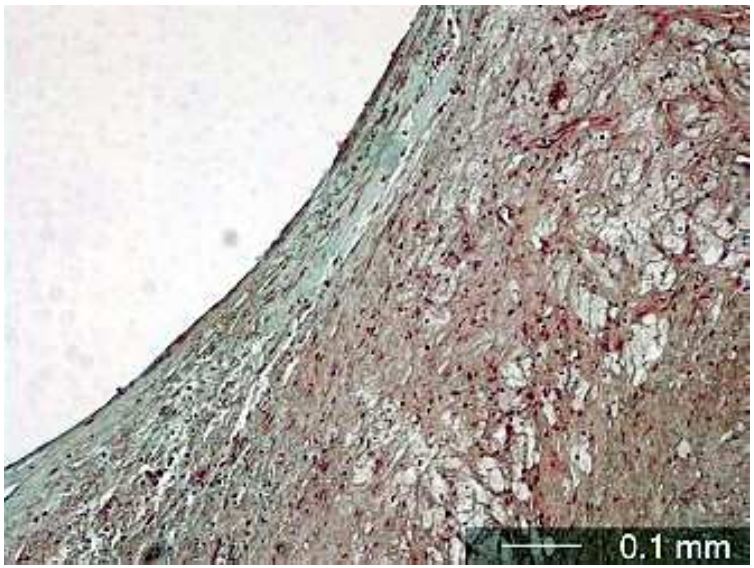
A Vulnerable carotid Plaque overlying a large atheromasic core in a Fibrous Cap Atheroma

