Vulnerable Plaque

Potential Targets for Imaging of Vulnerable Plaques

Angioplasty Summit TCT Asia Pacific 2007
Wednesday, April 25 ~ Friday, April 27, 2007
The Convention Center of Sheraton Walkerhill Hotel, Seoul, Korea

Erling Falk, Denmark

1st International Vulnerable Plaque Meeting

vpm2003

Meeting Directors

Patrick W. Serruys, MD
Antonio Colombo, MD
Christodoulos I. Stefanadis, MD
Johannes Schaar, MD

FINAL PROGRAM

June 17 - 18, 2003

Nomikos Centre Thira (Santorini), Greece

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Special article

Santorini declaration

Terminology for high-risk and vulnerable coronary artery plaques

Report of a Meeting on the Vulnerable Plaque, June 17 and 18, 2003, Santorini, Greece

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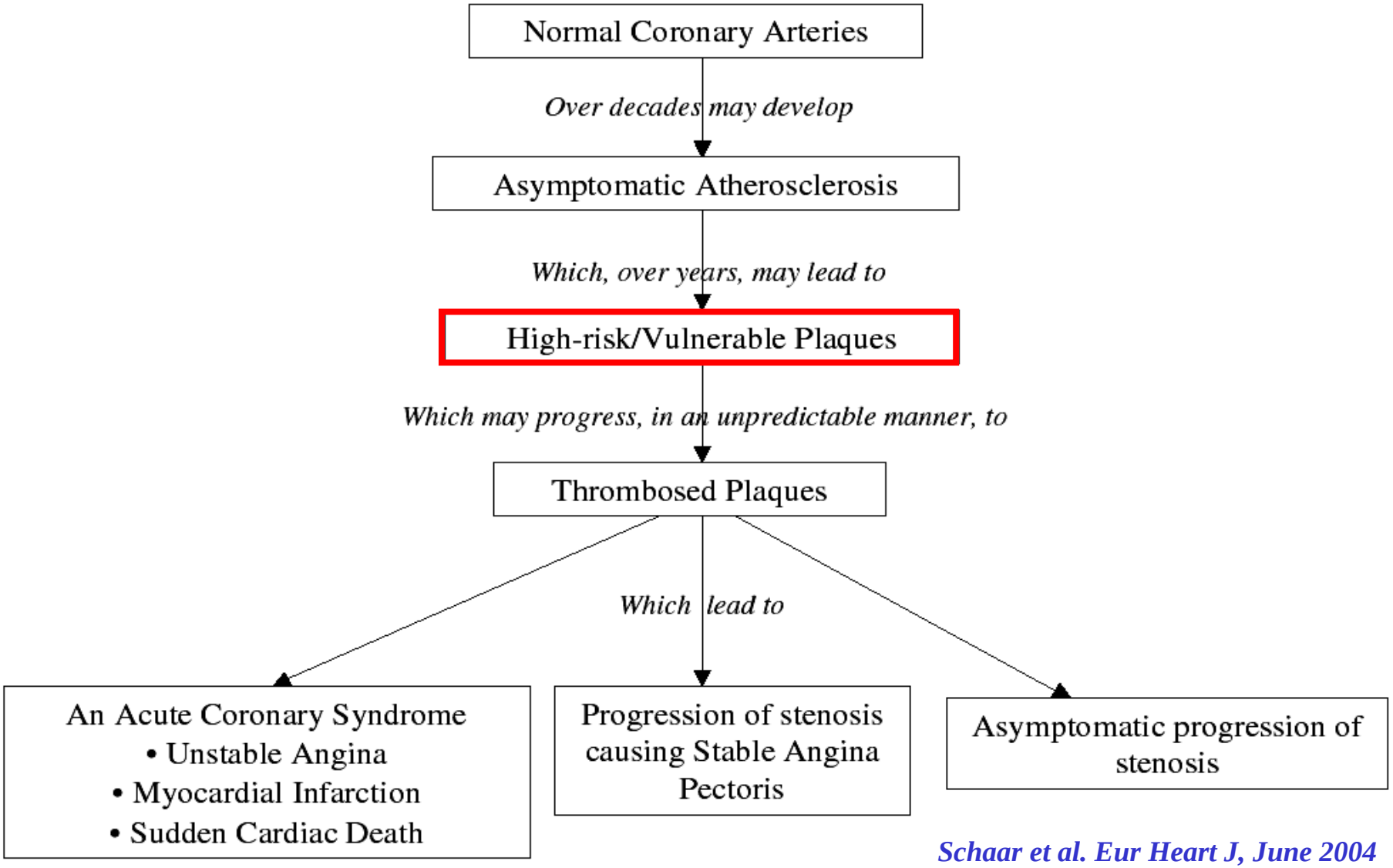
KEYWORDS
Vulnerable plaque;
High-risk plaque;
Acute coronary syndrome;
Terminology

A group of investigators met for two days in Santorini, Greece, to discuss progress in the field of identification and treatment of high risk/vulnerable atherosclerotic plaques and patients. Many differences in the manner in which terms are being utilized were noted. It was recognized that increased understanding of the pathophysiology of coronary thrombosis and onset of acute coronary syndromes has created the need for agreement on nomenclature. The participants spent considerable time discussing the topic and reached agreement on their own usage of the terms as described below. It is the hope that this usage might be of value to the larger community of scientists working in this field, and that widespread adoption of a common nomenclature would accelerate progress in the prevention of acute coronary events.

EHJ 2004;25:1077-82

Development of atherosclerosis and progression to thrombosis and clinical events



Schaar et al. Eur Heart J, June 2004

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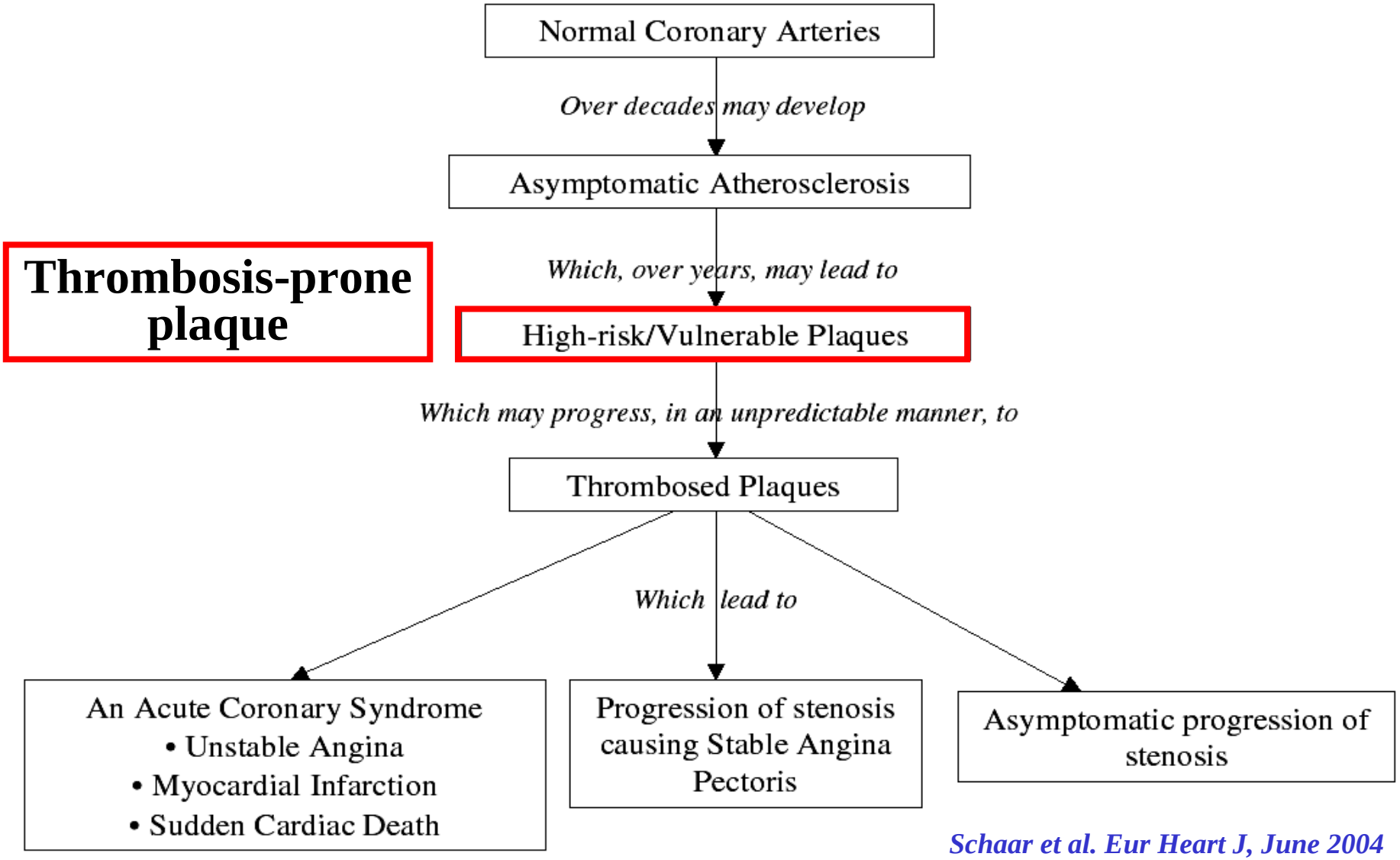
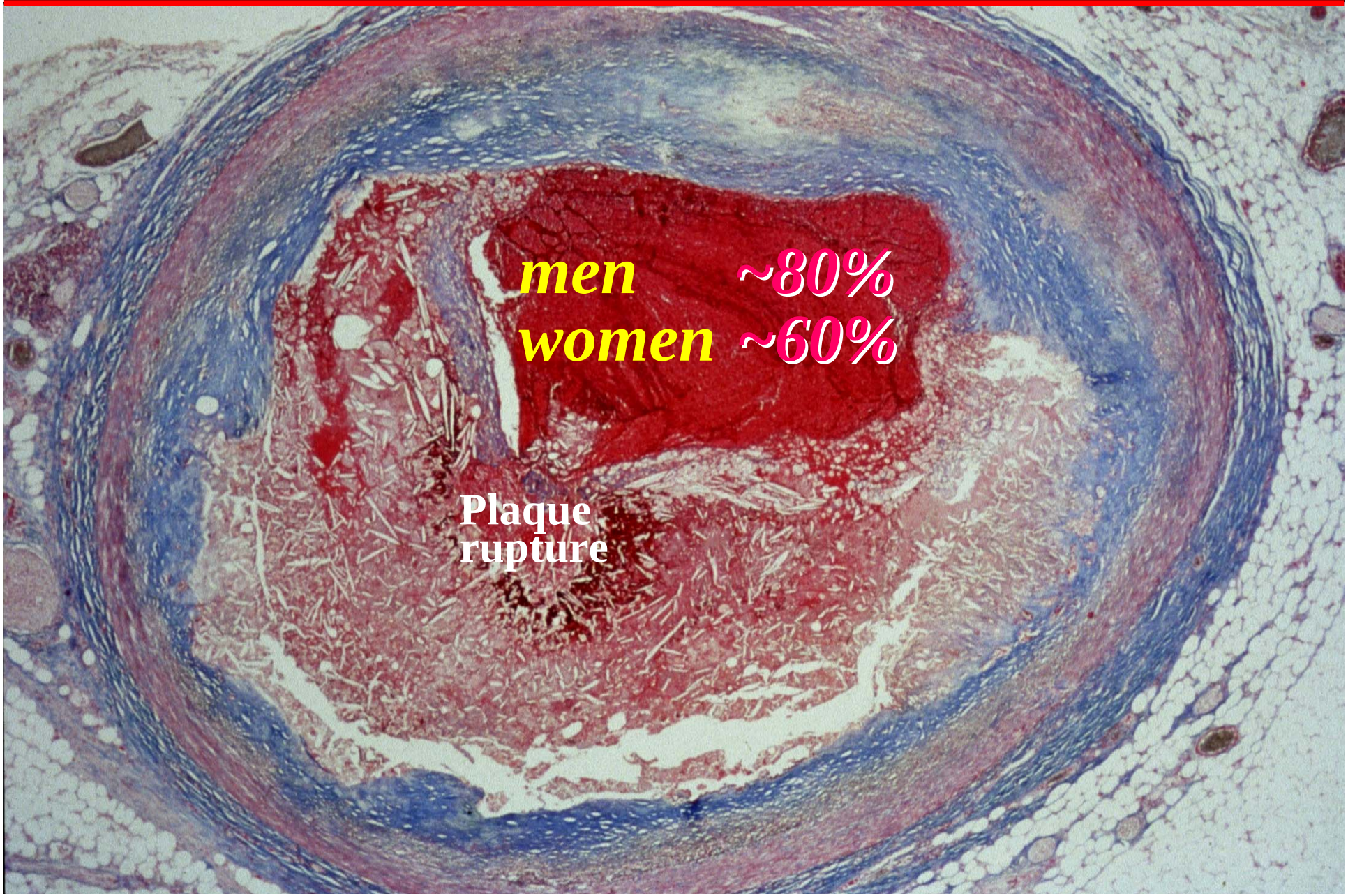


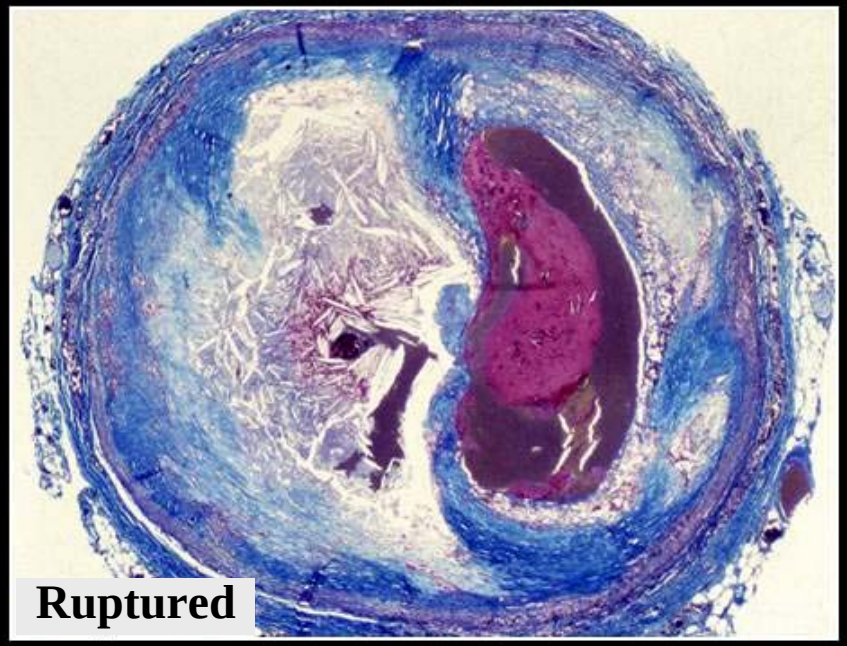
Thrombosis-prone plaque

Schaar et al. Eur Heart J, June 2004

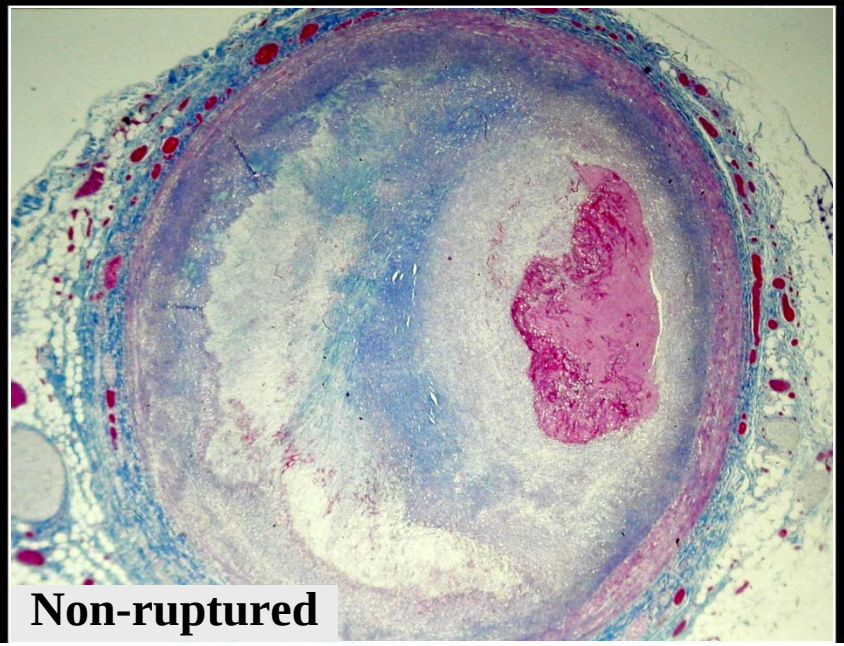
Plaque Rupture → Coronary Thrombosis



Thrombosis-prone = high-risk = *vulnerable plaque*



Ruptured



Non-ruptured

Coronary Thrombosis
plaque rupture

- men ~80%
- women ~60%

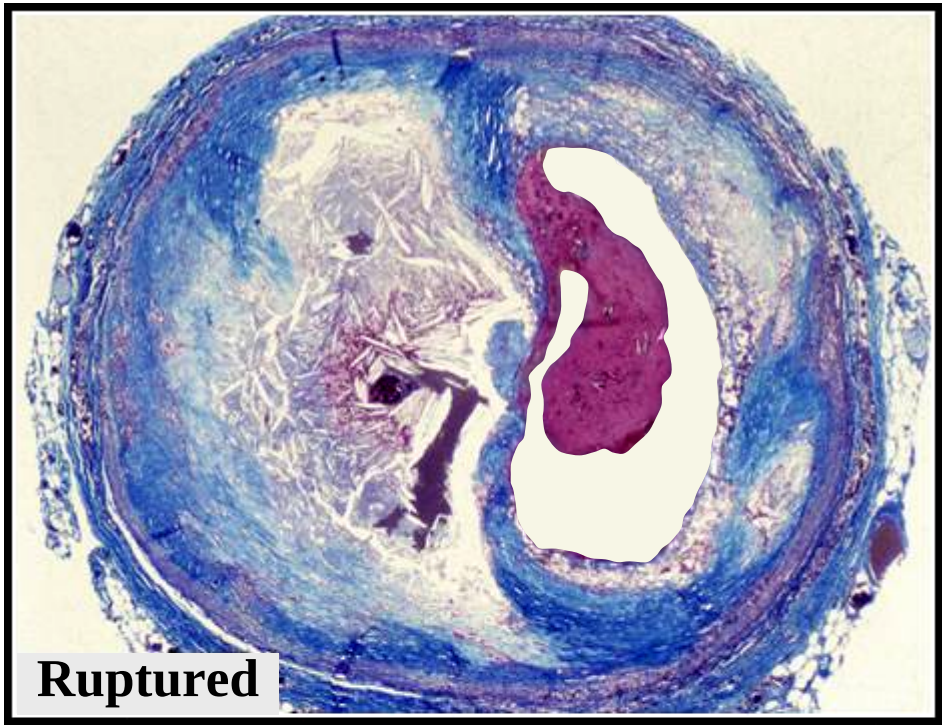
Fatal Coronary Thrombi Precipitated by Plaque Rupture

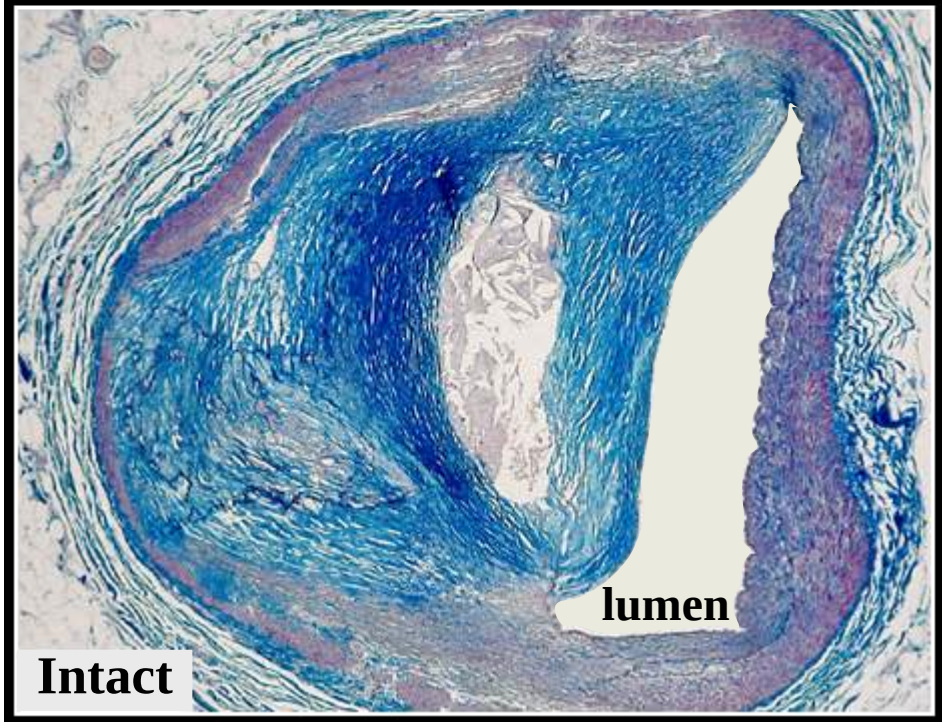
Patients	Age (yrs)*	n	Rupture	Study†
Hospital, —	—	19	19 = 100%	Chapman, 1965
Hospital, —	—	17	17 = 100%	Constantinides, 1966
Hospital, AMI + SCD	58	40	39 = 98%	Friedman et al., 1966
Hospital, AMI	62	88	71 = 81%	Bouch et al., 1970
Hospital, AMI	66	91	68 = 75%	Sinapius, 1972
Coroner, SCD	53	20	19 = 95%	Friedman et al., 1973
Hospital, AMI	67	76	69 = 91%	Horie et al., 1978
Hospital, AMI	67	49	40 = 82%	Falk, 1983
Coroner, SCD	<65	32	26 = 81%	Tracy et al., 1985
Medical exam, SCD	<70	61	39 = 64%	El Fawal et al., 1987
Hospital, AMI	—	83	52 = 63%	Yutani et al., 1987
Coroner, —	—	85	71 = 84%	Richardson et al., 1989
Hospital, AMI	63	20	12 = 60%	van der Wal et al., 1994
Coroner, SCD	—	202	143 = 71%	Davies, 1997
Hospital, AMI	69	291	218 = 75%	Arbustini et al., 1999
Hospital, AMI	61	61	56 = 92%	Shi et al., 1999
Hospital, AMI	69	100	81 = 81%	Kojima et al., 2000
Medical exam, SCD	48	125	74 = 59%	Virmani et al., 2000
Total AMI + SCD		**1,460**	**1,114 = 76%**	**Worldwide**