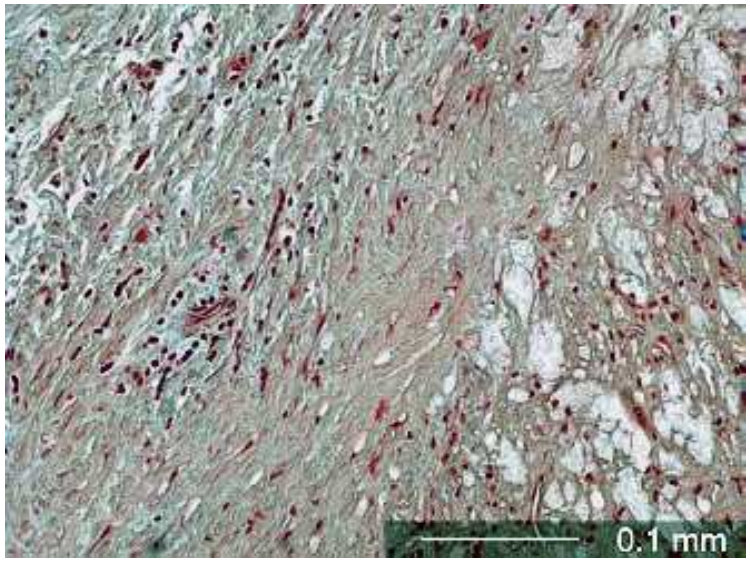


A Vulnerable carotid Plaque overlying an Healed Plaque Rupture





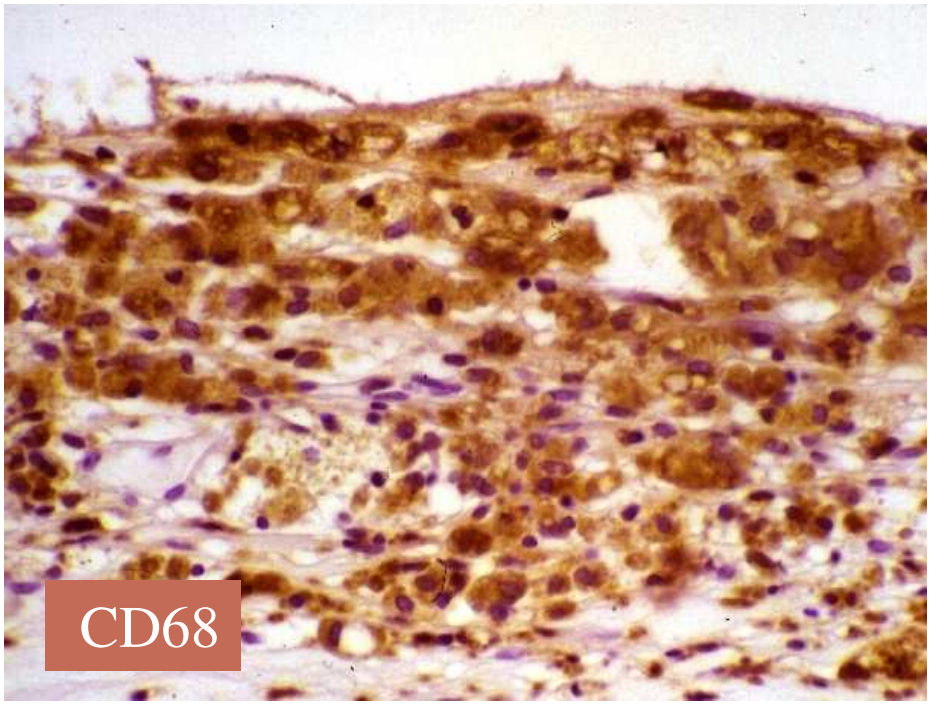


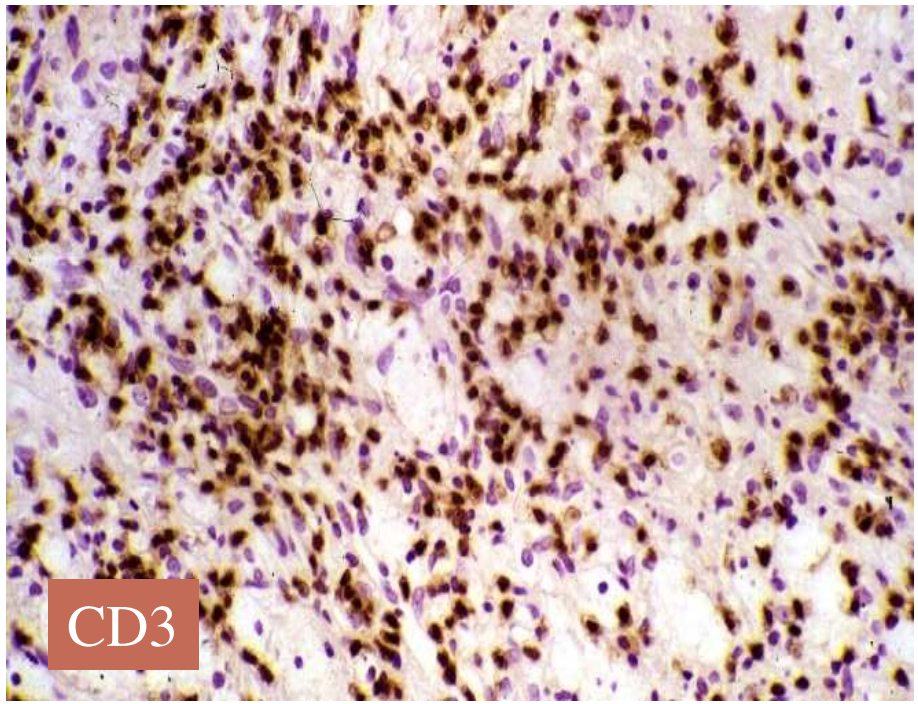


Inflammatory infiltrate

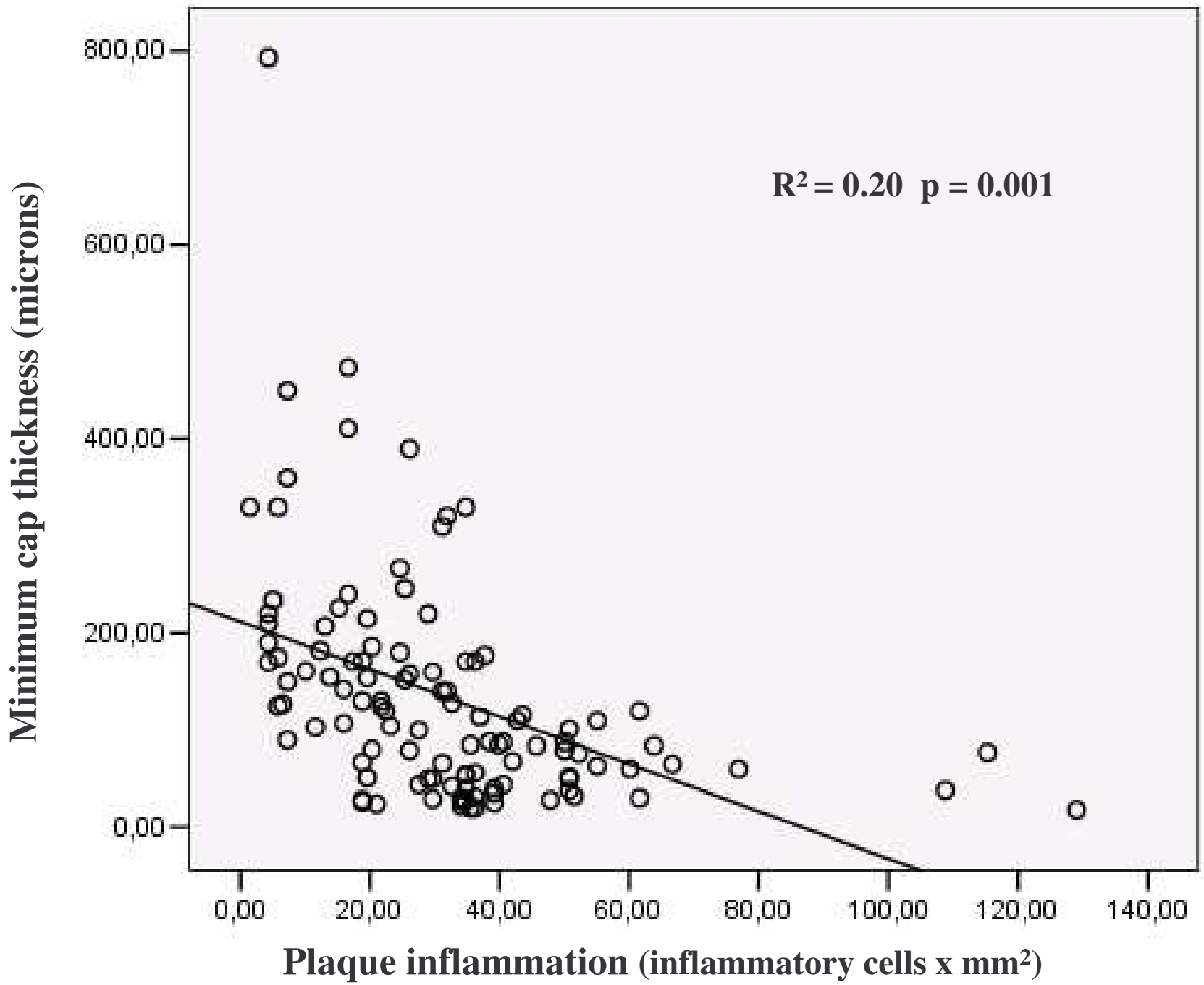
TOR VERGATA

Evaluation of plaque inflammation





number/ mm^2 of monocytes/macrophages (CD68+) and T-lymphocytes (CD3+)


Minimum cap thickness (microns)
800,00
600,00
400,00
200,00
0,00
$R^2 = 0.20$ p = 0.001
0,00
20,00
40,00
60,00
80,00
100,00
120,00
140,00
Plaque inflammation (inflammatory cells x mm²)

Types and Characteristics of Plaques in 209 Carotid Endoarterectomies

Morphological differences between stable, vulnerable and ruptured plaques

	Stable plaques (312 CS)* (I)	Vulnerable plaques (101 CS) * (II)	Ruptured plaques (59 CS) * (III)	P I vs. II	P I vs. III	P II vs.III
Cap thickness (µm ± SD)	156.1 ± 94.1	100.3 ± 32.3	92.2 ± 36.4	0.001	0.001	0.22
Cap Macrophage infiltration (N cell x hpf ± SD)	6.1 ± 10.8	50.7 ± 20.7	45.0 ± 20.1	0.001	0.001	0.13
Lipid-necrotic core (area % ± SD)	29.2 ± 22.3	43.7 ± 14.7	46.1 ± 13.5	0.001	0.001	0.29
Calcification (area % ± SD)	12.6 ± 15.9	3.3 ± 5.9	4.1 ± 6.1	0.001	0.001	0.46
Intraplaque hemorrhage (N, %)	61 (19.6%)	31 (30.7%)	41 (69.5%)	0.02	0.001	0.001
Fibrous tissue (area% ± SD)	37.9 ± 17.7	29.6 ± 16.6	25.6 ± 11.7	0.001	0.001	0.08