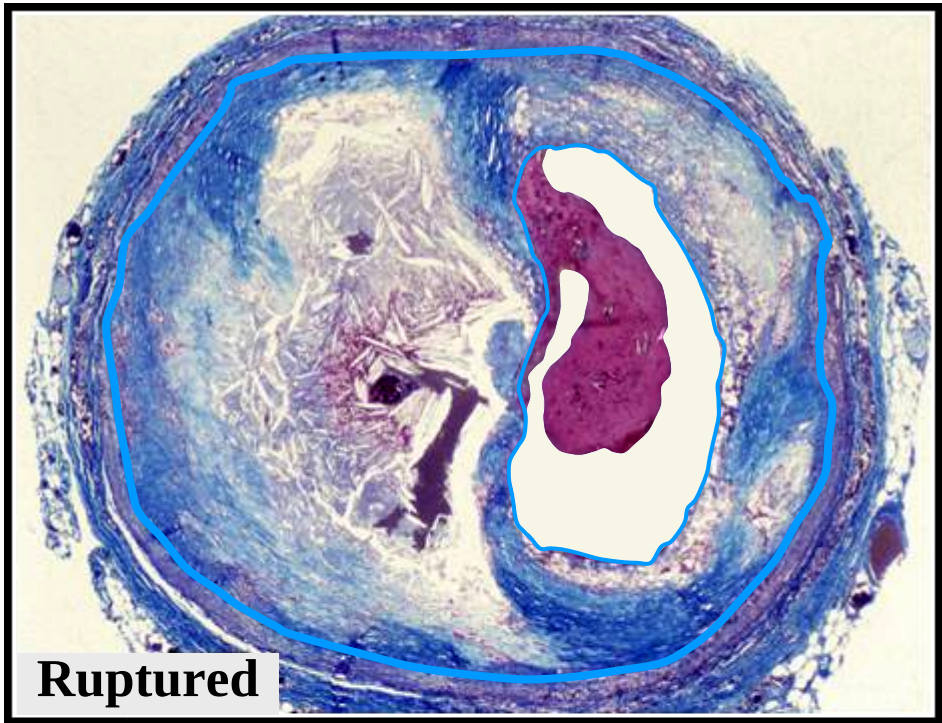
Falk. JACC 2006;47:C7-12

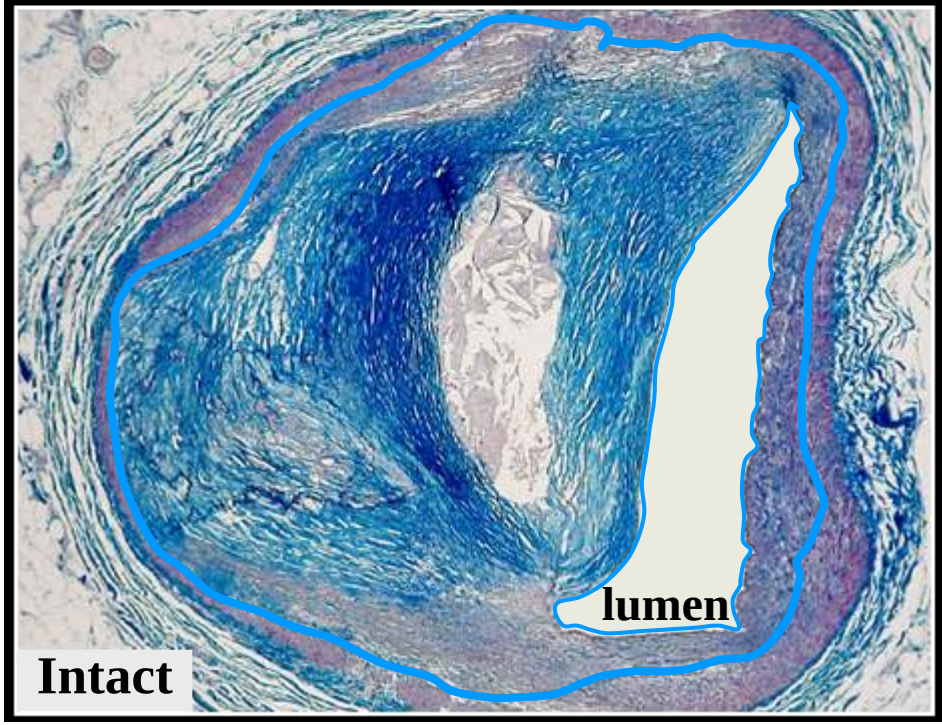
Coronary Atherosclerosis

ruptured vs intact plaque









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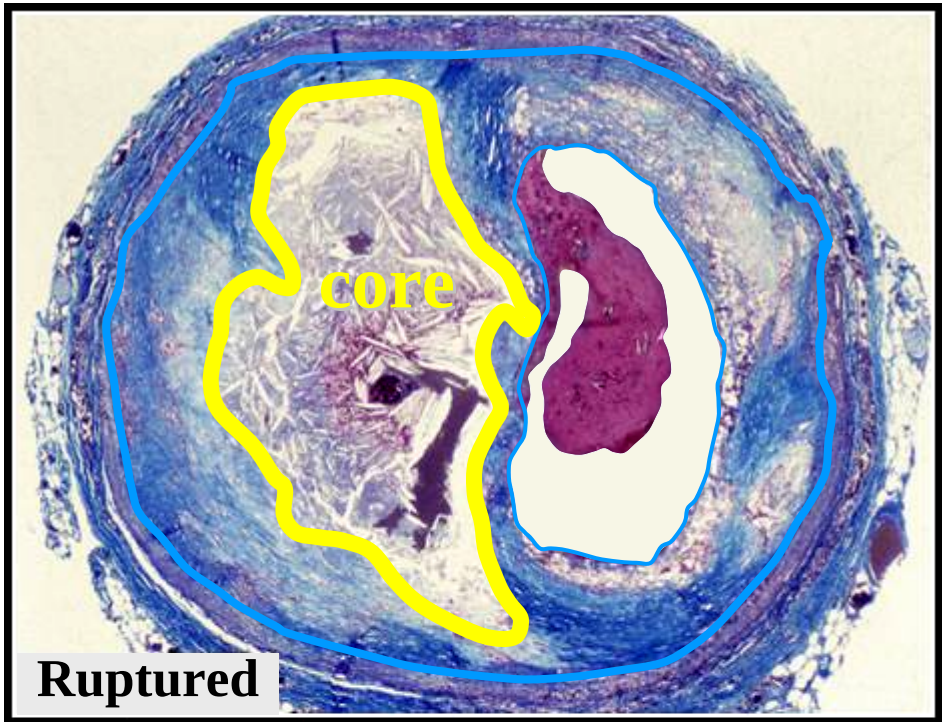
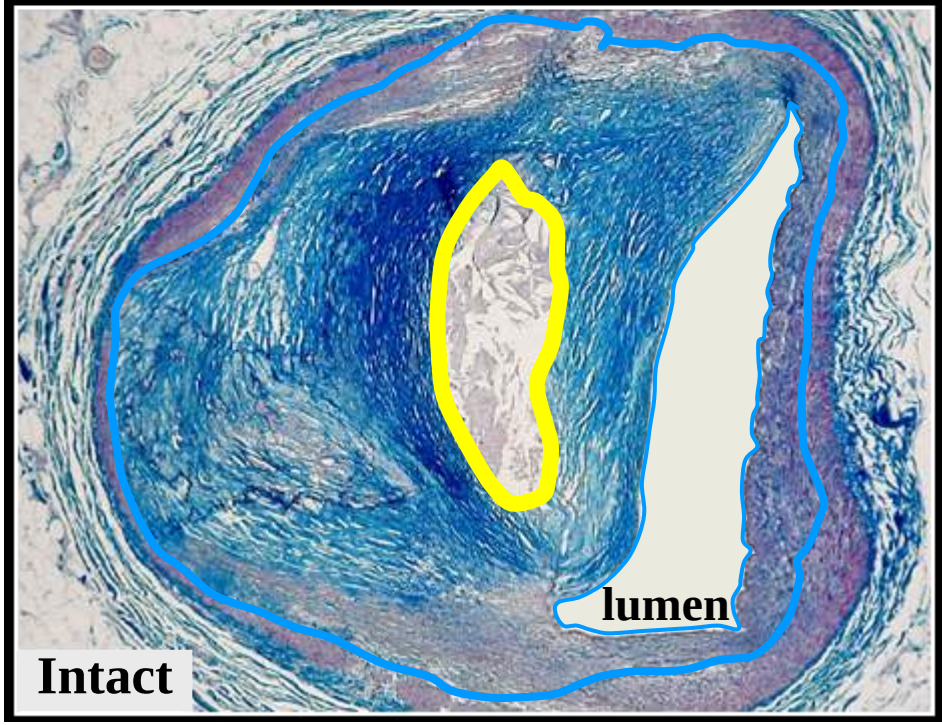
- **Plaque size↑**





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- **Plaque size↑**
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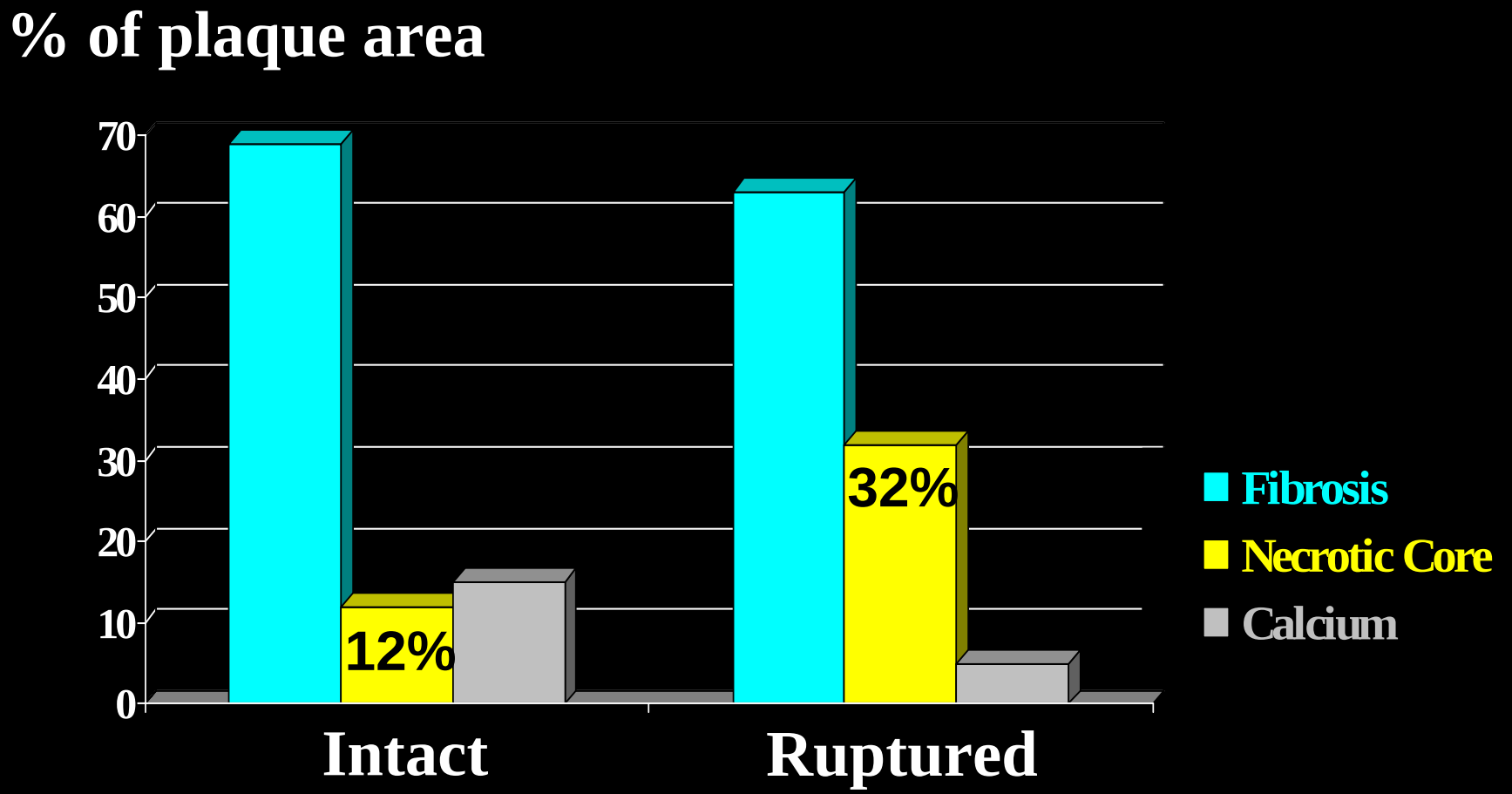
  - **~34% of plaque area***
  - **~3.8 mm^2 & ~9 mm long***

**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

Coronary Plaque Rupture

necrotic core in intact (stenotic) vs ruptured plaques



Gertz SD, Roberts WC. Am J Cardiol 1990;66:1368-72

Heart 2004;90:1385-91

MINI-SYMPOSIUM

Pathologic assessment of the vulnerable human coronary plaque

F D Kolodgie, R Virmani, A P Burke, A Farb, D K Weber, R Kutys, A V Finn, H K Gold

Plaque type	Necrotic core (%) Mean (SD)	No. cholesterol clefts (%)	Macrophage infiltration of fibrous cap (%)
Rupture	34 (17)$^{\Omega,\ \ni}$	12 (12)*,†	26 (20)$^{\psi,\tau,\varpi}$
TCFA	24 (17)	8 (9)	14 (10)$^{\psi}$
Erosion	14 (14)$^{\Omega}$	2 (5)*	10 (12)$^{\tau}$
Stable (stenotic)	12 (25)$^{\ni}$	4 (6)†	3 (0.7)$^{\varpi}$
p Value	Ω0.003, $\ni$0.01	*0.002, †0.04	ψ0.005, τ<0.0001, ϖ0.0001

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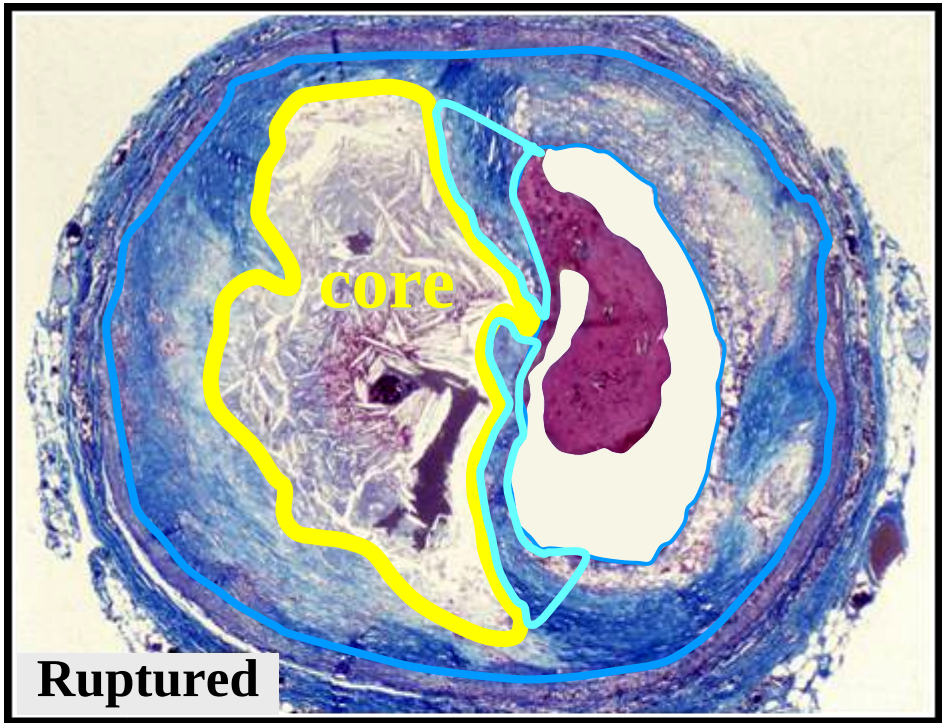
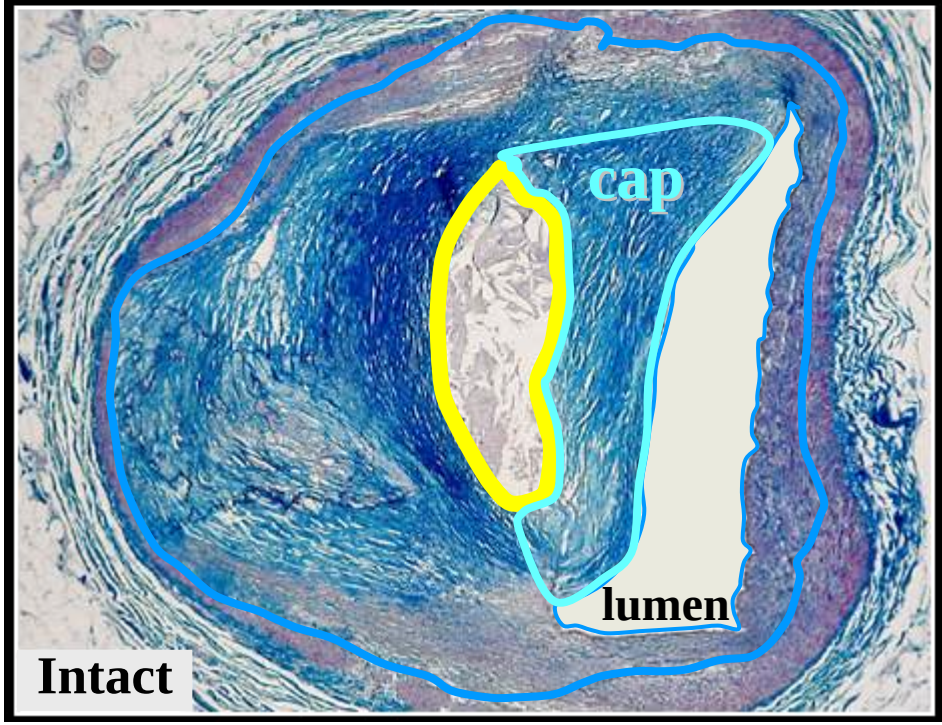
Overlap:

Necrotic core >10% of an average *stable* plaque





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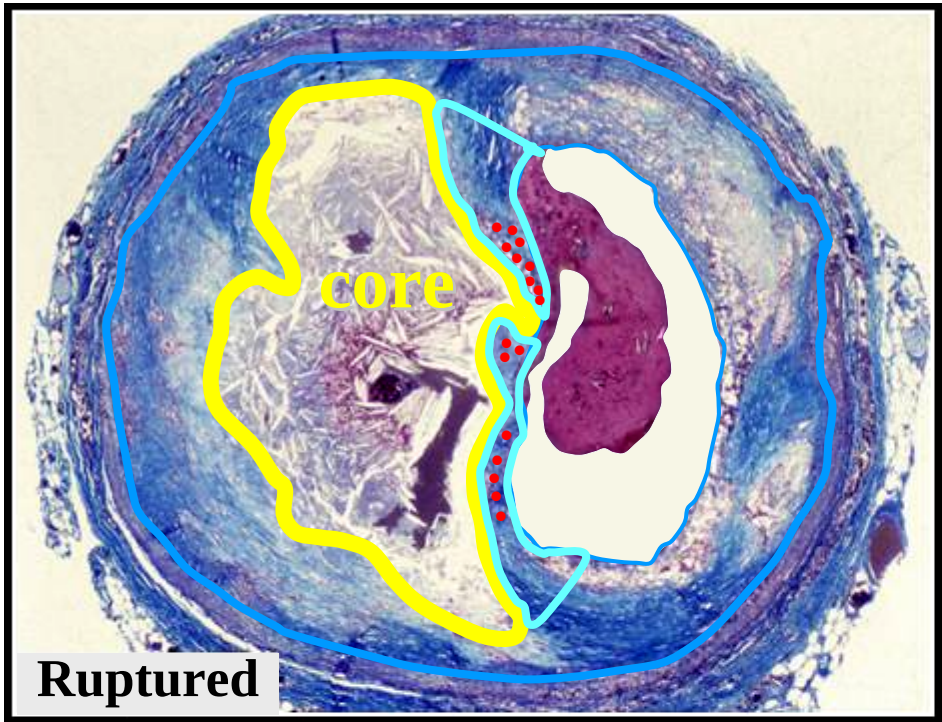