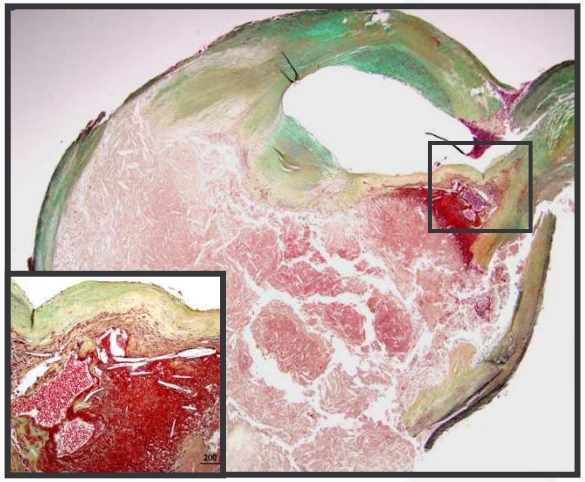
(*) CS = carotid segments

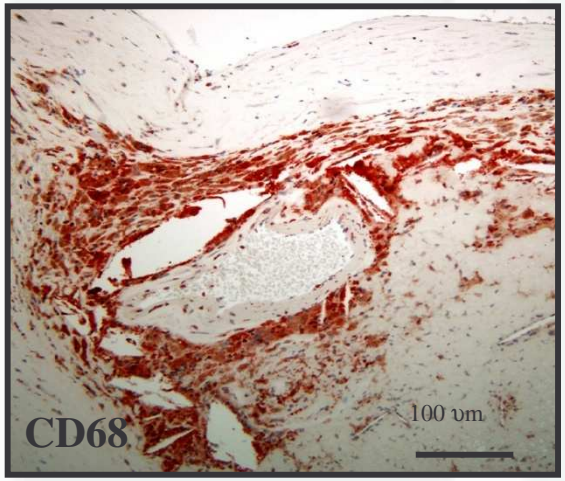
Correlation of Vulnerable Plaques (Thin Cap Fibro-Atheroma) with symptoms and association with other plaque types

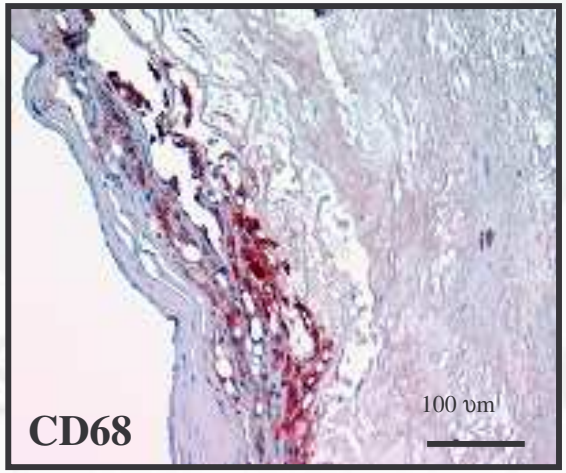
	(I) Stroke (N=63)	(II) TIA (N=69)	(III) Asympto-matics (N=77)	I vs II P	I vs III P	II vs III P
Pts with TCFA, (%)	**31 / 63 (49.2)**	**27 / 69 (39.7)**	**27 / 77 (35.1)**	0.25	0.11	0.61
1 TCFA	27 (42.9)	20 (29.4)	22 (28.6)			
> 1 TCFA	4 (6.3)	7 (10.3)	5 (6.5)			
TCFA associated with:						
acute thrombotic plaques	**26 / 51 (51.0)**	**7 / 18 (38.9)**	**7 / 16 (43.8)**	0.38	0.61	0.77
healed plaque rupture	**4 / 8 (50.0)**	**7 / 22 (31.8)**	**13 / 35 (37.1)**	0.36	0.50	0.68
stable plaques	**1 / 4 (25.0)**	**13 / 29 (44.8)**	**7 / 26 (26.9)**	0.45	0.93	0.17

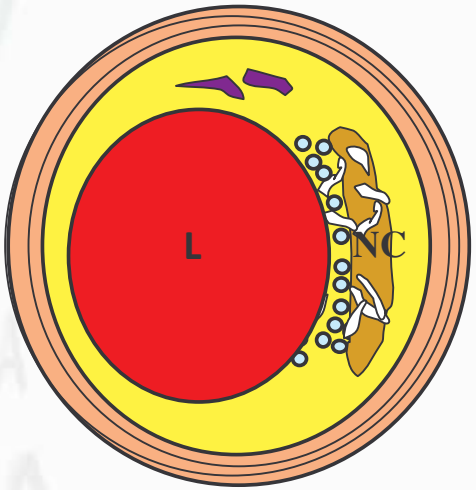
TCFA: correlation with cross sectional stenosis

80% of TCFA in stenosis<70%





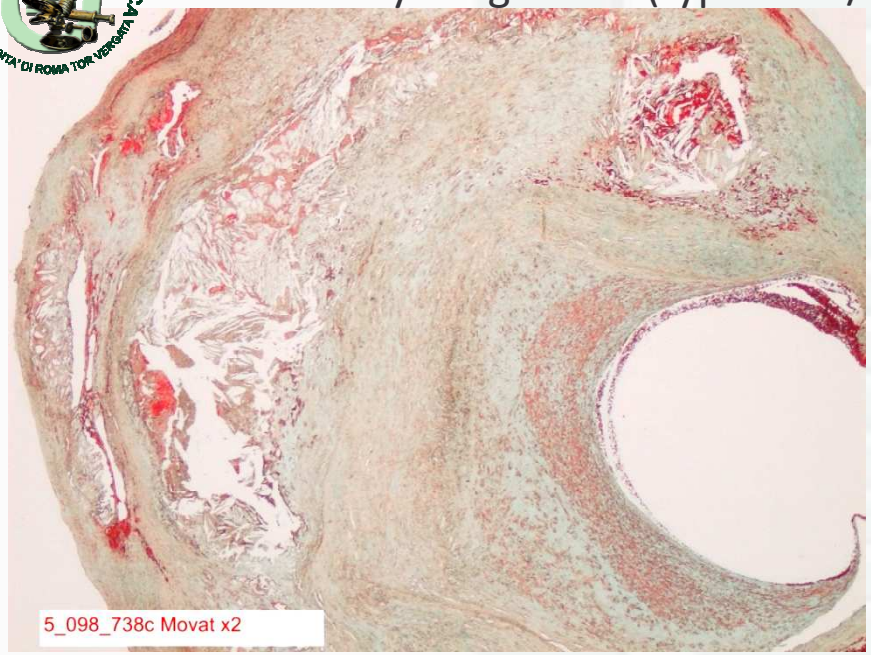


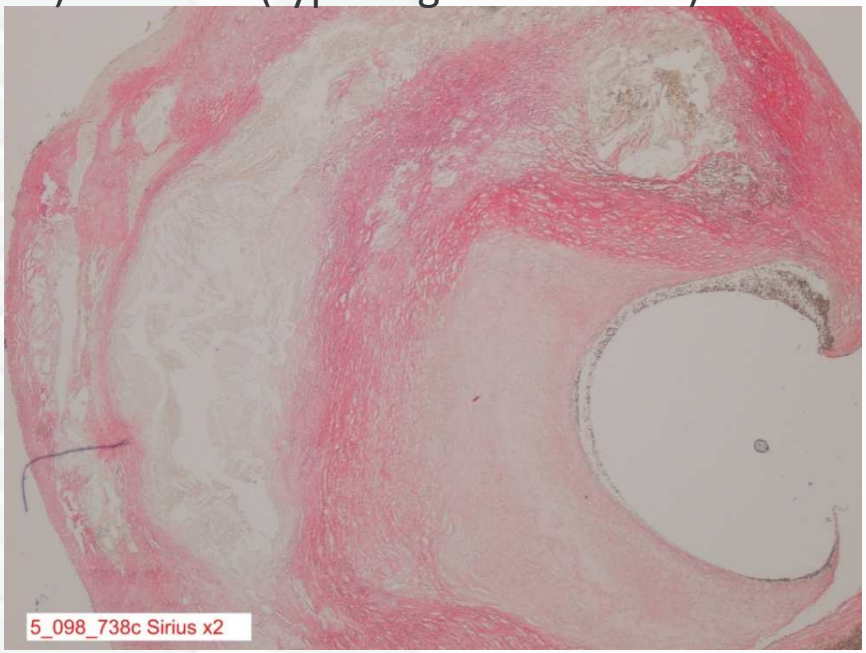


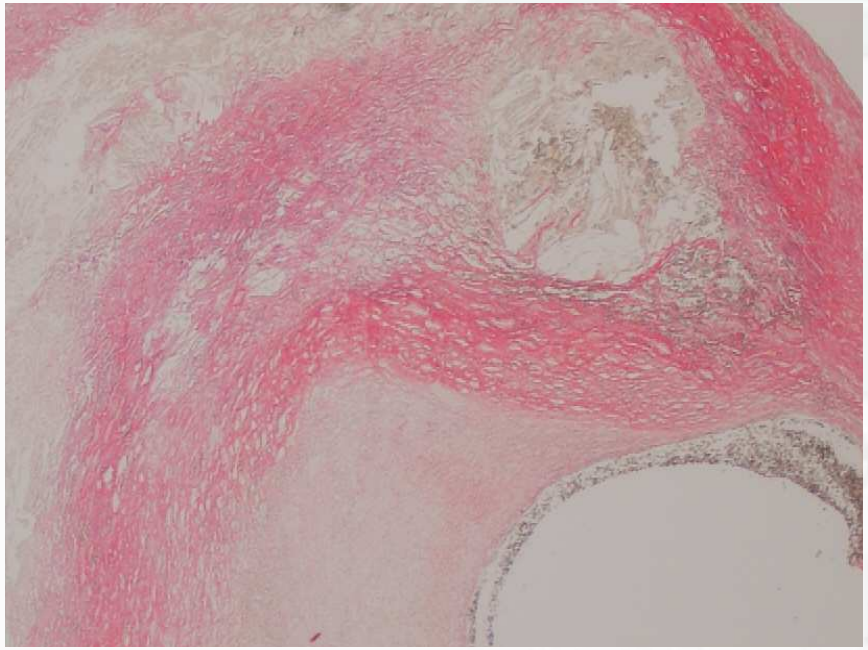
(Mauriello A, Sangiorgi G et al, JACC, submitted)

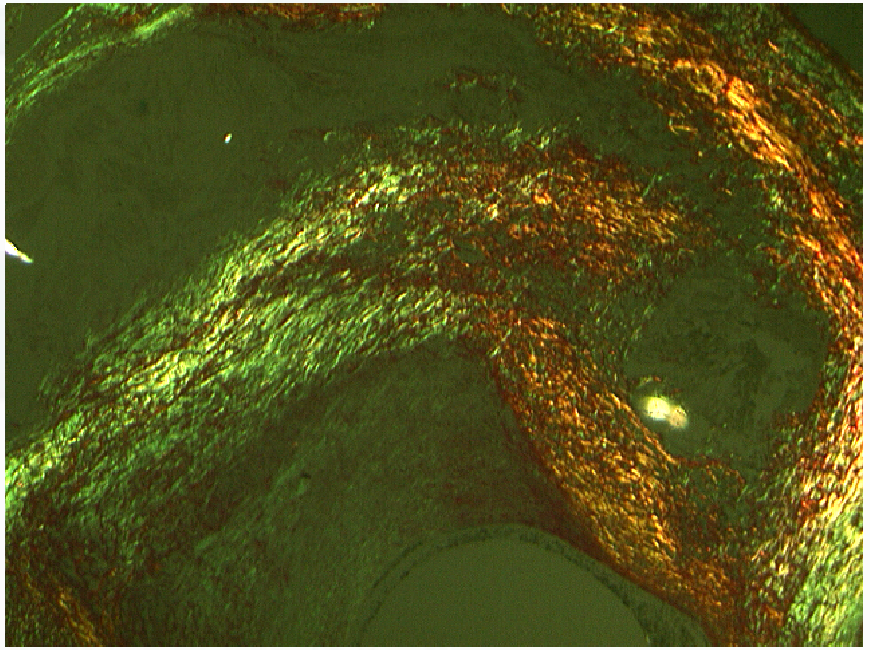
Healed Plaque Rupture:

layering of old (type I red/yellow) and new (type III green-whitish)