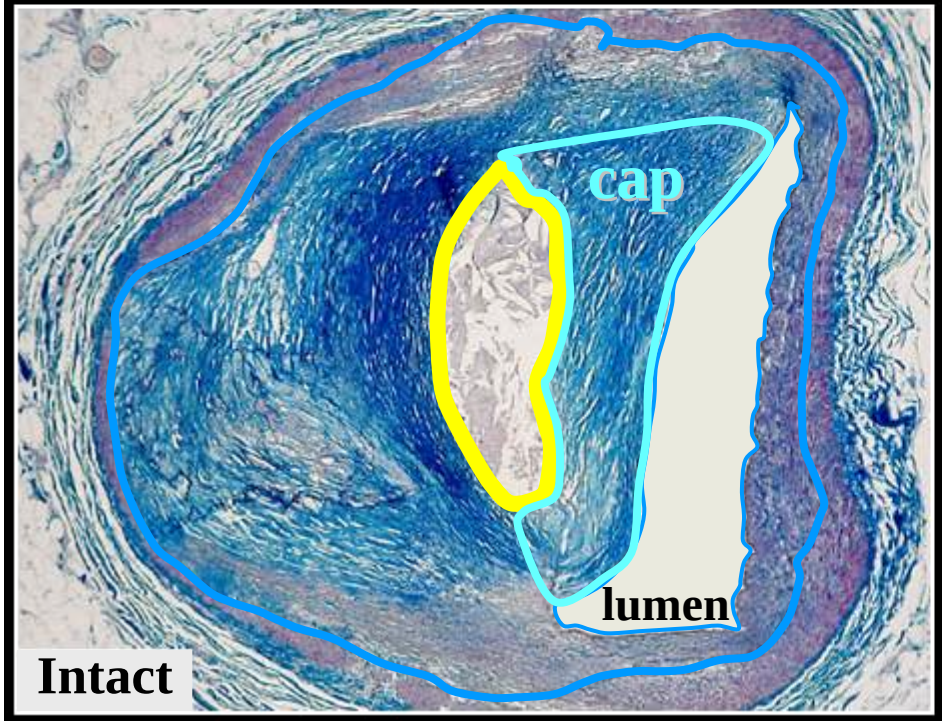

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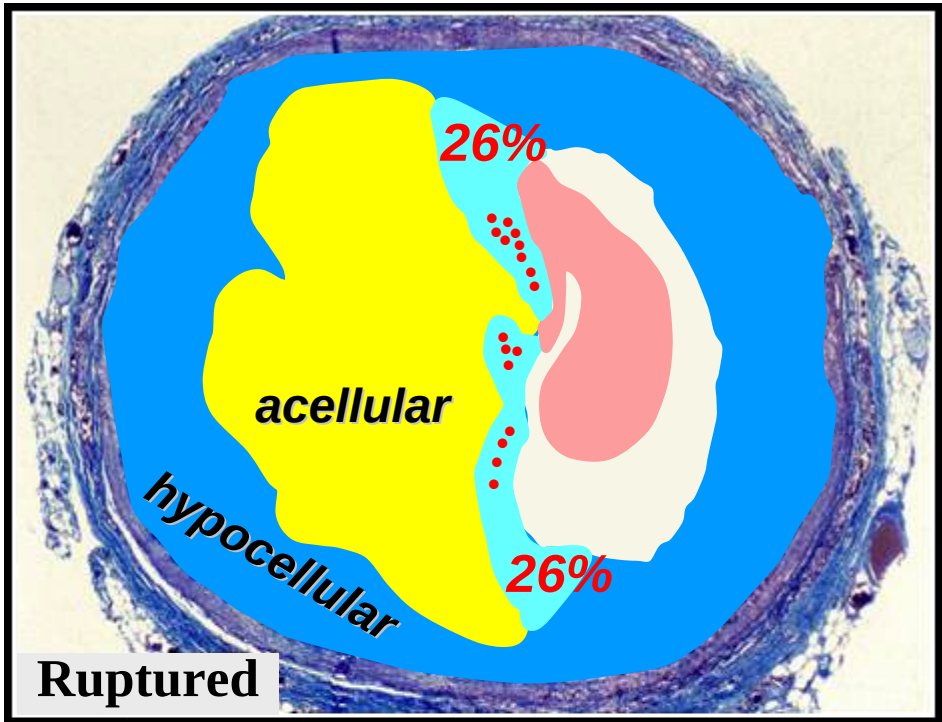

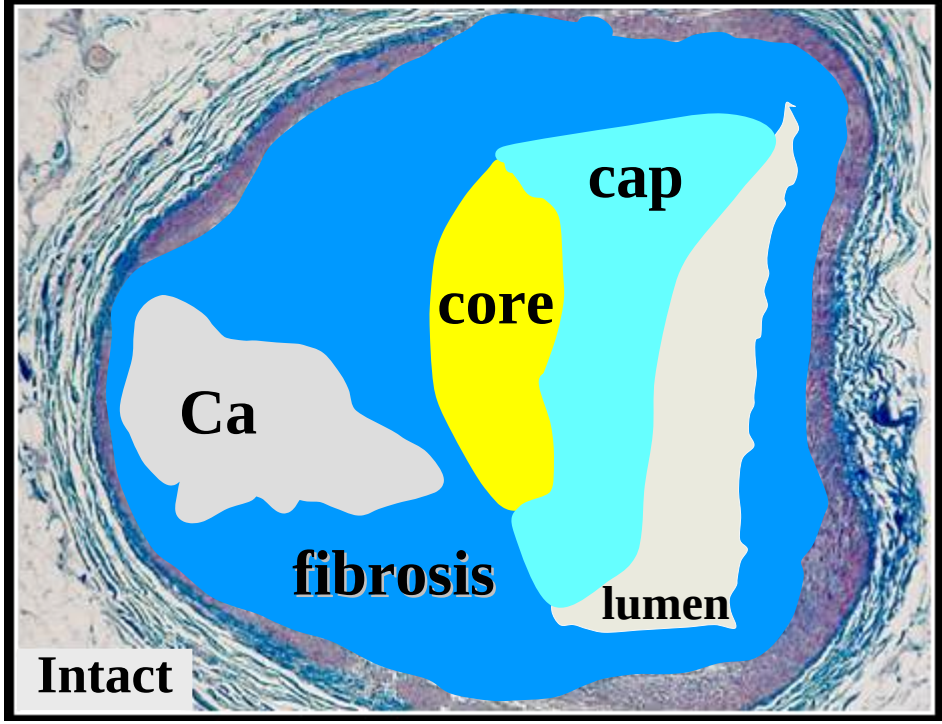

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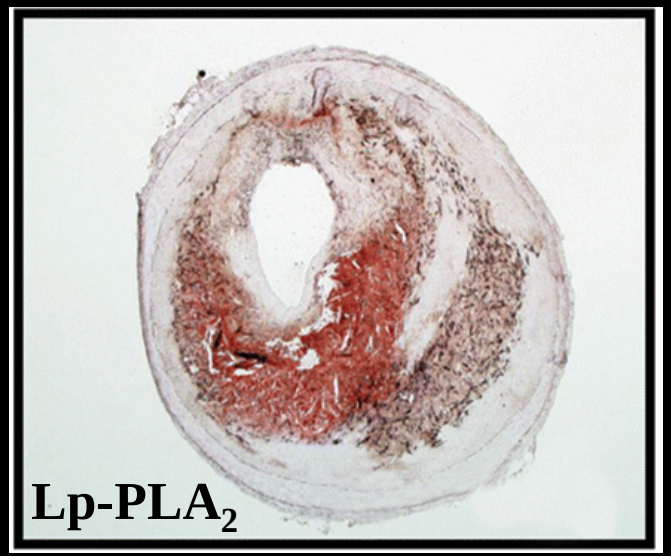
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

TABLE 2. Morphometric Assessment of Vessel Area, Stenosis, Necrotic Core Size, and Macrophages Density in a Large Series of Paraffin-Embedded Human Coronary Sections (n=488) From Sudden Coronary Death Patients

Plaque Type	IEL Area (mm^2)	Stenosis (%)	Necrotic Core Area (%)	Macrophage (%CD68)
Pathologic intimal thickening (n=125)	6.5±4.0	43.0±16.1	0.1±0.4	0.1±0.2
Fibroatheroma (n=262)	9.2±4.9	64.5±17.8	11.2±13.2	1.1±1.5
Thin-cap fibroatheroma (n=46)	12.8±7.9	67.0±15.5	21.6±23.7	2.0±1.9
Plaque rupture (n=55)	13.2±6.4	79.8±14.4	29.0±19.0	5.3±5.4
P value	<0.0001**	<0.0001*	<0.0001***	<0.0001*



Mean ~ SD

Kolodgie, …, Virmani. Lp-associated PLA_2 … . ATVB 2006;26:2523-9

Heart 1996;76:312-6

Clinically stable angina pectoris is not necessarily associated with histologically stable atherosclerotic plaques

Allard C van der Wal, Anton E Becker, Karel T Koch, Jan J Piek, Peter Teeling, Chris M van der Loos, George K David

***Conclusion*—The inverse relation between the extent of inflammatory activity in plaque tissues of culprit lesions and the clinical stability of the ischaemic syndrome supports the concept that reduction of inflammation favours plaque stabilisation. At the same time, the considerable overlap between groups indicates that patients with clinically stable angina do not all have histologically stable plaques.**

Plaque inflammation: considerable overlap

(dis)similar syndromes

Considerable overlap between

1. Chr. stable angina, n=28
2. Unstable angina, n=18
3. Acute rest angina, n=12

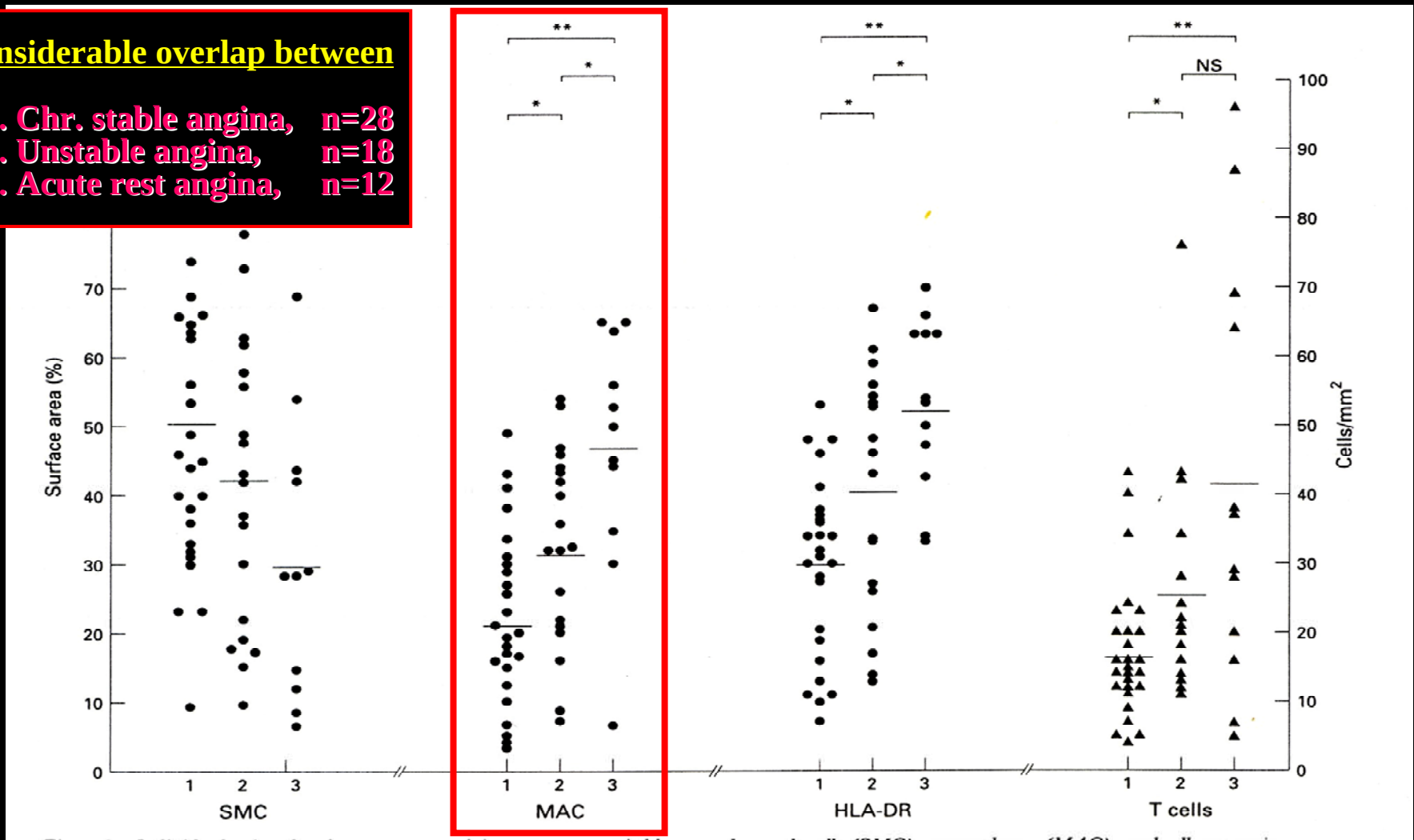
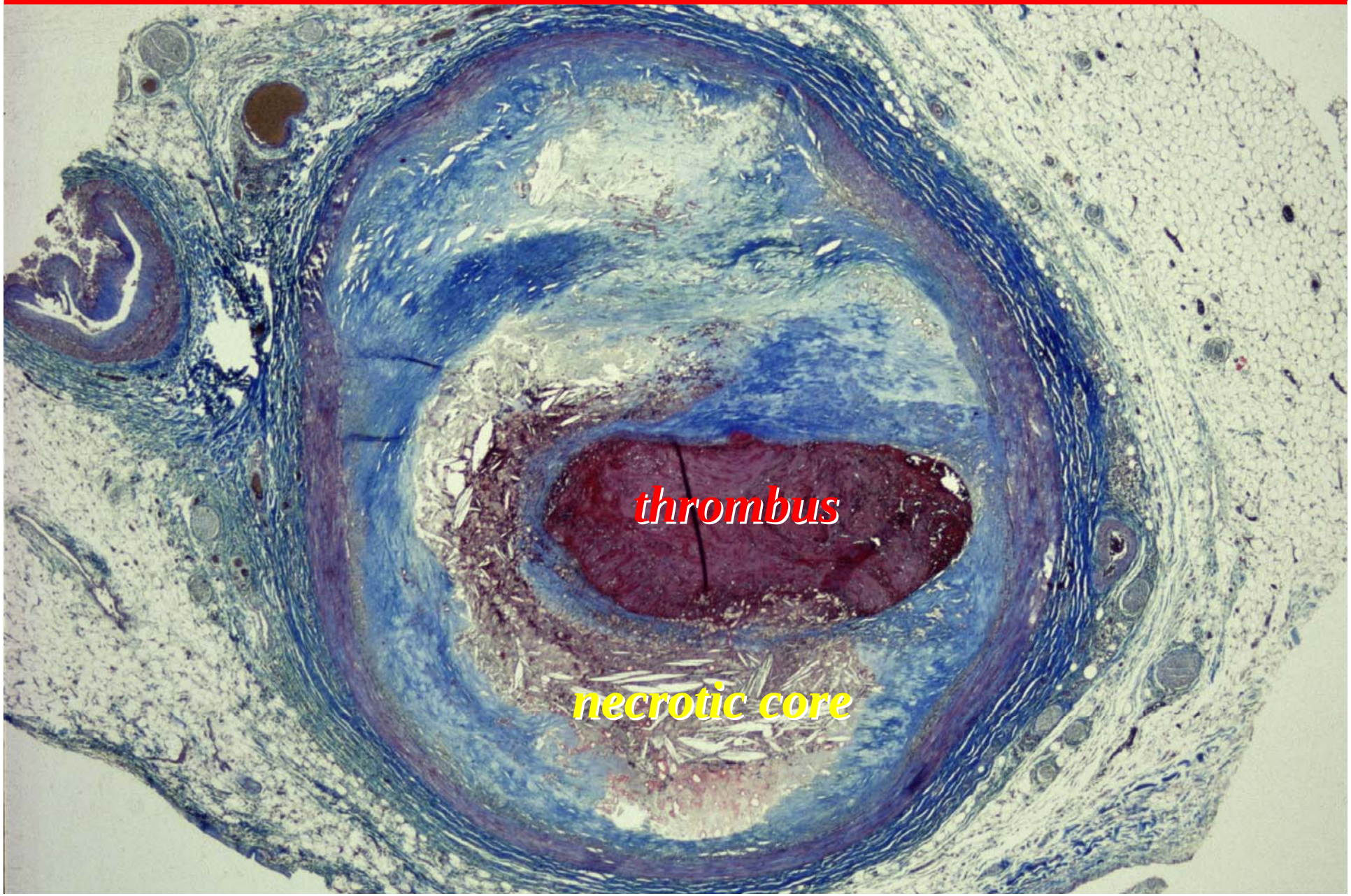


*Figure 2 Individual point plots for percentages of tissue areas occupied by smooth muscle cells (SMC), macrophages (MAC), and cells expressing HLA-DR (HLA-DR) and the number of T lymphocytes per mm² for each atherectomy specimen in the three patient groups. Note the considerable overlap between the three groups. Bars represent mean values. *P < 0·05; **P < 0·005.*

van der Wal et al. Heart 1996;76:312-6

Plaque rupture: role of inflammation



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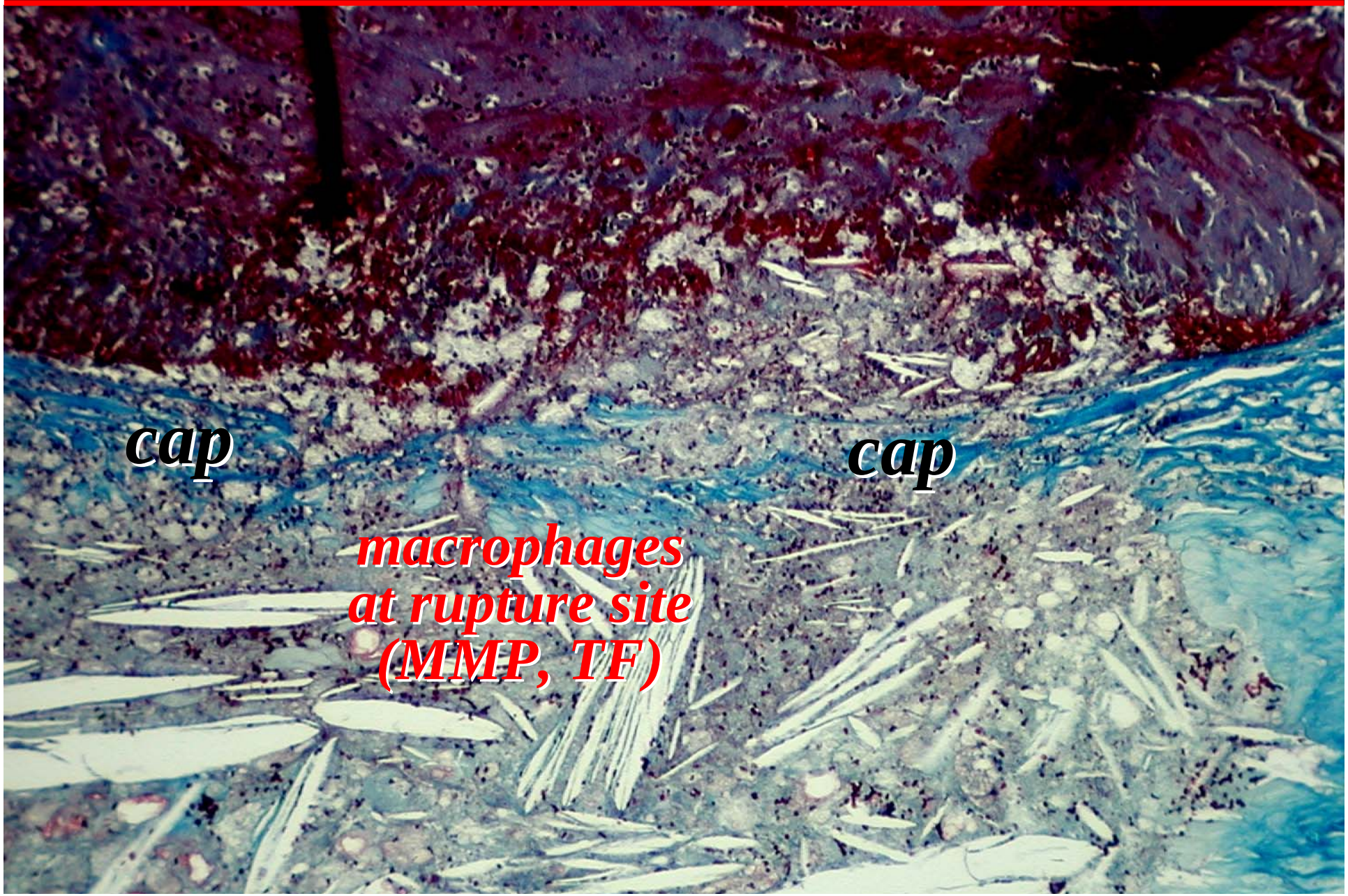

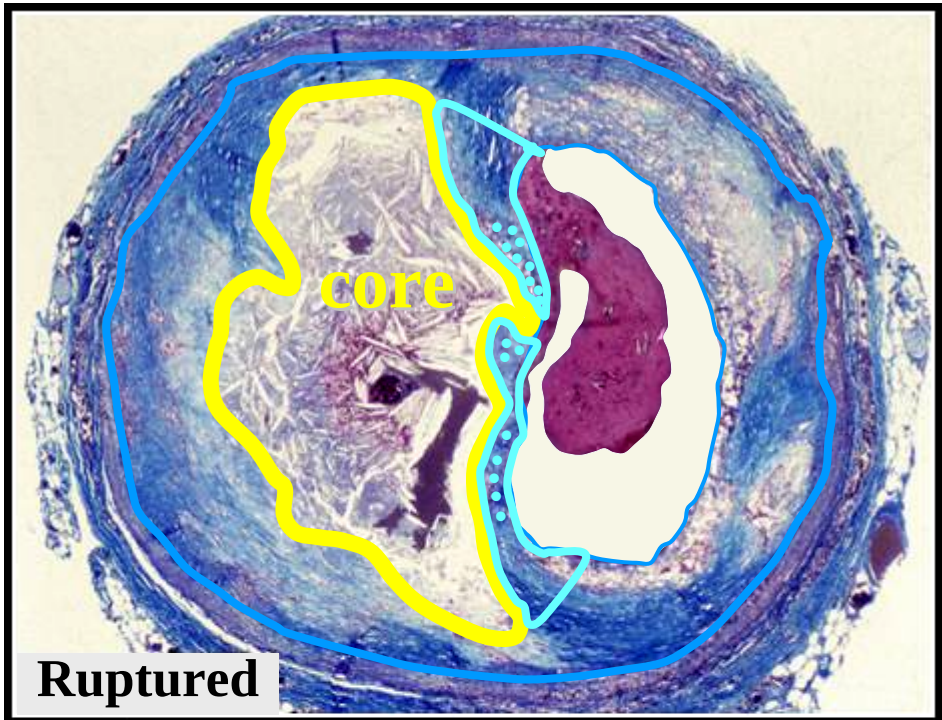

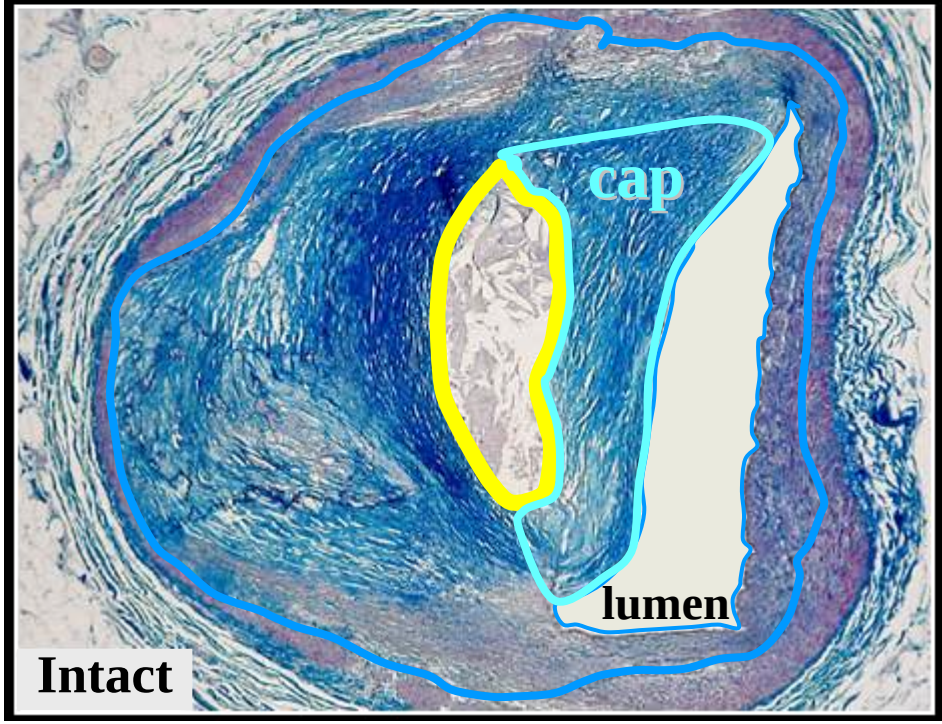

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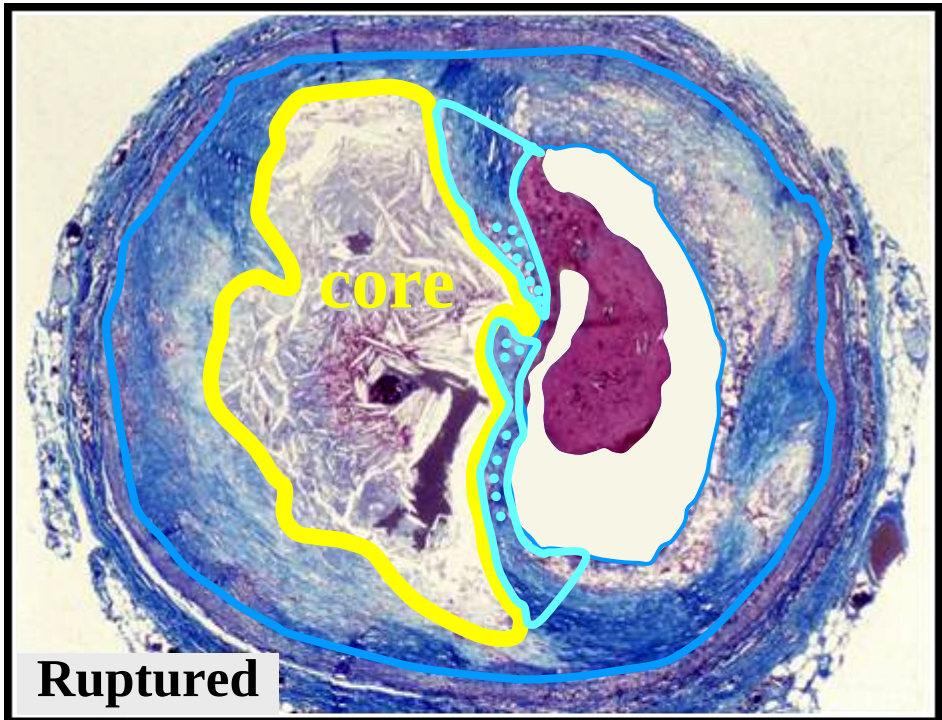

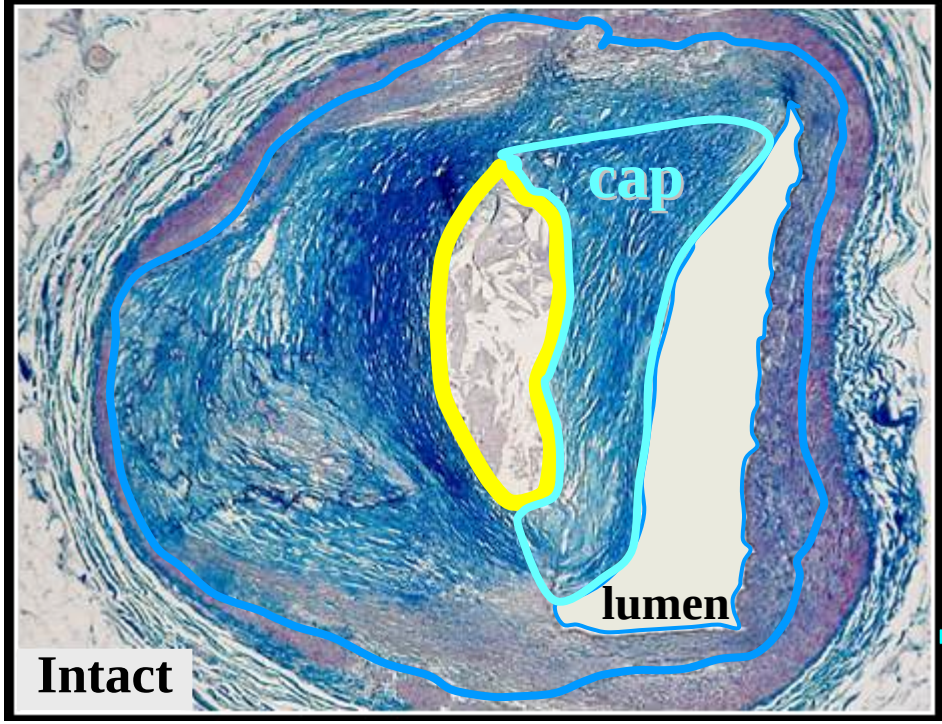

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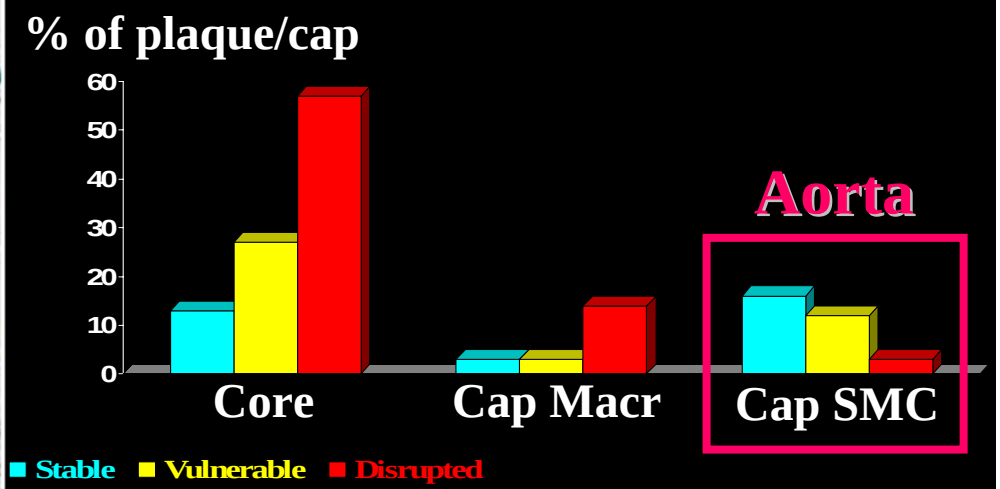

Davies et al. Br Heart J 1993;69:377-81

Heart 2004;90:1385-91

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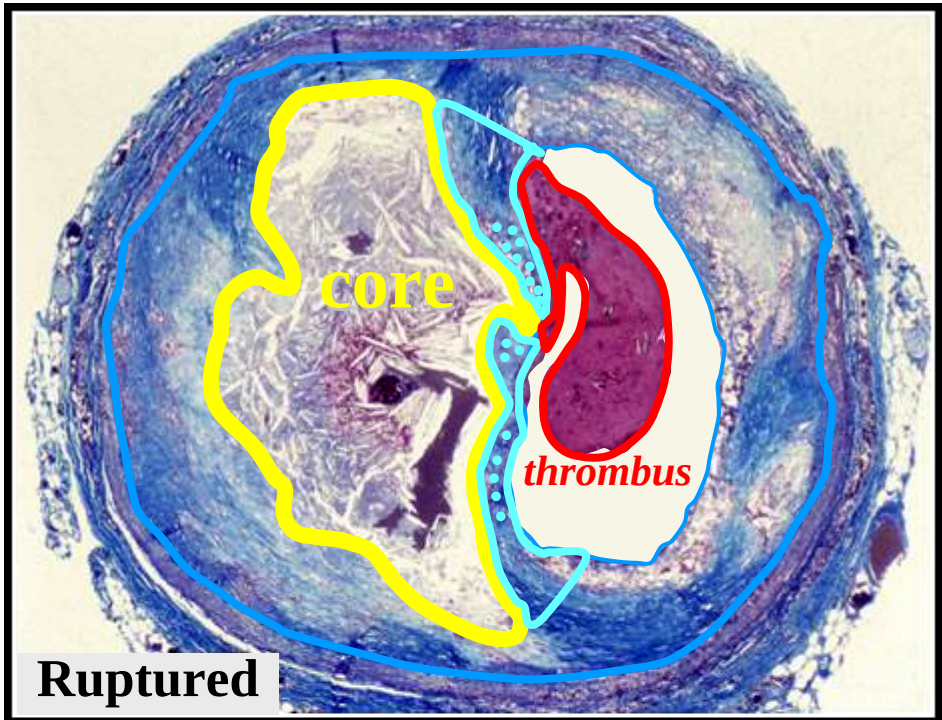

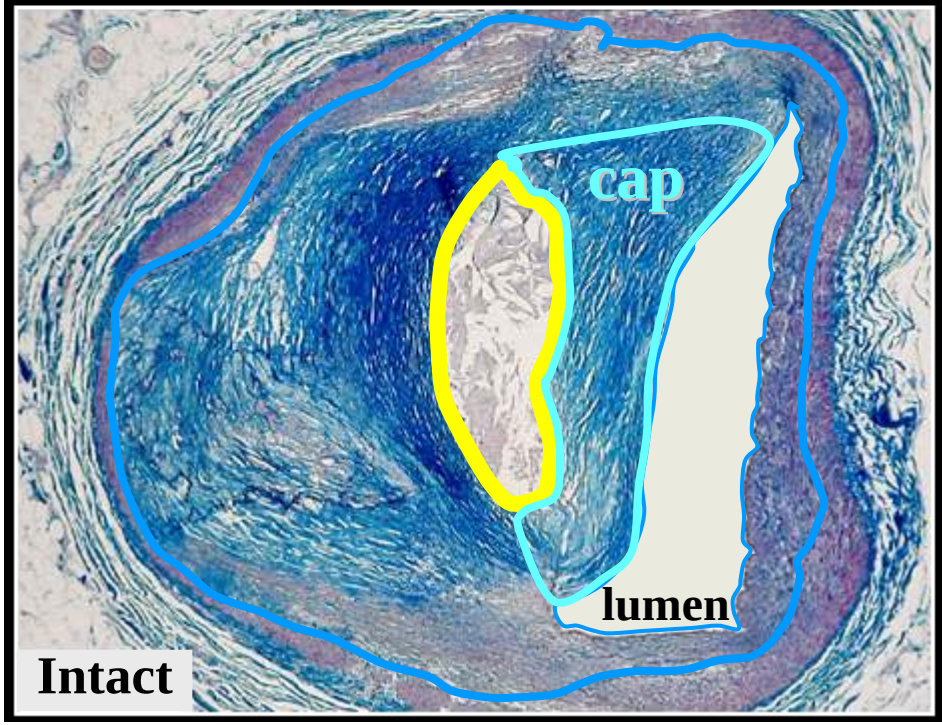

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Fatal Coronary Thrombi Precipitated by Plaque Rupture

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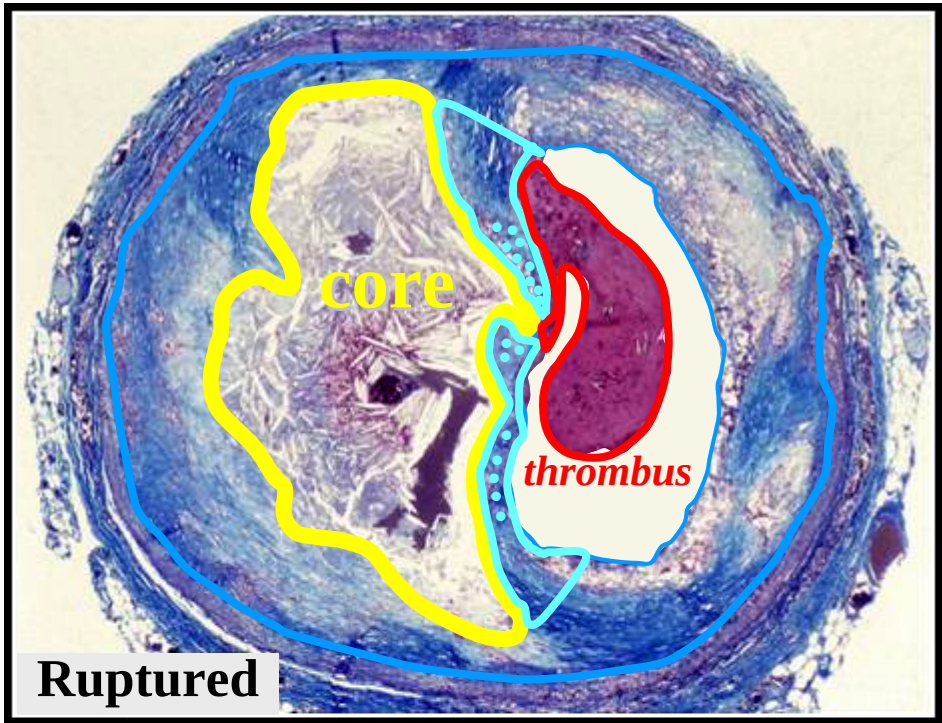
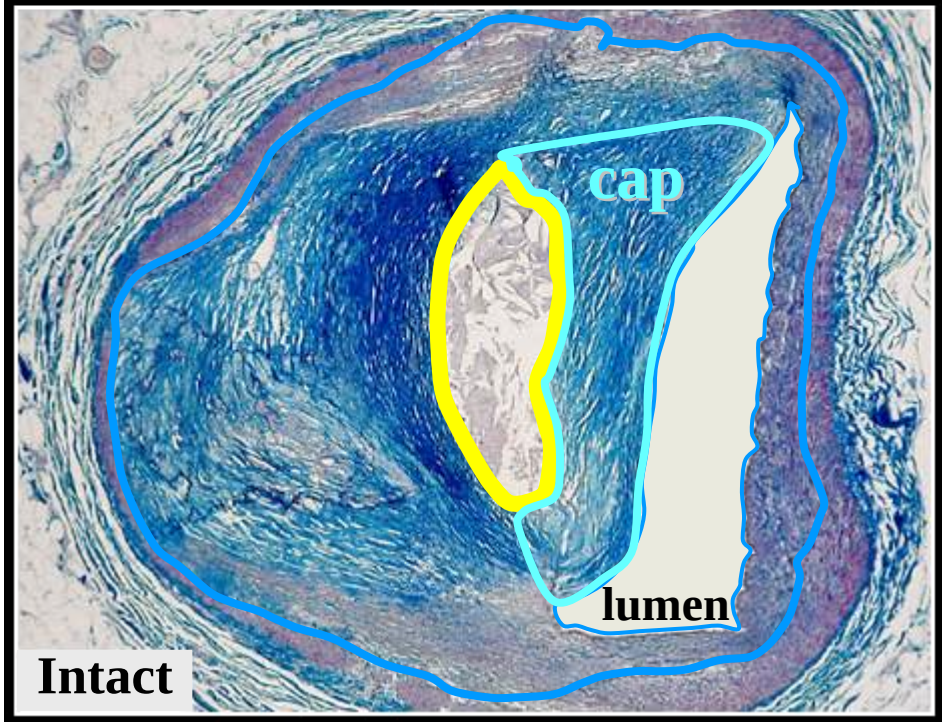
Coroner, SCD	53	20	19 = 95%	Friedman et al., 1973
Hospital, AMI	67	76	69 = 91%	Horie et al., 1978
Hospital, AMI	67	49	40 = 82%	Falk, 1983
Coroner, SCD	<65	32	26 = 81%	Tracy et al., 1985
Medical exam, SCD	<70	61	39 = 64%	El Fawal et al., 1987
Hospital, AMI	—	83	52 = 63%	Yutani et al., 1987
Coroner, —	—	85	71 = 84%	Richardson et al., 1989
Hospital, AMI	63	20	12 = 60%	van der Wal et al., 1994
Coroner, SCD	—	202	143 = 71%	Davies, 1997
Hospital, AMI	69	291	218 = 75%	Arbustini et al., 1999
Hospital, AMI	61	61	56 = 92%	Shi et al., 1999
Hospital, AMI	69	100	81 = 81%	Kojima et al., 2000
Medical exam, SCD	48	125	74 = 59%	Virmani et al., 2000
Total AMI + SCD		**1,460**	**1,114 = 76%**	**Worldwide**

Falk. JACC 2006;47:C7-12





Coronary Atherosclerosis
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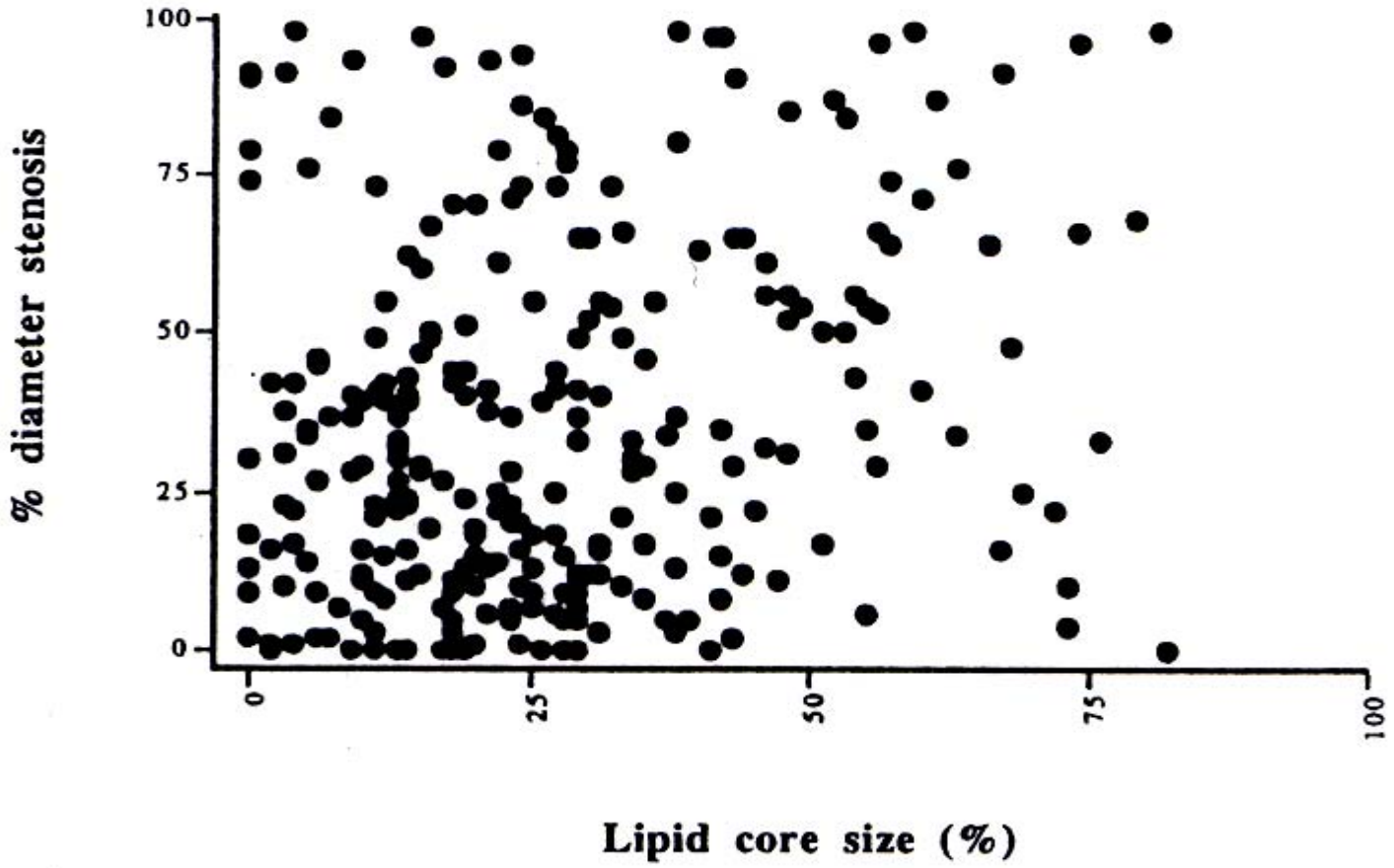
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

Vulnerable Plaque

Relation of Characteristics to Degree of Stenosis in Human Coronary Arteries

Jessica M. Mann, MD; Michael J. Davies, MD, FACC, FRCP

No correlation!