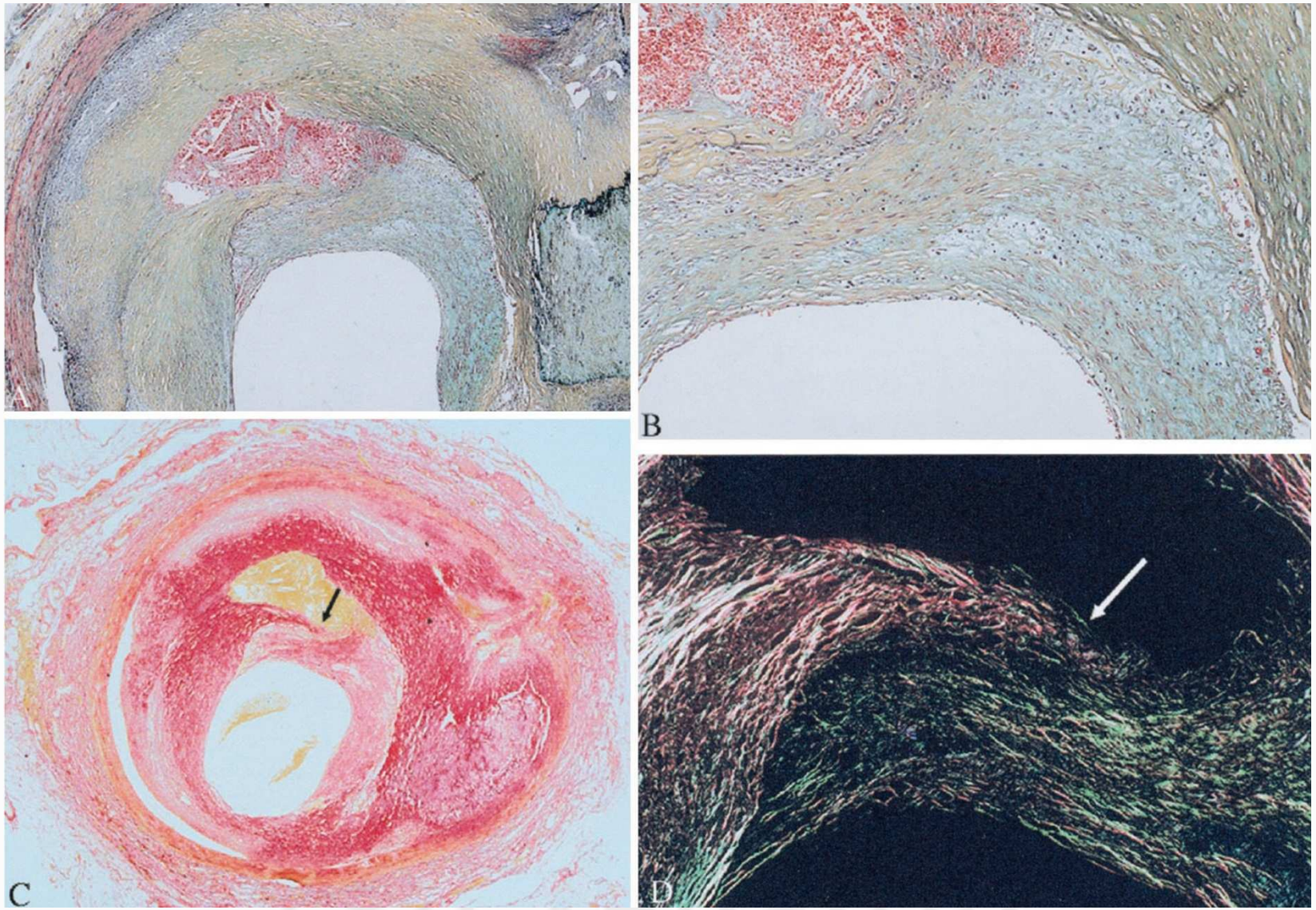




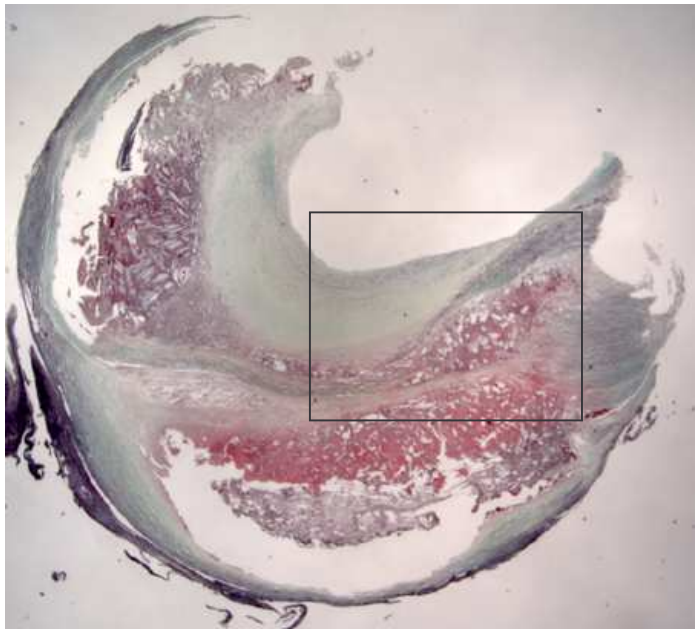


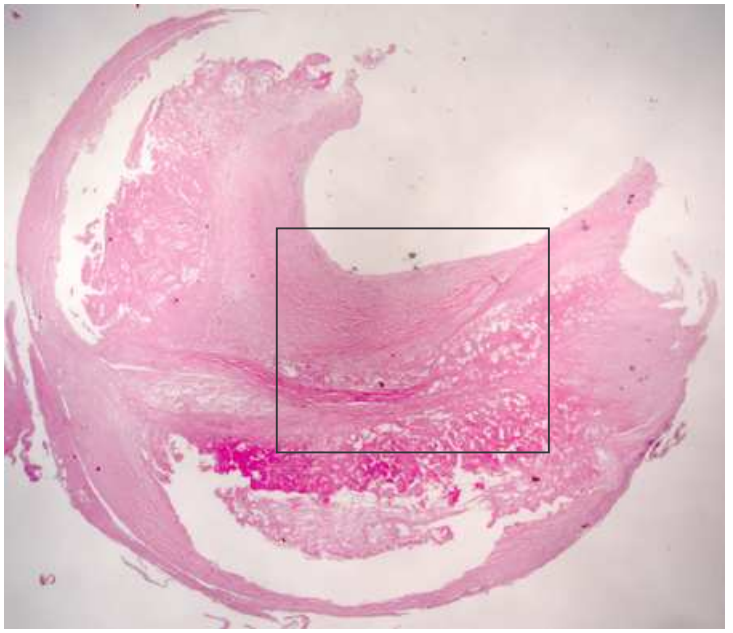
Healed Plaque Ruptures and Sudden Coronary Death.

Evidence That Subclinical Rupture Has a Role in Plaque Progression *(Allen P. Burke, MD; Frank D. Kolodgie, PhD; Andrew Farb, MD; Deena K. Weber, BS; Gray T. Malcom, PhD; John Smialek, MD; Renu Virmani, MD. Circulation. 2001;103 934-940)*

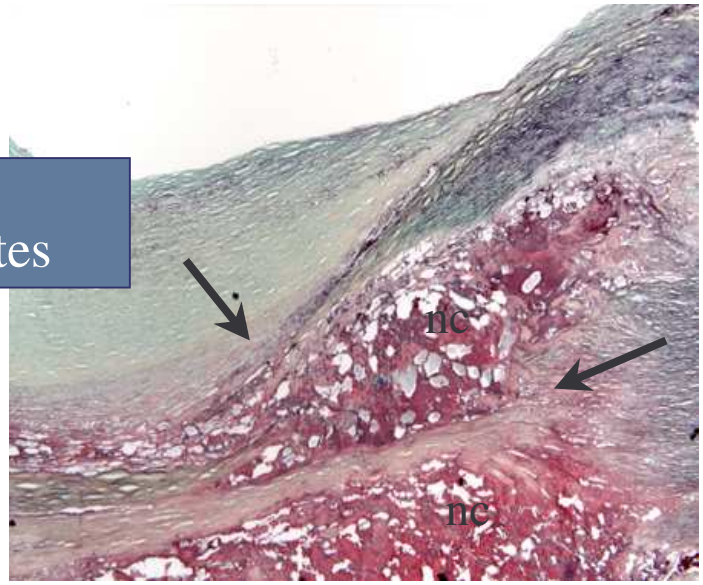


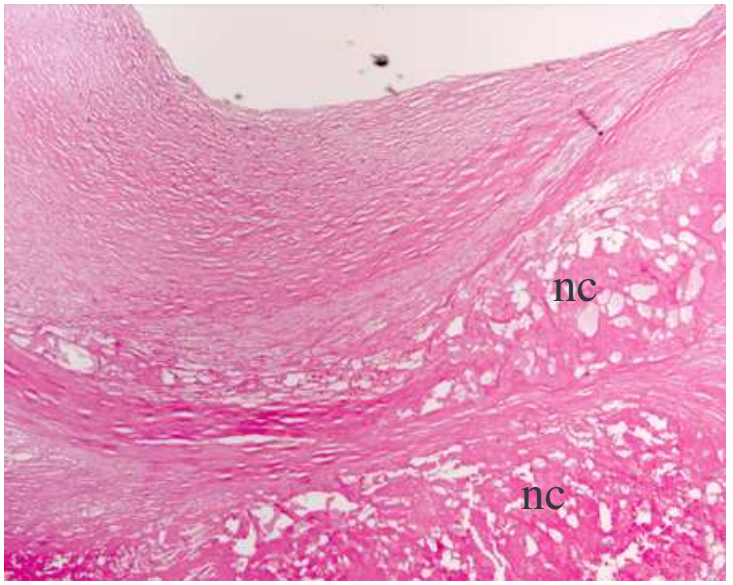
Are Rupture and Healing cyclic stages in plaque evolution?





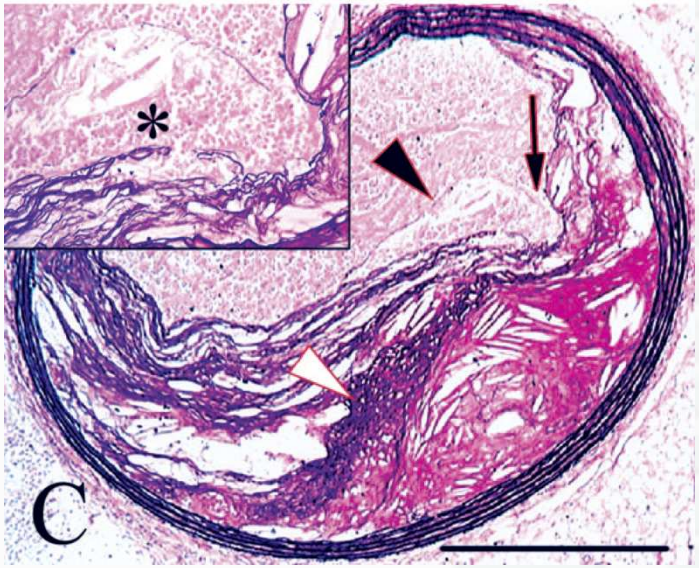
Previous rupture sites





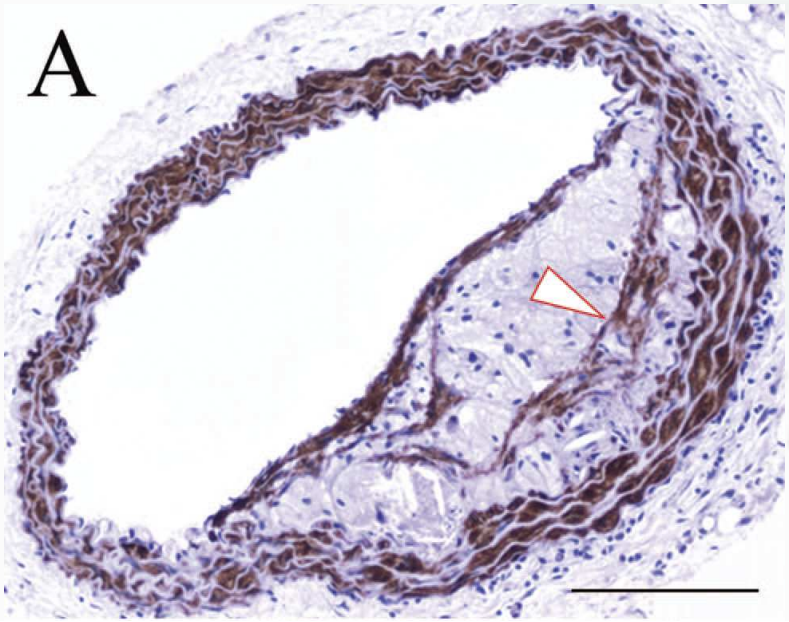
Experimental Evidence of healed Plaque rupture in fat feeding ApoE Knockout mice

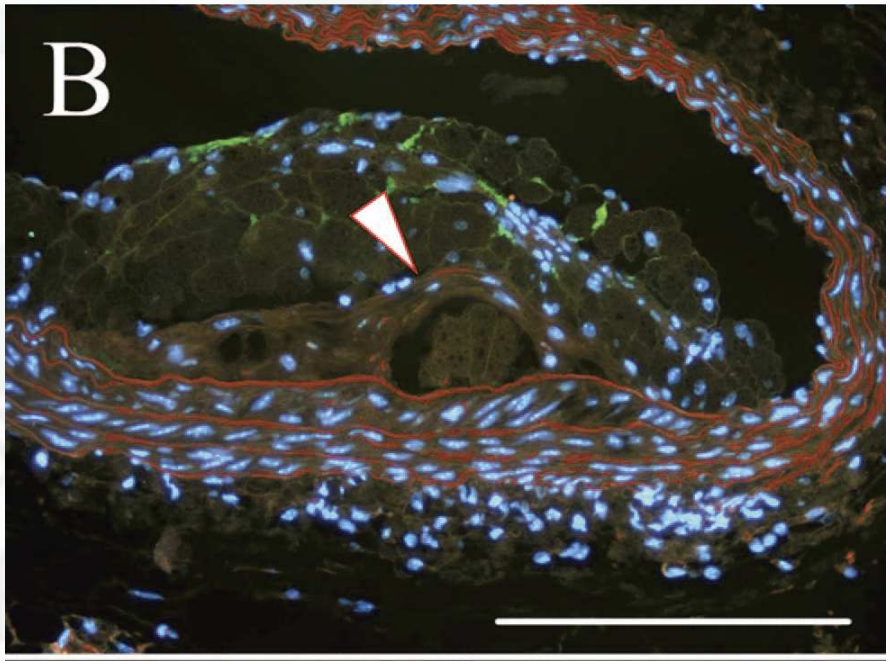
Johnson J. et al Circulation. 2005;11:1422-1430



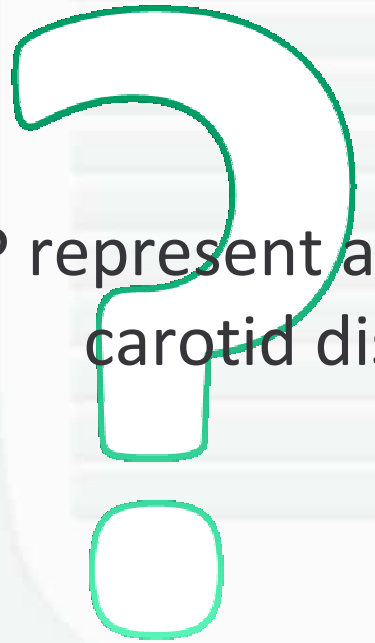
-After **8** weeks of fat feeding, the number of buried fibrous caps averaged **0.290.05 per animal** (n173).

-After **9** weeks, this number rose to **1.050.15** per animal (n37).





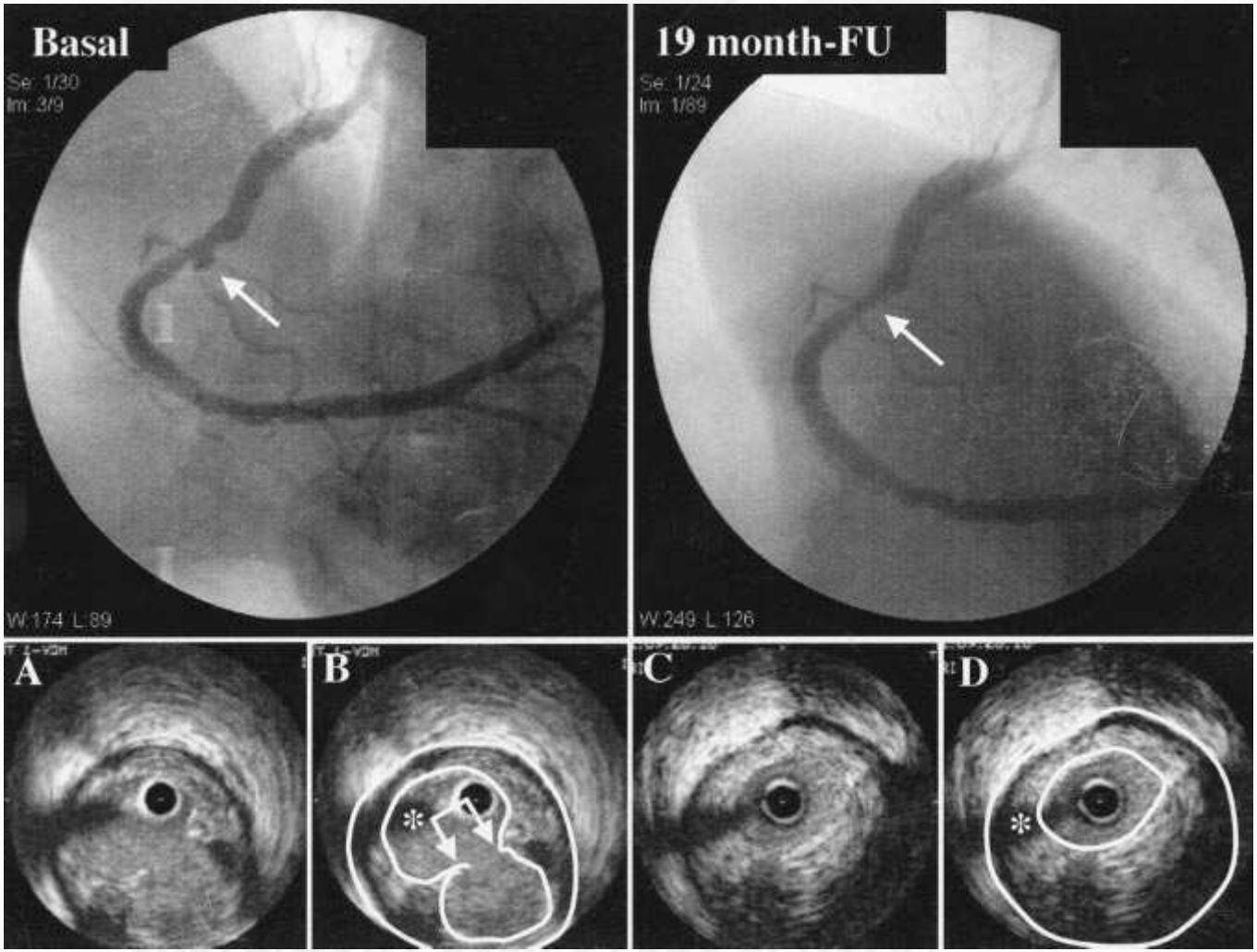
Does TAP represent a reversible stage of carotid disease ?