Circ 1996; 94:928-31

Coronary Remodeling & Plaque Vulnerability

positive but weak correlation with lipid core and macr

TABLE 2. Comparison of Remodeling as a Continuous Variable Versus the Other Pathological Characteristics Assessed

Pathological Characteristic	Mean (SD)	Correlation Coefficient Against Remodeling	*P*
Lipid core, %	32.2 (23.3)	0.4*	<0.0001
Macrophage count	12.9 (12.4)	0.3*	0.007
Eccentricity, degrees	49.7 (58.3)	0.2†	0.04
Change in target site medial wall thickness behind plaque	52.3 (38.4)	−0.05	0.6
Change in target site medial wall thickness at plaque free segment	63.8 (58.7)	0.4*	<.0001
Change in target site adventitial wall thickness behind plaque	264.7 (95.2)	−0.3†	0.02
Change in target site adventitial wall thickness at plaque free segment	85.7 (84.9)	0.3*	0.001
Vessel calcification	1.6 (1.1)	−0.02	0.8
Inflammatory cell count behind the plaque	0.4 (0.8)	0.01	0.9
Inflammatory cell count at the plaque free segment	0.8 (1.1)	0.2†	0.03

*Correlation significant at the 0.01 level (2-tailed).

Varnava, Mills, Davies. Circ 2002;105:939-43

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Varnava, Mills, Davies. Circ 2002;105:939-43

Relation of Arterial Geometry to Luminal Narrowing and Histologic Markers for Plaque Vulnerability: The Remodeling Paradox

GERARD PASTERKAMP, MD, PHD,*†‖ ARJAN H. SCHONEVELD, MSC,*‖
ALLARD C. VAN DER WAL, MD, PHD,‡ CHRISTIAN C. HAUDENSCHILD, MD, PHD,§
RUUD J.G. CLARIJS, MD,* ANTON E. BECKER, MD, PHD,‡ BEREND HILLEN, MD, PHD,†
CORNELIUS BORST, MD, PHD, FACC*

Utrecht and Amsterdam, the Netherlands and Rockville, Maryland

Objective. To relate local arterial geometry with markers that are thought to be related to plaque rupture.

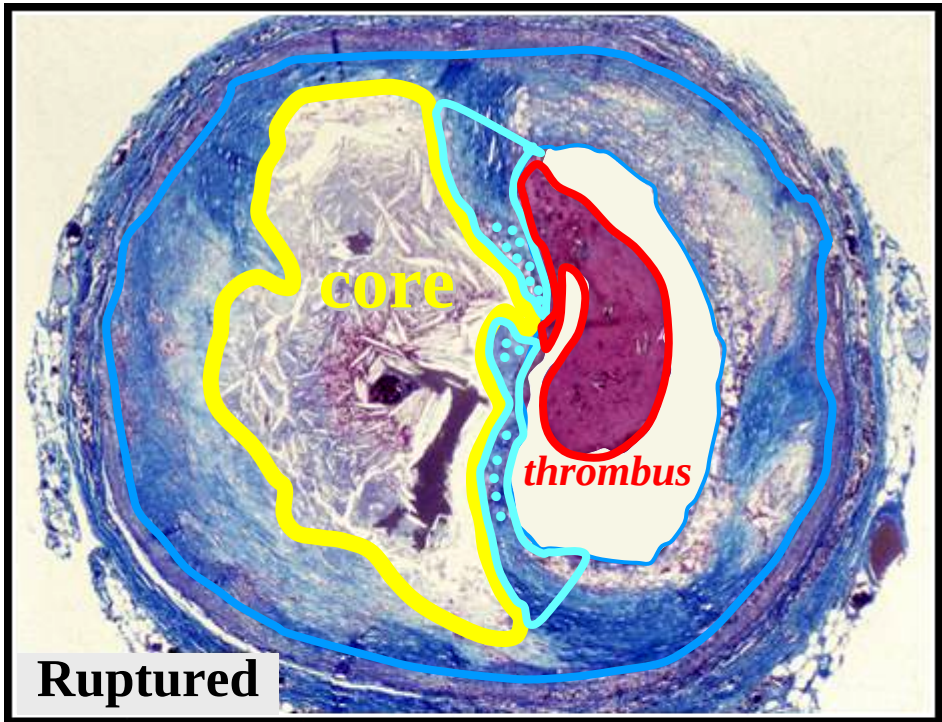
Background. Plaque rupture often occurs at sites with minor luminal stenosis and has retrospectively been characterized by colocalization of inflammatory cells. Recent studies have demonstrated that luminal narrowing is related with the mode of atherosclerotic arterial remodeling.

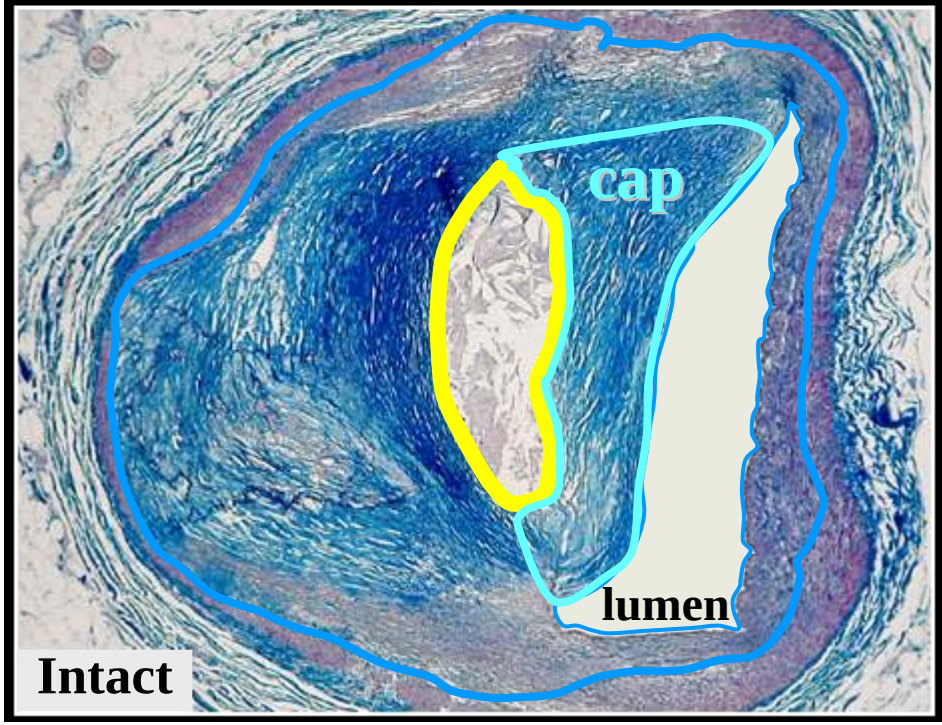
Methods. We obtained 1,521 cross section slices at regular intervals from 50 atherosclerotic femoral arteries. Per artery, the slices with the largest and smallest lumen area, vessel area and plaque area were selected for staining on the presence of macrophages (CD68), T-lymphocytes (CD45RO), smooth muscle cells (alpha-actin) and collagen.

Results. Inflammation of the cap or shoulder of the plaque was observed in 33% of all cross sections. Significantly more CD68 and CD45RO positive cells, more atheroma, less collagen and less alpha-actin positive staining was observed in cross sections with the largest plaque area and largest vessel area vs. cross sections with the smallest plaque area and smallest vessel area, respectively. No difference in the number of inflammatory cells was observed between cross sections with the largest and smallest lumen area.

Conclusion. Intraindividually, pathohistologic markers previously reported to be related to plaque vulnerability were associated with a larger plaque area and vessel area. In addition, inflammation of the cap and shoulder of the plaque was a common finding in the atherosclerotic femoral artery.

(J Am Coll Cardiol 1998;32:655–62)





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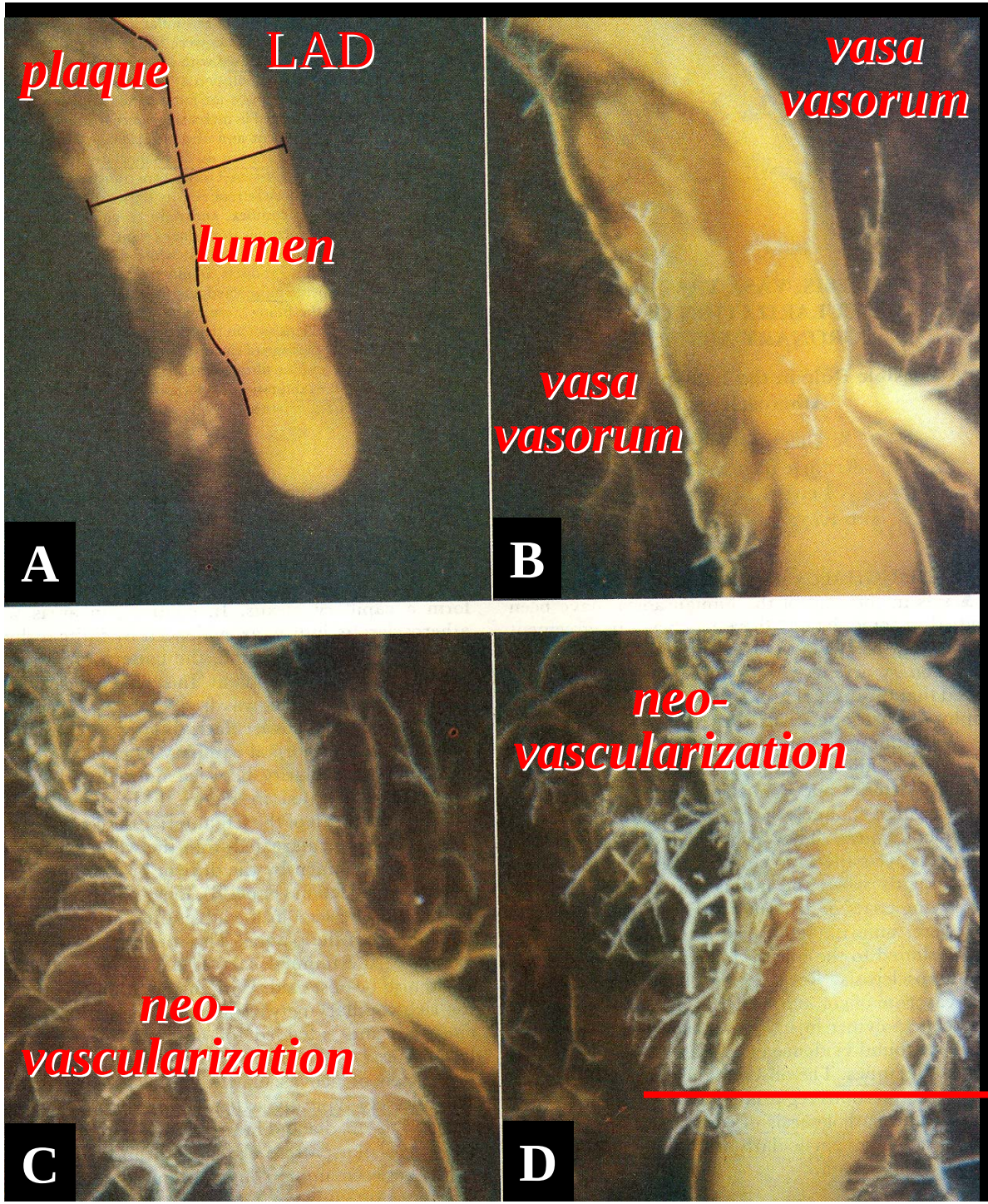
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*



Barger et al.

Panels C & D, with further filling:

Rich capillary network confined to the plaque,
= adventitia-derived neovascularization

- ***Leaky***
  exudation
- ***Fragile***
  hemorrhage

Lower edge of plaque

Intraplaque Hemorrhage and Progression of Coronary Atheroma

Frank D. Kolodgie, Ph.D., Herman K. Gold, M.D., Allen P. Burke, M.D., David R. Fowler, M.D., Howard S. Kruth, M.D., Deena K. Weber, M.S., Andrew Farb, M.D., L.J. Guerrero, B.S., Motoya Hayase, M.D., Robert Kutys, M.S., Jagat Narula, M.D., Ph.D., Aloke V. Finn, M.D., and Renu Virmani, M.D.

ABSTRACT

BACKGROUND

Intraplaque hemorrhage is common in advanced coronary atherosclerotic lesions. The relation between hemorrhage and the vulnerability of plaque to disruption may involve the accumulation of free cholesterol from erythrocyte membranes.

METHODS

We stained multiple coronary lesions from 24 randomly selected patients who had died suddenly of coronary causes with an antibody against glycophorin A (a protein specific to erythrocytes that facilitates anion exchange) and Mallory's stain for iron (hemosiderin), markers of previous intraplaque hemorrhage. Coronary lesions were classified as lesions with pathologic intimal thickening, fibrous-cap atheromas with cores in an early or late stage of necrosis, or thin-cap fibrous atheromas (vulnerable plaques). The arterial response to plaque hemorrhage was further defined in a rabbit model of atherosclerosis.

NEJM 2003 Dec;349:2316-25

Intimal Neovascularization in Human Coronary Atherosclerosis:

Its Origin and Pathophysiological Significance

MASATO KUMAMOTO, MD, YUTAKA NAKASHIMA, MD, AND KATSUO SUEISHI, MD

To investigate the histopathological characteristics of the newly formed vessels in the atherosclerotic intima of human coronary arteries, we conducted postmortem angiography in 31 cases, including 11 with myocardial infarction. Vessels were examined three-dimensionally under the stereoscope. In addition, we evaluated 25 anterior descending coronary arteries unrelated to the occurrence of myocardial infarction by light microscopy using 3-mm stepwise sections and 5-μm serial sections. Histological alterations were analyzed morphometrically to determine the correlation between the degree of intimal neovascularization and the growth of the endothelium into the atherosclerotic intima from the adventitia or lumen. There was a significant positive correlation between the density of new vessels in the intima and the incidence of luminal stenosis, the extent of chronic inflammatory infiltrate, the formation of granulation tissue, or the atheromatous changes, whereas the vascular density decreased in the extensively hyalinized and calcified intima. The newly formed intimal vessels originated mainly from the adventitial vasa vasorum and also partly from the proper coronary lumen. The intimal vessels that originated from the adventitia occurred approximately 28 times more frequently than those that originated from the luminal side. The frequency of former vessels increased as the luminal stenosis became more severe, whereas the latter vessels were found most frequently in the presence of 40% and 50% stenosis. Vessels originating from the proper lumen were more often associated with fresh or old hemorrhage. We conclude that intimal neovascularization largely originates from the adventitia and is closely associated with the extent of coronary stenosis and the histological inflammatory reaction. HUM PATHOL 26:450–456.

Human Pathol 1995;26:450-6

Angiogenesis and lymphangiogenesis and expression of lymphangiogenic factors in the atherosclerotic intima of human coronary arteries☆

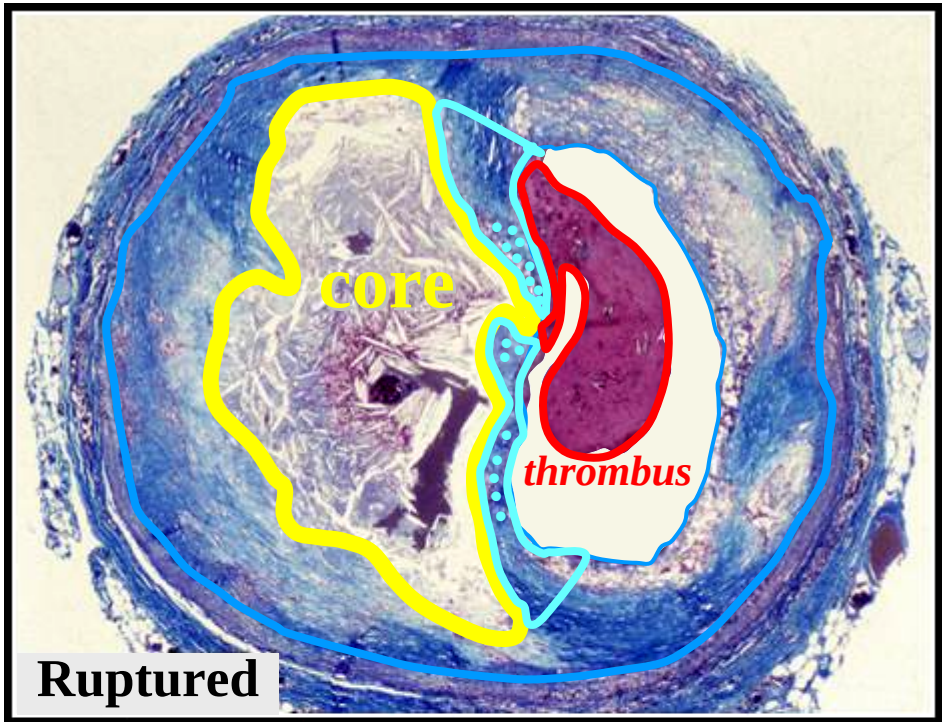
Toshiaki Nakano MD[a,b], Yutaka Nakashima MD, PhD[a], Yoshikazu Yonemitsu MD, PhD, FAHA[a,*], Shinji Sumiyoshi MD[a], Young-Xiang Chen PhD[a], Yuri Akishima MD[c], Toshiharu Ishii MD, PhD[c], Mitsuo Iida MD, PhD[b], Katsuo Sueishi MD, PhD[a]

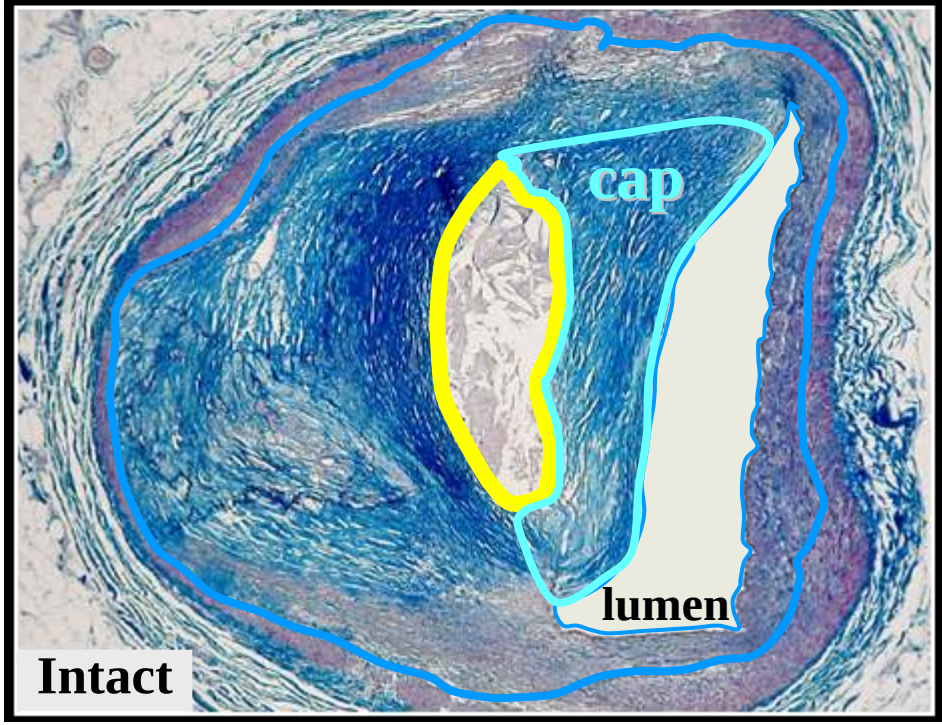
[a]*Division of Pathophysiological and Experimental Pathology, Department of Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[b]*Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[c]*Department of Pathology, School of Medicine, Toho University, Tokyo, Japan*

Keywords:
Coronary artery;
VEGF-C;
Atherosclerosis;
Angiogenesis;
Lymphangiogenesis

Summary Little information regarding the development of lymphangiogenesis in coronary atherosclerosis is available. We immunohistochemically investigated the correlation among intimal neovascularization (CD34 for angiogenesis and lymphatic vessel endothelial hyaluronan receptor-1 [LYVE-1] and podoplanin for lymphangiogenesis), the expression of lymphangiogenic factors (vascular endothelial growth factor [VEGF]-C and VEGF-D), and the progression of atherosclerosis using 169 sections of human coronary arteries from 23 autopsy cases. The more the atherosclerosis advanced, the more often the neointimas contained newly formed blood vessels ($P < .0001$). Vascular endothelial growth factor-C was expressed mostly in foamy macrophages and in some smooth muscle cells, whereas VEGF-D was abundantly expressed in both. The number of VEGF-C–expressing cells, but not that of VEGF-D–expressing cells, was increased as the lesion advanced and the number of intimal blood vessels increased ($P < .01$). Lymphatic vessels were rare in the atherosclerotic intima (LYVE-1 vs CD34 = 13 vs 3955 vessels) compared with the number seen in the adventitia (LYVE-1 vs CD34 = 360 vs 6921 vessels). The current study suggests that VEGF-C, but not VEGF-D, may contribute to plaque progression and be a regulator for angiogenesis rather than lymphangiogenesis in coronary atherosclerotic intimas. Imbalance of angiogenesis and lymphangiogenesis may be a factor contributing to sustained inflammatory reaction during human coronary atherogenesis.

Human Pathol
2005;36;330-40





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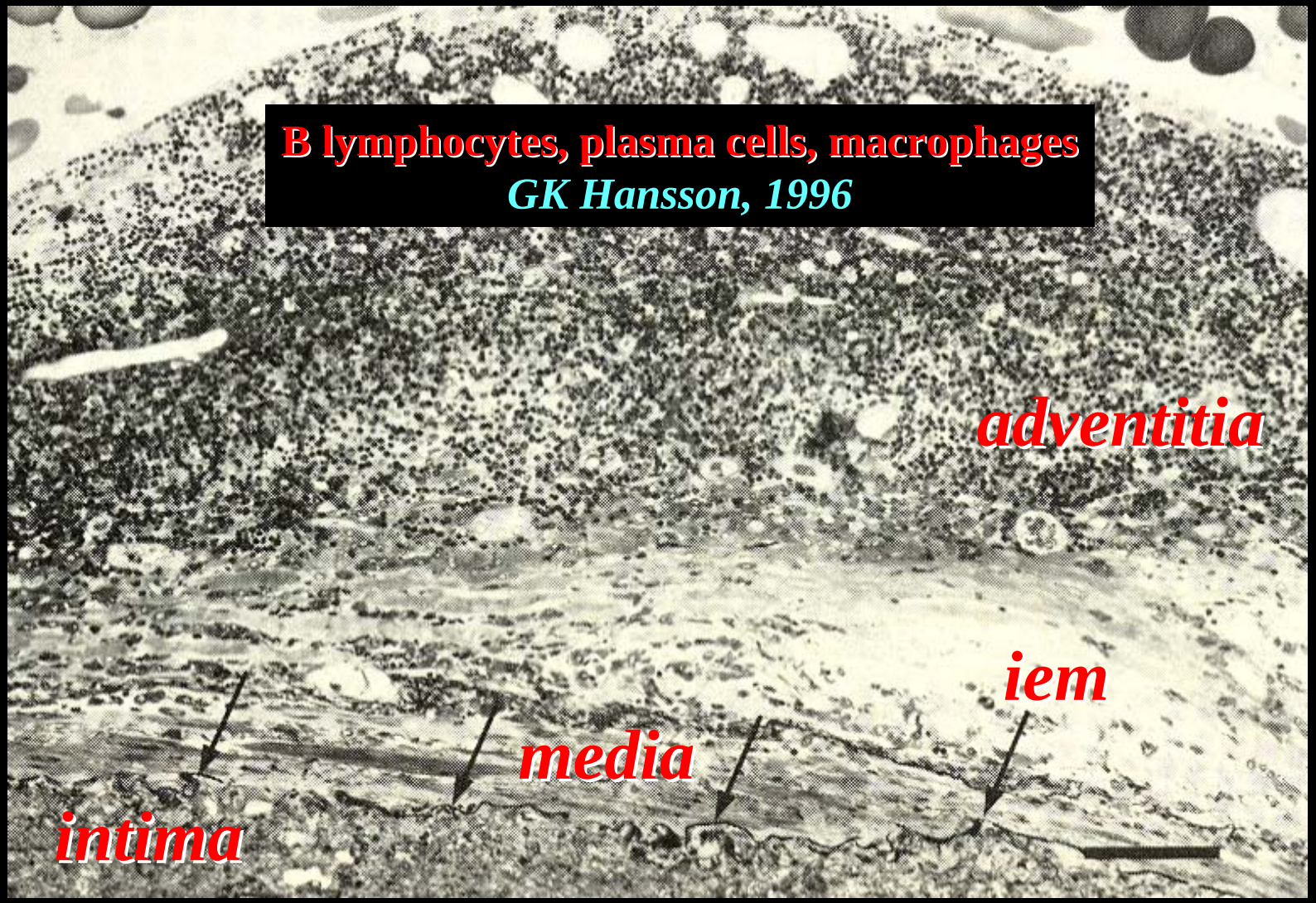
  - **intraplaque hemorrhage**
- **Perivascular inflammation**

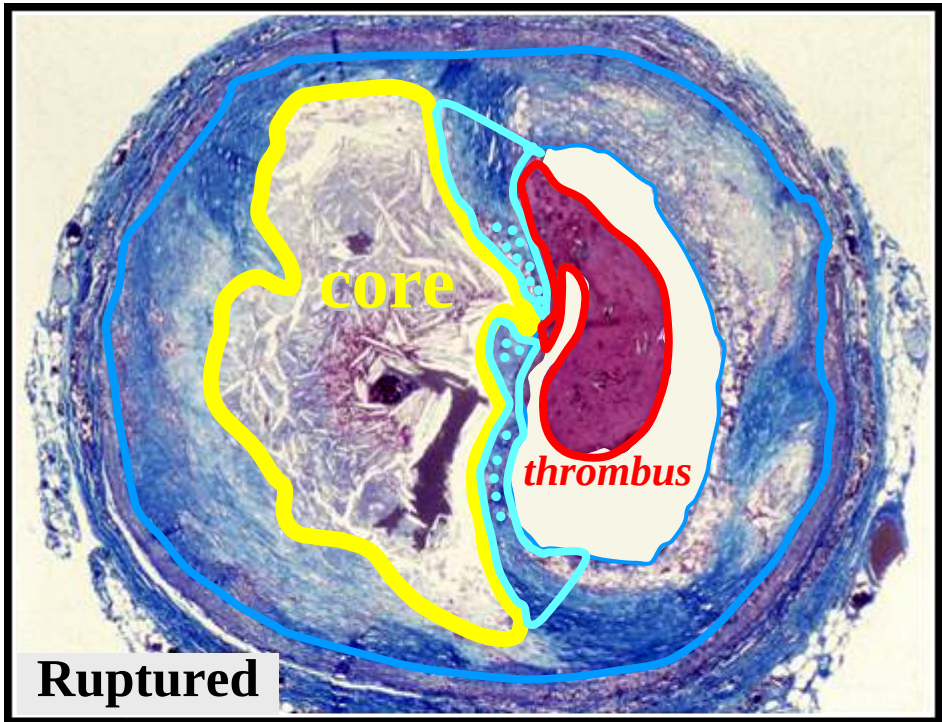
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

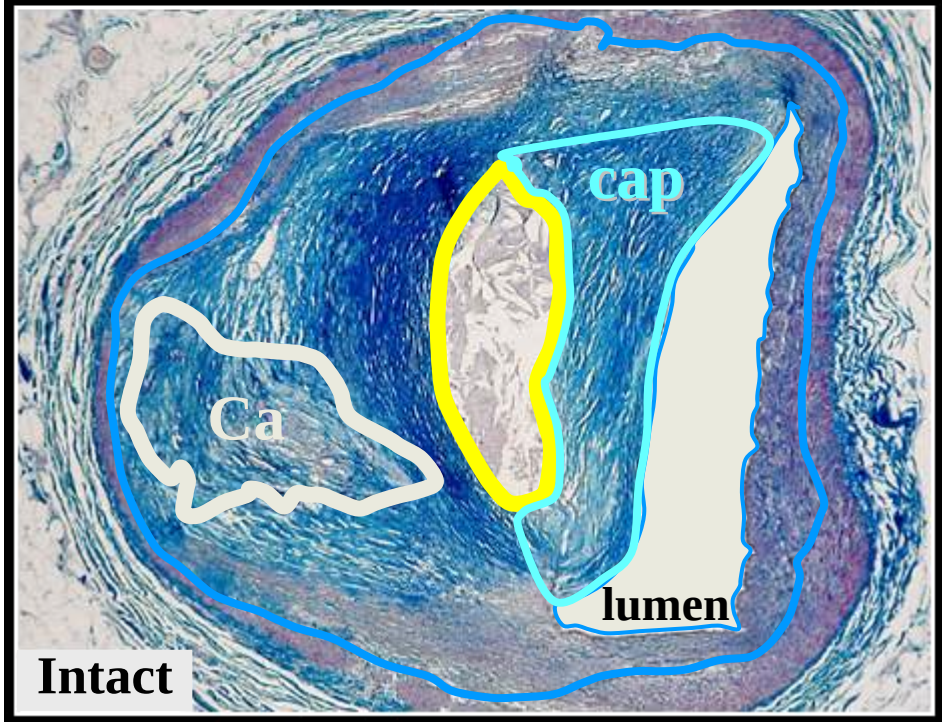
Coronary artery from patient with AMI

(peri)adventitial inflammation



Kohchi et al. Circulation 1985:71:709-16





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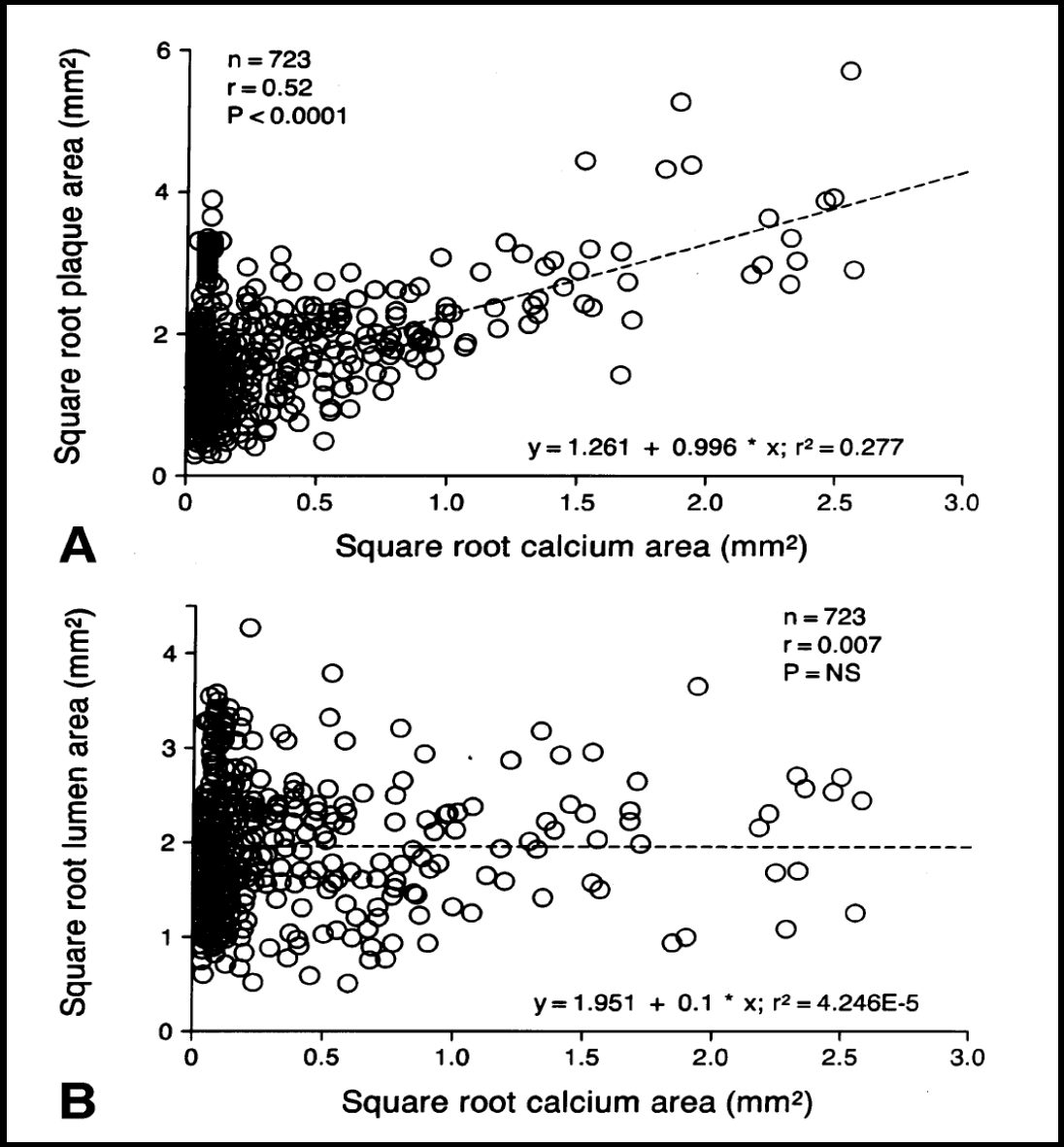
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

Coronary Calcium: ~Plaque, ≠Lumen



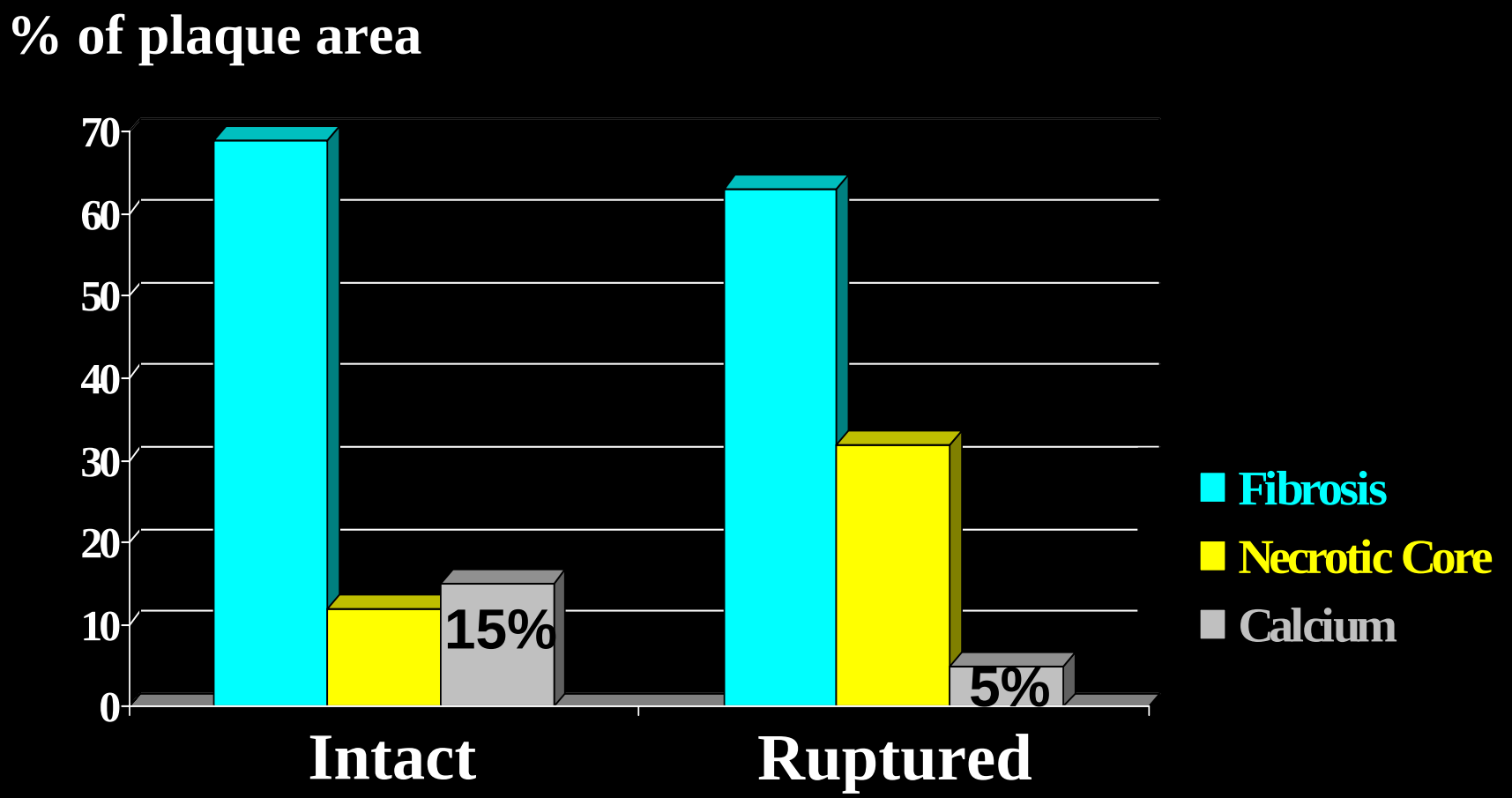
Plaque

Lumen

Sangiorgi G et al. JACC 1998;31:126-33

Coronary Plaque Rupture

calcification in intact (stenotic) vs ruptured plaques



Gertz SD, Roberts WC. Am J Cardiol 1990;66:1368-72

Spotty Calcification Typifies the Culprit Plaque in Patients With Acute Myocardial Infarction

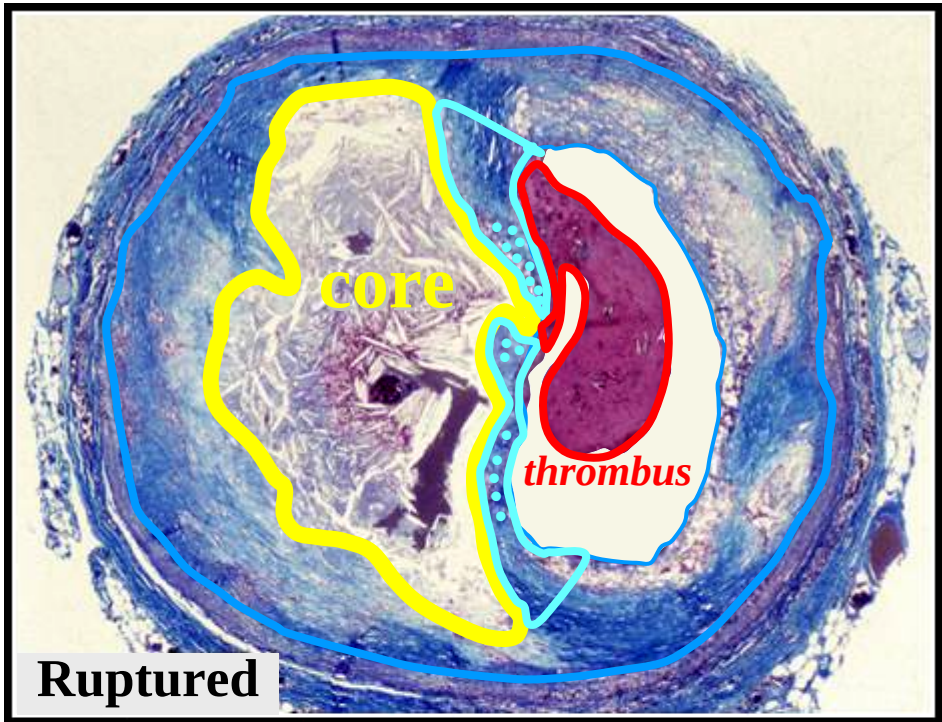
An Intravascular Ultrasound Study

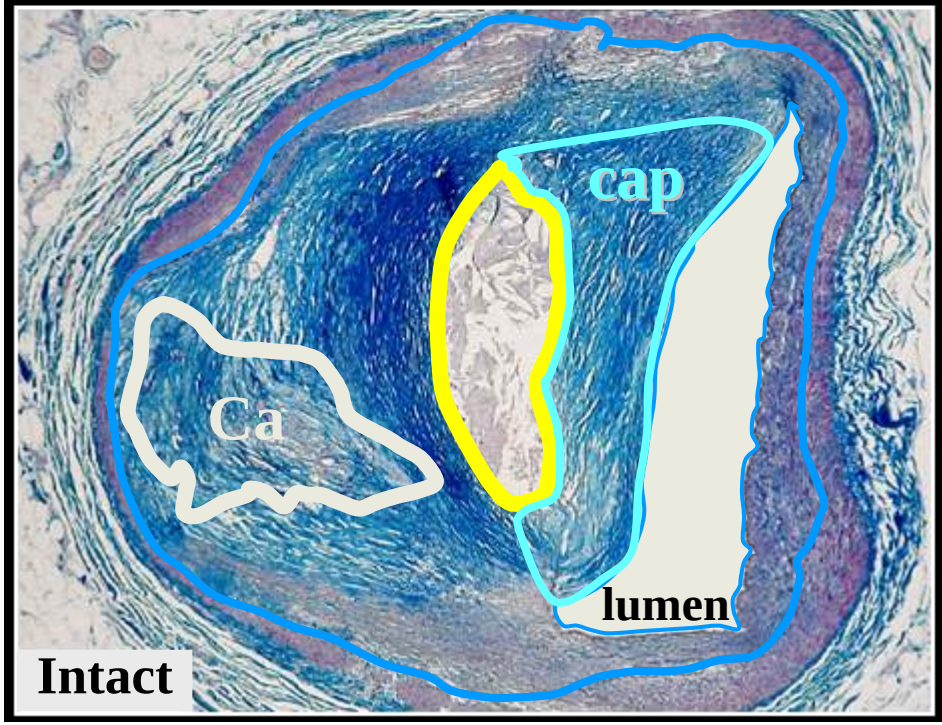
Shoichi Ehara, MD; Yoshiki Kobayashi, MD; Minoru Yoshiyama, MD; Kenei Shimada, MD; Yoshihisa Shimada, MD; Daiju Fukuda, MD; Yasuhiro Nakamura, MD; Hajime Yamashita, MD; Hiroyuki Yamagishi, MD; Kazuhide Takeuchi, MD; Takahiko Naruko, MD; Kazuo Haze, MD; Anton E. Becker, MD; Junichi Yoshikawa, MD; Makiko Ueda, MD

Background—Calcification is a common finding in human coronary arteries; however, the relationship between calcification patterns, plaque morphology, and patterns of remodeling of culprit lesions in a comparison of patients with acute coronary syndromes (ACS) and those with stable conditions has not been documented.