“in vivo” evidence of a ruptured plaque healing in a coronary

Angiography

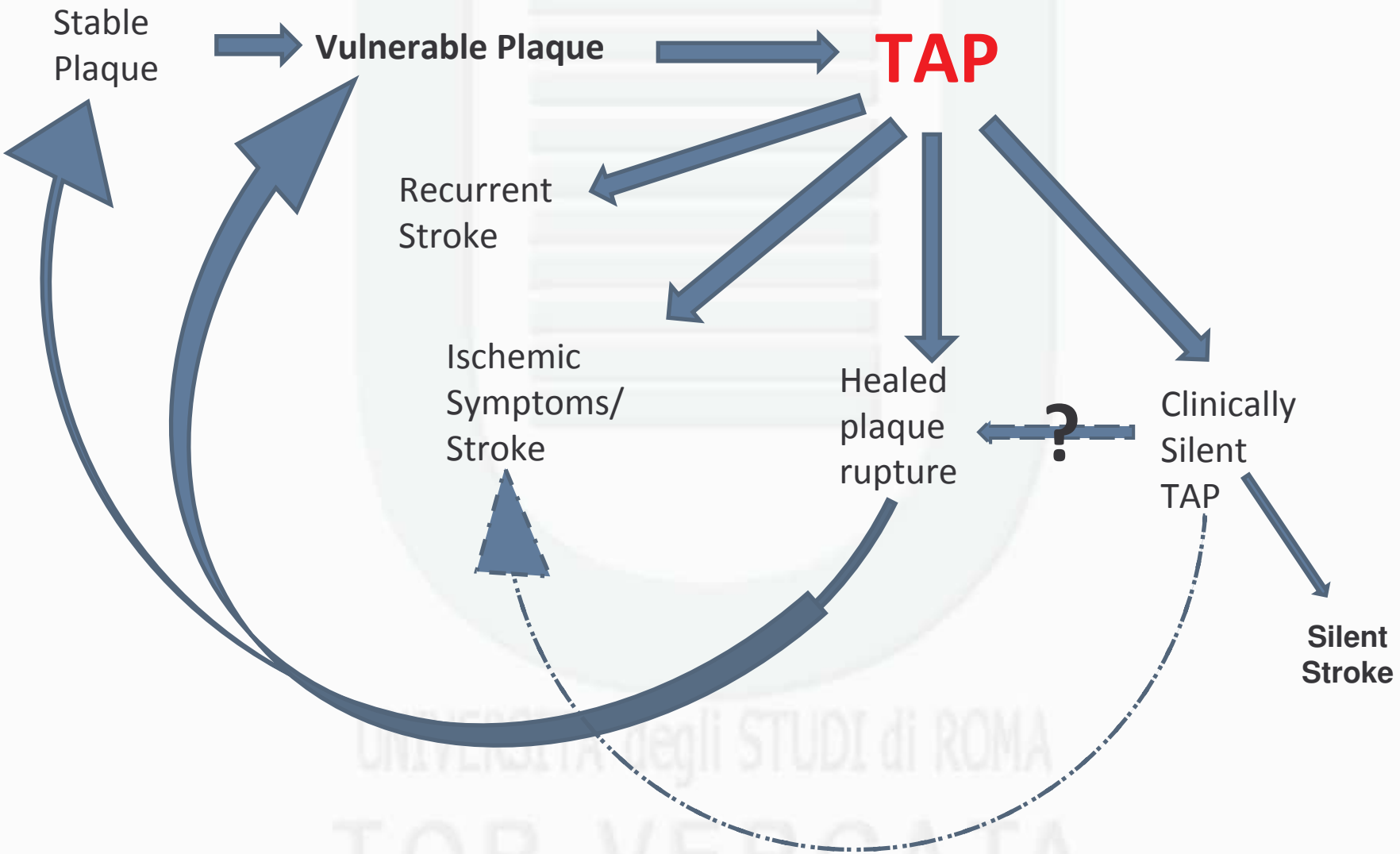
IVUS



Evolution of Spontaneous Atherosclerotic Plaque Rupture With Medical Therapy -Long-Term Follow-Up With Intravascular Ultrasound

Gilles Rioufol et al (Circulation. 2004;110:2875-2880.)

TAP is at the crossroads of the natural history of carotid disease



Future perspectives

Imaging techniques promise to become an invaluable and powerful tool to validate morphologic data on the natural history of carotid disease.

The cooperative study group of carotid arteriosclerotic disease

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