Methods and Results—Preinterventional intravascular ultrasound (IVUS) images of 178 patients were studied, 61 with acute myocardial infarction (AMI), 70 with unstable angina pectoris (UAP), and 47 with stable angina pectoris (SAP). The frequency of calcium deposits within an arc of less than 90° for all calcium deposits was significantly different in culprit lesions of patients with AMI, UAP, and SAP ($P<0.0001$). Moreover, the average number of calcium deposits within an arc of <90° per patient was significantly higher in AMI than in SAP ($P<0.0005$; mean±SD, AMI 1.4±1.3, SAP 0.5±0.8). Conversely, calcium deposits were significantly longer in SAP patients ($P<0.0001$; mean±SD, AMI 2.2±1.6, UAP 1.9±1.8, and SAP 4.3±3.2 mm). In AMI patients, the typical pattern was spotty calcification, associated with a fibrofatty plaque and positive remodeling. In ACS patients showing negative remodeling, no calcification was the most frequent observation. Conversely, SAP patients had the highest frequency of extensive calcification.

Conclusions—Our observations show that IVUS allows the identification of vulnerable plaques in coronary arteries, not only by identifying a fibrofatty plaque and positive remodeling, but also by identifying a spotty pattern of calcification.
(*Circulation*. 2004;110:3424-3429.)





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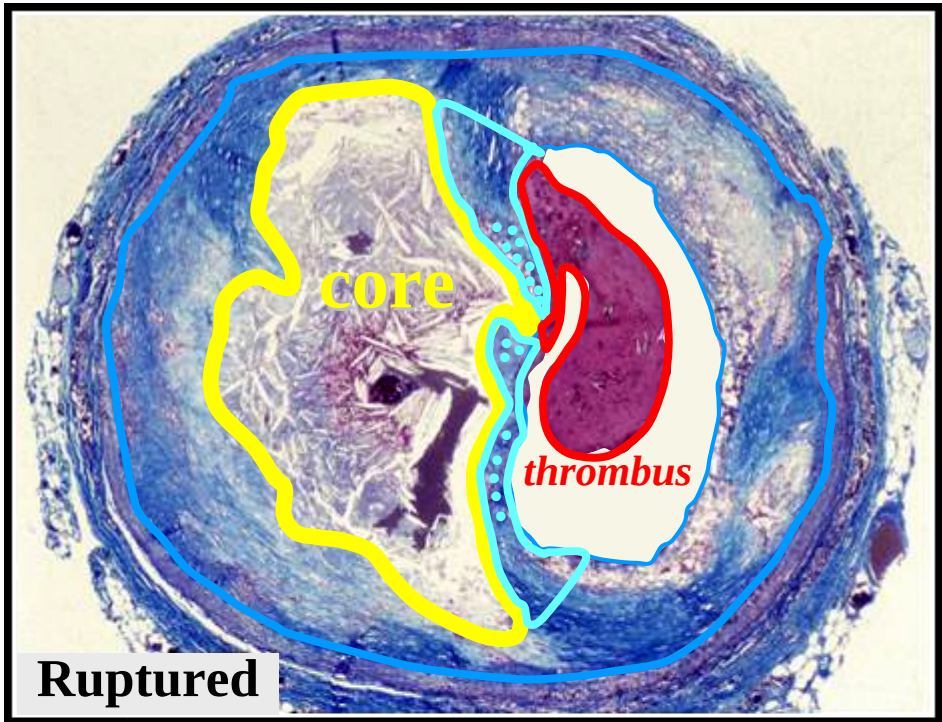
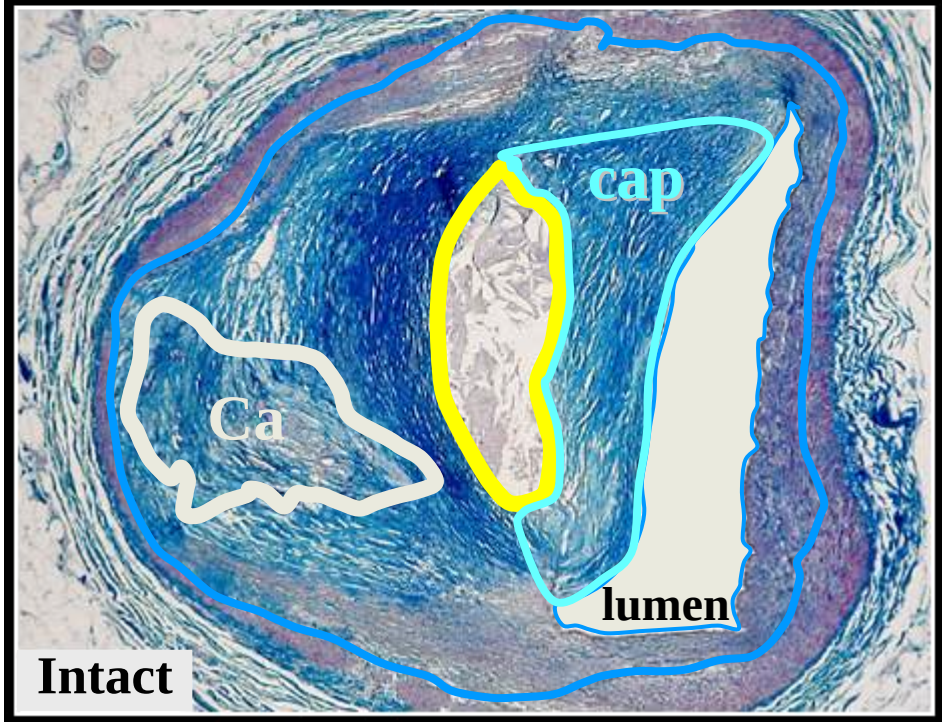
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*





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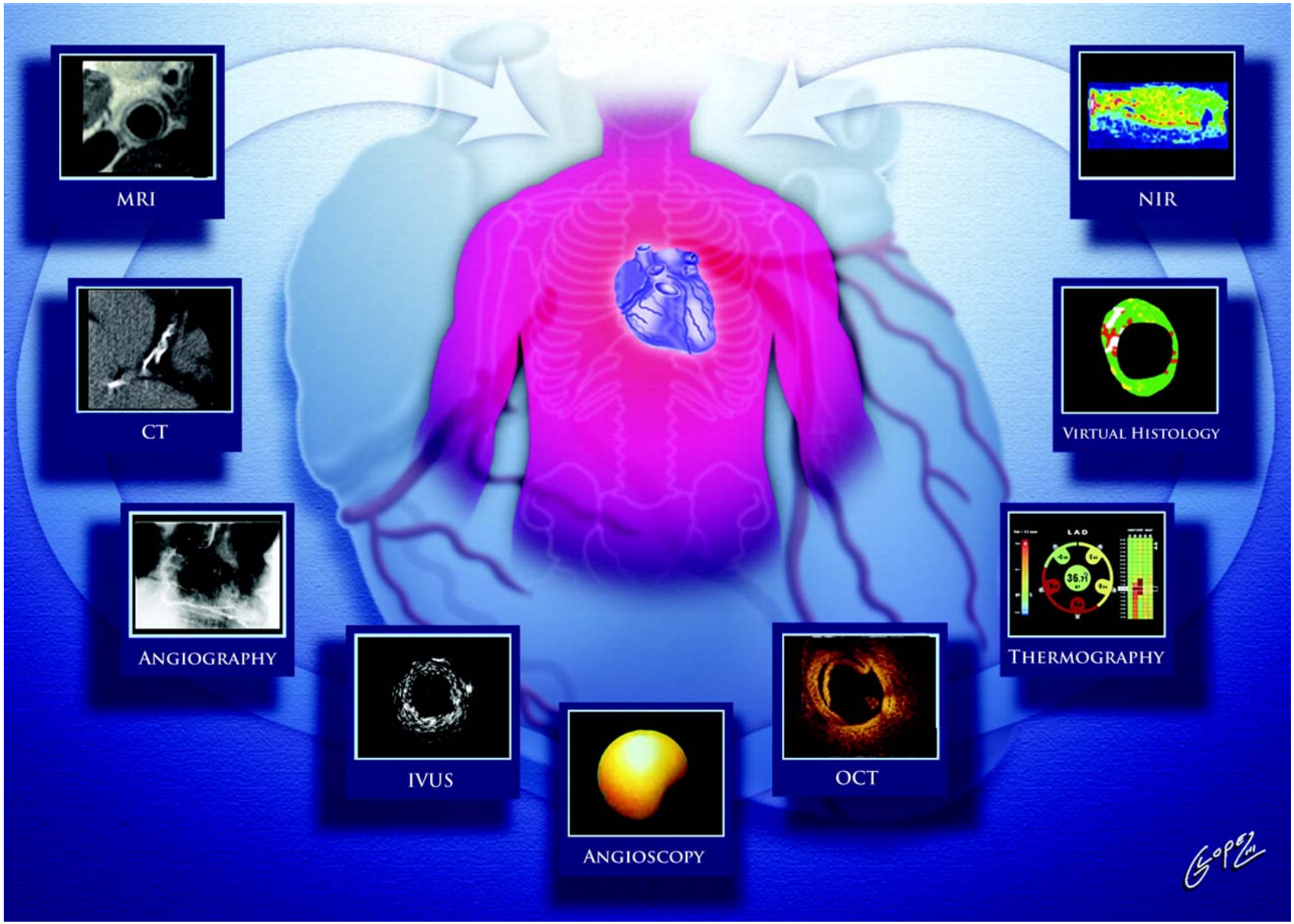
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

Finding Vulnerable Atherosclerotic Plaques

Madjid et al. ATVB 2004;24:1775-82



Vulnerable plaque(s) → Vulnerable patient

Diffuse and Active Inflammation Occurs in Both Vulnerable and Stable Plaques of the Entire Coronary Tree

A Histopathologic Study of Patients Dying of Acute Myocardial Infarction

Alessandro Mauriello, MD,* Giuseppe Sangiorgi, MD, FESC,† Stefano Fratoni, MD,*
Giampiero Palmieri, MD,* Elena Bonanno, MD,* Lucia Anemona, MD,*
Robert S. Schwartz, MD, FACC, FAHA,‡ Luigi Giusto Spagnoli, MD*

Rome, Italy; and Minneapolis, Minnesota

OBJECTIVES This study was undertaken to define and compare geographic coronary artery inflammation in patients who were dying of acute myocardial infarction (AMI), chronic stable angina (SA), and noncardiac causes (CTRL).

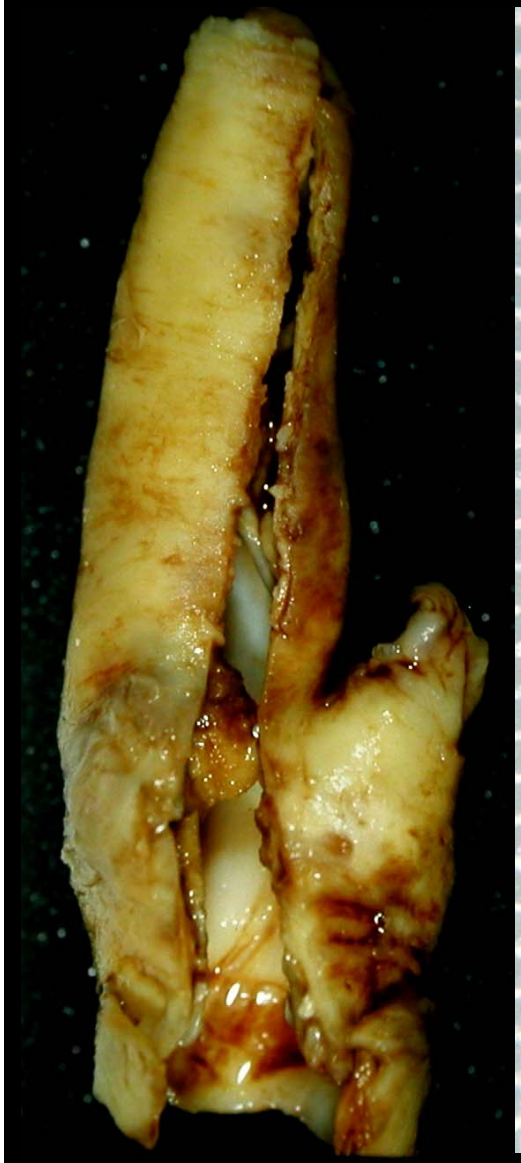
BACKGROUND Biochemical markers and flow cytometry provide indirect evidence of diffuse coronary inflammation in patients dying of acute coronary syndromes. Yet no histopathologic studies have corroborated these findings. A key unanswered question is whether the inflammatory burden involves the entire coronary tree or is limited to a few plaques.

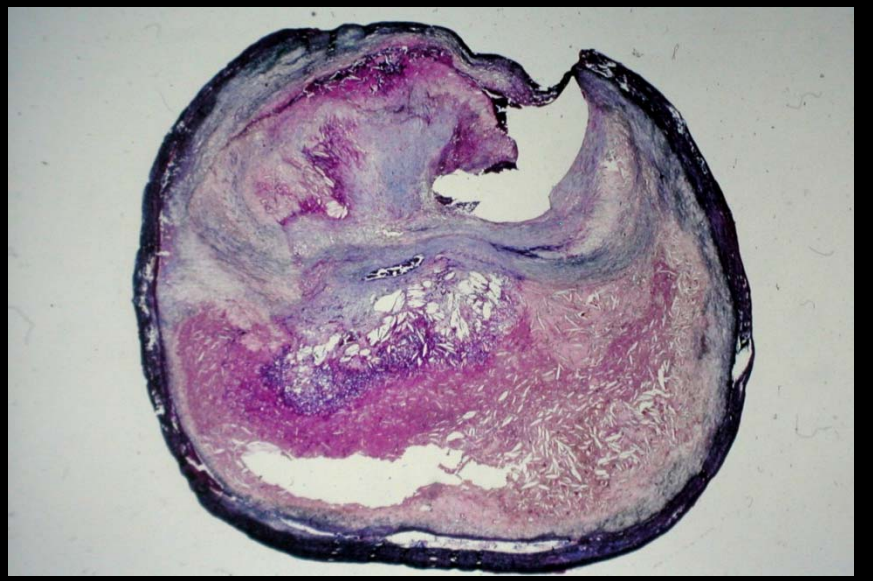
METHODS We examined 544 coronary artery segments from 16 patients with AMI, 109 segments from 5 patients with SA, and 304 coronary segments from 9 patients with CTRL.

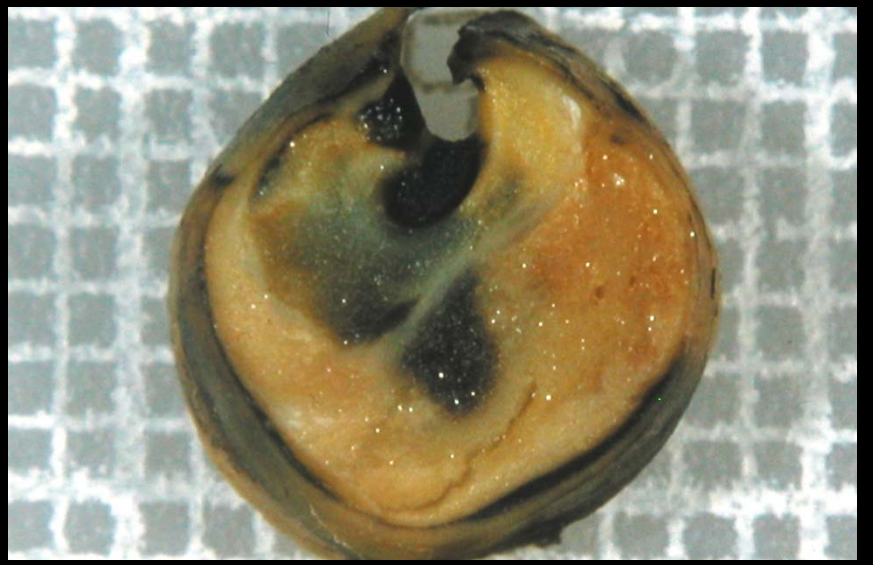
RESULTS An average of 6.8 ± 0.5 vulnerable segments per patient were found in the AMI group (in addition to culprit lesions) compared with an average of 0.8 ± 0.3 and 1.4 ± 0.3 vulnerable lesions/patient in the SA and CTRL groups, respectively. The AMI group, independent of the type of plaque observed, showed significantly more inflammatory infiltrates compared with the SA and CTRL groups (121.6 ± 12.4 cell × mm^2 vs. 37.3 ± 11.9 cell × mm^2 vs. 26.6 ± 6.8 cell × mm^2, $p = 0.0001$). In AMI patients, active inflammation was not only evident within the culprit lesion and vulnerable plaques but also involved stable plaques. These showed a three- to four-fold higher inflammation than vulnerable and stable plaques from the SA and CTRL groups, respectively.

CONCLUSIONS This histopathologic study found that both vulnerable and stable coronary plaques of patients dying of AMI are diffusely infiltrated by inflammatory cells. (J Am Coll Cardiol 2005;45: 1585–93)

Carotid Atherosclerosis
endarterectomi specimens







Carotid Plaque → Stroke ~ CAD → AMI

Extracranial Thrombotically Active Carotid Plaque as a Risk Factor for Ischemic Stroke

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Context Recent studies suggest that factors other than the degree of carotid stenosis are involved in ischemic stroke pathogenesis, especially modifications of plaque composition and related complications.

Objective To examine the role of carotid plaque rupture and thrombosis in ischemic stroke pathogenesis in patients undergoing carotid endarterectomy, excluding those with possible cardiac embolization or with severe stenosis of the circle of Willis.

Design, Setting, and Patients A total of 269 carotid plaques selected from an Interinstitutional Carotid Tissue Bank were studied by histology after surgical endarterectomy between January 1995 and December 2002. A total of 96 plaques were from patients with ipsilateral major stroke, 91 plaques from patients with transient ischemic attack (TIA), and 82 plaques from patients without symptoms.

Main Outcome Measures Differences in the frequency of thrombosis, cap rupture, cap erosion, inflammatory infiltrate, and major cardiovascular risk factors between study groups.

Results A thrombotically active carotid plaque associated with high inflammatory infiltrate was observed in 71 (74.0%) of 96 patients with ipsilateral major stroke (and in all 32 plaques from patients operated within 2 months of symptom onset) compared with 32 (35.2%) of 91 patients with TIA ($P<.001$) or 12 (14.6%) of 82 patients who were without symptoms ($P<.001$). In addition, a fresh thrombus was observed in 53.8% of patients with stroke operated 13 to 24 months after the cerebrovascular event. An acute thrombus was associated with cap rupture in 64 (90.1%) of 71 thrombosed plaques from patients with stroke and with cap erosion in the remaining 7 cases (9.9%). Ruptured plaques of patients affected by stroke were characterized by the presence of a more severe inflammatory infiltrate, constituted by monocytes, macrophages, and T lymphocyte cells compared with that observed in the TIA and asymptomatic groups ($P=.001$). There was no significant difference between groups in major cardiovascular risk factors.

Conclusion These results demonstrate a major role of carotid thrombosis and inflammation in ischemic stroke in patients affected by carotid atherosclerotic disease.

JAMA. 2004;292:1845-1852 www.jama.com

PATIENTS WITH SUBSTANTIAL carotid artery narrowing are at increased risk for major stroke,[1-6] but the pathogenic mechanisms linking carotid atherosclerosis and ischemic brain injury still need to be fully clarified. Clinical trials designed to evaluate the beneficial effects of endarterectomy in symptomatic and asymptomatic patients have focused on carotid stenosis severity and plaque ulceration as risk factors for cerebrovascular events. The results of the European Carotid Surgery Trial[2,3] and the North American Symptomatic Carotid

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JAMA. 2004;292:1845-1852 www.jama.com

Macrophages are associated with lipid-rich carotid artery plaques, echolucency on B-mode imaging, and elevated plasma lipid levels

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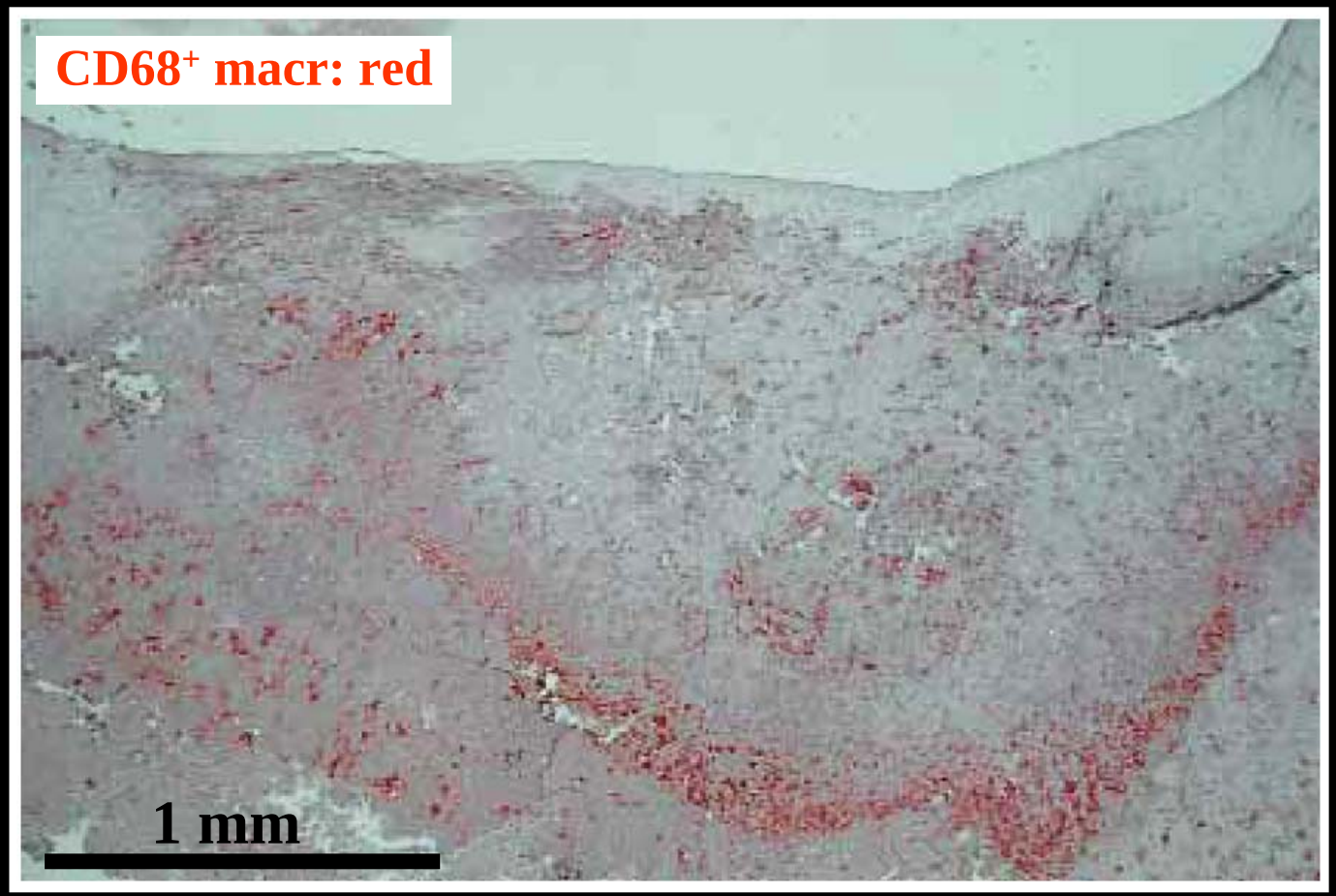
Objective: Atherosclerosis may be regarded as an inflammatory disease dominated by macrophages. We tested whether macrophages in carotid artery atherosclerotic plaques are associated with echolucency on B-mode ultrasound imaging, lipid levels, inflammatory markers, and aspirin use.
Methods: We studied 106 patients undergoing carotid endarterectomy having ≥50% carotid artery stenosis and previous ipsilateral hemispheric neurologic symptoms.
Results: Macrophages were particularly common in plaques with a high content of lipid and hemorrhage and, conversely, rare in plaques dominated by calcification and fibrous tissue. Macrophage density in carotid artery plaques classified by B-mode ultrasound imaging as echolucent (n = 56), intermediate (n = 25), or echorich (n = 25) was 1.8% ± 0.2%, 1.5% ± 0.4%, and 1.0% ± 0.2% (±SE), respectively (analysis of variance, $P = .02$). A computer-generated measure of plaque echolucency, gray-scale median, was associated with increased macrophage density ($r = –0.31$; $P = .002$). Furthermore, plasma and low-density lipoprotein cholesterol levels were associated with carotid artery macrophage density ($r = 0.26$, $P = .008$ and $r = 0.23$, $P = .02$); this was most pronounced in patients with lipid-rich plaques. Macrophage density was not associated with plasma levels of acute-phase reactants. Finally, macrophage density in carotid artery plaques of users (n = 55) and nonusers of aspirin (n = 51) was 1.2% ± 0.2% and 1.8% ± 0.2% (*t* test, $P = .01$).
Conclusions: Increased macrophage density in carotid atherosclerotic plaques was associated with lipid content, plaque echolucency, and increased plasma and low-density lipoprotein cholesterol levels. Furthermore, use of aspirin was associated with reduced macrophage density in carotid artery plaques. (J Vasc Surg 2002;35:137-45.)

Symptomatic plaques, n=106

Symptomatic Carotid Plaques

macr ~1.6% of plaque area (≠ plasma hsCRP)

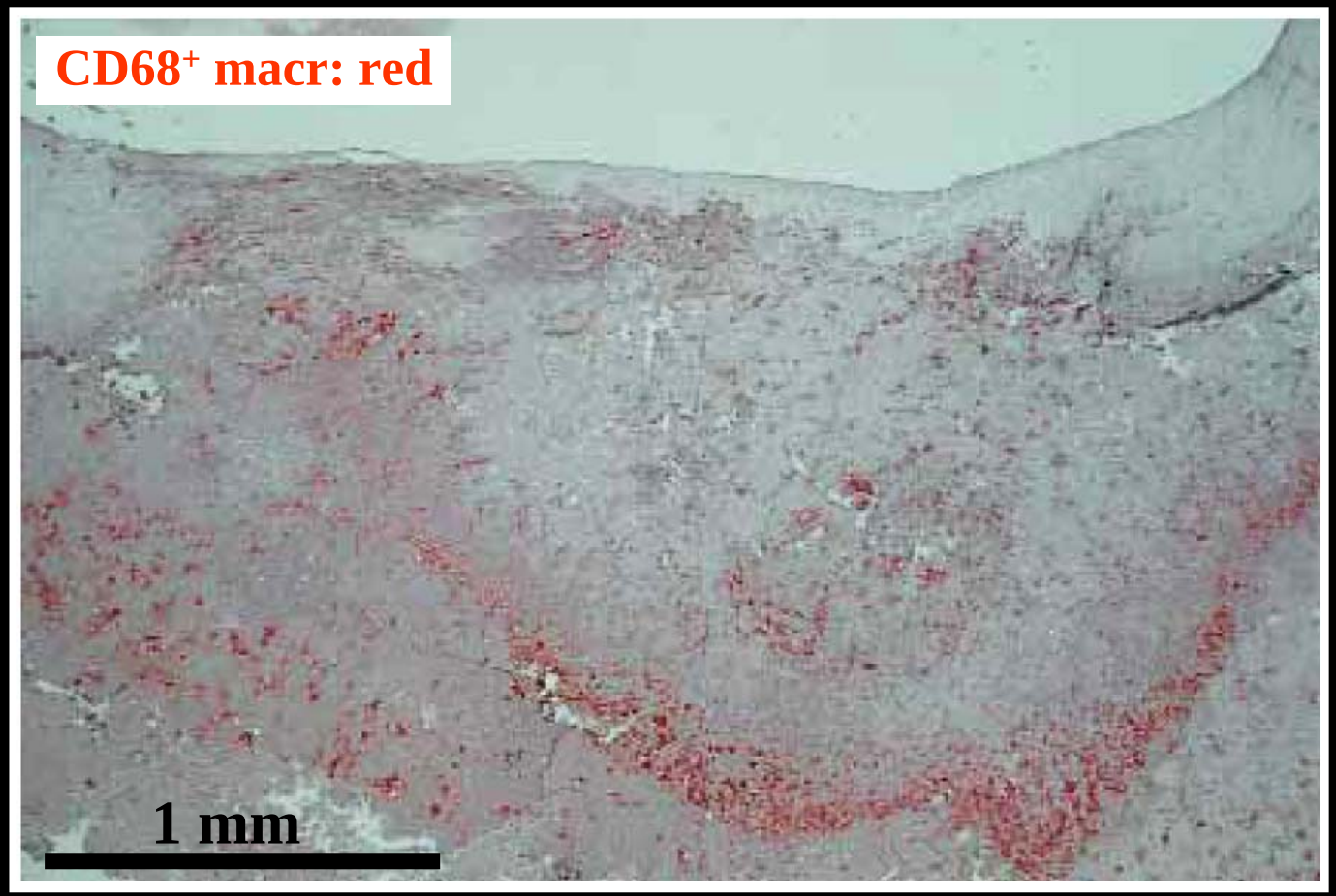


n=106

Grønholdt MLM et al. J Vasc Surg 2002;35:137-45

Symptomatic Carotid Plaques

lipid-rich core ~40% of plaque area



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Statin Treatment Is Not Associated With Consistent Alterations in Inflammatory Status of Carotid Atherosclerotic Plaques

A Retrospective Study in 378 Patients Undergoing Carotid Endarterectomy

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Background and Purpose—Anti-inflammatory qualities are held partially responsible for the reduction of cardiovascular events after statin treatment. We examined the phenotype of carotid atherosclerotic plaques harvested during carotid endarterectomy in relation to the previous use of different statins prescribed in clinical practice.

Methods—Three hundred and seventy-eight patients were included. Atherosclerotic plaques were harvested, immunohistochemically stained and semiquantitively examined for the presence of macrophages (CD68), smooth muscle cells, collagen and fat. Adjacent atherosclerotic plaques were used to study protease activity and interleukin levels. Patients' demographics were recorded and blood samples were stored.

Results—Serum cholesterol, low-density lipoprotein, apolipoprotein B, and C-reactive protein levels were lower in patients treated with statins compared with patients without statin treatment. Atheromatous plaques were less prevalent in patients receiving statins compared with patients without statin therapy (29% versus 42%, $P=0.04$). An increase of CD68 positive cells was observed in patients receiving statins compared with nonstatin treatment ($P=0.05$). This effect was specifically related to atorvastatin treatment. In patients treated with atorvastatin, the increased amount of CD68 positive cells were not associated with increased protease activity. In contrast, a dose-dependent decrease in protease activity was shown in the atorvastatin group. Interleukin 6 expression was lower in plaques obtained from patients treated with statins ($P=0.04$).

Conclusions—Statin use may exert pleiotropic effects on plaque phenotype. However, not the presence of macrophages but activation with subsequent protease and cytokine release may be attenuated by statin use. **(*Stroke*. 2006;37:2054-2060.)**

TABLE 3. Plaque Characteristics

Plaque Characteristics (%/number)	No Statin	All Statins	*P* Value	Pravastatin	Simvastatin	Atorvastatin	*P* Value
Minor collagen	25%/32	24%/59	0.86	12%/5	28%/25	26%/25	0.10
Heavy collagen	75%/97	76%/187		88%/38	72%/64	75%/73	
Minor SMC	34%/44	33%/80	0.72	23%/10	36%/32	33%/32	0.35
Heavy SMC	66%/84	68%/166		77%/33	64%/58	67%/65	
Minor calcifications	48%/62	47%/117	0.97	43%/19	49%/45	46%/45	0.96
Heavy calcifications	52%/67	53%/132		57%/25	51%/46	54%/53	
Minor Mϕ	53%/68	43%/106	0.05	61%/26	44%/40	34%/33	0.01
Heavy Mϕ	47%/59	57%/141		40%/17	56%/50	66%/65	
Fibrous	29%/37	33%/83	0.04	32%/14	31%/28	37%/36	0.59
F-Atheromatous	29%/38	38%/94		43%/19	34%/31	37%/36	
Atheromatous	42%/54	29%/72		25%/11	35%/32	26%/26	
Mϕ quantitative (median/IQR)	0.3/0.01–0.3	0.4/0.1–1.3	0.16	0.2/0.01–1.0	0.4/0.1–1.2	0.6/0.1–1.5	0.04
MMP 8 (median/IQR)	6.3/2.9–12	5.8/2.7–9.8	0.32	3.6/0.0–9.3	6.9/3.7–9.3	6.2/3.1–13.2	0.25
MMP 9 (median/IQR)	1.7/0.8–5.2	2.1/1.0–4.9	0.43	1.4/0.8–3.8	2.6/0.9–5.8	2.1/1.3–4.8	0.39
IL 6 (median/IQR)	11.0/4.2–23	6.9/1.6–48	0.04	4.8/0.4–13.9	6.9/2.2–19.6	7.9/2.1–19.5	0.29
IL 8 (median/IQR)	34.4/0.6–97	42.9/7.3–138	0.29	32.4/0.8–178	43.3/8.8–113	44.1/6.8–152	0.95

Plaque stainings are in absolute numbers and percentages. Parametrically distributed variables are presented with mean and standard deviation, whereas nonparametric variables are presented with median and interquartile range (IQR). Mϕ indicates CD68 staining; SMC, smooth muscle cell staining.

Verhoeven et al, Stroke 2006;37:2054-60

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Mϕ quantitative (median/IQR)	0.3/0.01–0.3	0.4/0.1–1.3	0.16	0.2/0.01–1.0	0.4/0.1–1.2	0.6/0.1–1.5	0.04

Macr density: ~0.4% of plaque

Verhoeven et al, Stroke 2006;37:2054-60

In Vivo ^{18}F-Fluorodeoxyglucose Positron Emission Tomography Imaging Provides a Noninvasive Measure of Carotid Plaque Inflammation in Patients

JACC 2006;48:1818 –24

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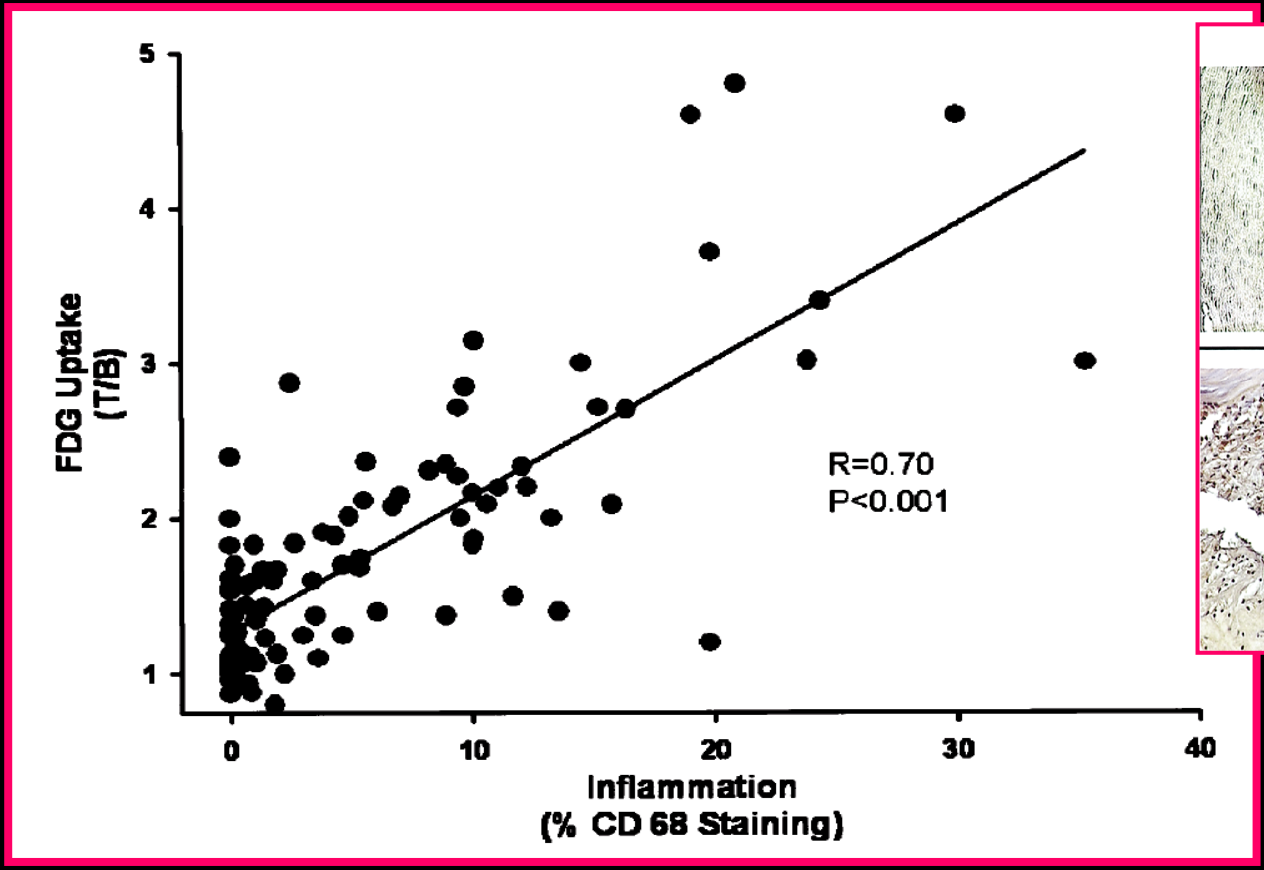
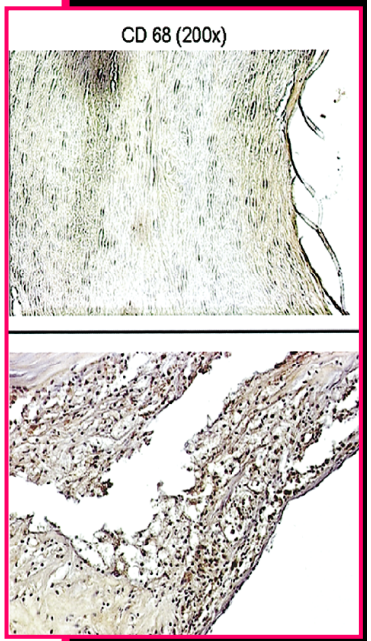
PET-FDG





Macr in plaque

HISTOPATHOLOGY OF CAROTID ATHEROSCLEROTIC DISEASE

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STROKE IS THE third leading cause of death in the United States, constituting approximately 700,000 cases each year, of which about 500,000 are first attacks and 200,000 are recurrent attacks. Ischemic stroke accounts for the majority of all strokes (88%), followed by intracerebral hemorrhage (9%) and subarachnoid hemorrhage (3%). Patients with substantial carotid narrowing are at increased risk for major stroke; however, recent studies suggest that factors other than the degree of carotid stenosis are involved in ischemic stroke pathogenesis. Atherosclerotic plaque of the stenotic carotid artery is the underlying cause of the majority of ischemic strokes and specific plaque characteristics have been associated with ischemic brain injury. Several studies have demonstrated that the mechanisms of plaque instability in the carotid circulation are similar to those in the coronary circulation. The purpose of this review is to characterize atherosclerotic carotid disease in light of our knowledge of coronary atherosclerosis and relate carotid plaque morphology to cerebral ischemic syndromes. Histological examination of the carotid plaque specimen should provide insights into the underlying plaque morphology that is responsible for the disease and should help determine the potential treatments that are likely to be beneficial in the prevention of a subsequent event.

KEY WORDS: Atherosclerotic carotid disease, Cerebral ischemic syndromes, Stroke

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Neurosurgery 2006;59(S3):219-27

CONCLUSION

Although the histopathology of carotid atherosclerotic disease resembles coronary atherosclerosis, there are distinct differences. While small mural thrombi are common, occlusive luminal thrombosis is typically not a major feature of carotid disease (varying from 3% for posterior circulation infarcts to 29% of total anterior circulation infarcts). Plaque ulceration is another common feature of carotid atherosclerosis, but infrequent in the coronary circulation. Similar to coronary disease, symptomatic carotid disease is predominantly associated with plaque rupture, but plaque erosion, an important subset of coronary thrombosis, is uncommon in the carotid circulation (10%). Calcified nodule, another cause of thrombosis, is perhaps more frequent in the carotid artery compared with the coronary circulation. Although there is a higher incidence of plaque rupture in symptomatic carotid disease compared with asymptomatic patients, the extent of lipid area, necrotic core size, and calcification may not be different. Not all cerebrovascular ischemia originates from the carotid atherosclerotic plaque and may frequently arise from atherosclerotic aortic arch disease. Therefore, in patients presenting with ischemic stroke, assessment of both the carotid artery and aortic arch is indicated. Finally, it is important to emphasize that the severity of luminal narrowing does not always correlate with the presence of a vulnerable plaque, and that other lesion morphologies, many of which are still under investigation, are involved in the pathogenesis of ischemic stroke. Further detailed pathological studies of endarterectomy specimens are required to identify specific morphological features that discriminate between asymptomatic and symptomatic carotid plaques, and to correlate the histological findings with existing diagnostic imaging models.

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Ruptured plaque carotid (*vs* coronary)

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- **Vessel size (blood flow)↑**
- **Plaque size↑**
- **Plaque ulceration (defect+thrombus)↑**
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  - **symptomatic 74% (asymptomatic: 32%)**

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- **Necrotic core size**
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Although the histopathology of carotid atherosclerotic disease resembles coronary atherosclerosis, there are distinct differences. While small mural thrombi are common, occlusive luminal thrombosis is typically not a major feature of carotid disease (varying from 3% for posterior circulation infarcts to 29% of total anterior circulation infarcts). Plaque ulceration is another common feature of carotid atherosclerosis, but infrequent in the coronary circulation. Similar to coronary disease, symptomatic carotid disease is predominantly associated with plaque rupture, but plaque erosion, an important subset of coronary thrombosis, is uncommon in the carotid circulation (10%). Calcified nodule, another cause of thrombosis, is perhaps more frequent in the carotid artery compared with the coronary circulation. Although there is a higher incidence of plaque rupture in symptomatic carotid disease compared with asymptomatic patients, the extent of lipid area, necrotic core size, and calcification may not be different. Not all cerebrovascular ischemia originates from the carotid atherosclerotic plaque and may frequently arise from atherosclerotic aortic arch disease. Therefore, in patients presenting with ischemic stroke, assessment of both the carotid artery and aortic arch is indicated. Finally, it is important to emphasize that the severity of luminal narrowing does not always correlate with the presence of a vulnerable plaque, and that other lesion morphologies, many of which are still under investigation, are involved in the pathogenesis of ischemic stroke. Further detailed pathological studies of endarterectomy specimens are required to identify specific morphological features that discriminate between asymptomatic and symptomatic carotid plaques, and to correlate the histological findings with existing diagnostic imaging models.

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Ruptured plaque carotid (*vs* coronary)

- **Vessel size (blood flow)↑**
- **Plaque size↑**
- **Plaque ulceration (defect+thrombus)↑**
- **Total occlusion↓ & thromboembolism↑**
- **Plaque rupture (*vs* erosion)↑**
  - **symptomatic 74% (asymptomatic: 32%)**
- **Plaque hemorrhage↑↑↑**
- **Necrotic core size**
  - **ruptured ~ intact plaques (*vs* coronary)**
- **Cap thickness↑**
  - **ruptured: 72 μm (*vs* 23 μm in coronary)**
  - **symptomatic: 270 ± 300 μm**
  - **asymptomatic: 500 ± 500 μm**
- **Cap inflammation↓**
  - **ruptured: 14 ± 11% (*vs* 26% in coronary**
  - **symptomatic: 1114 ± 1104 macr**
  - **asymptomatic: 385 ± 622 macr**