Angioplasty Summit TCT Asia Pacific

Pathogenesis, Detection, and Treatment of Vulnerable Plaque

Sponsored by Clinical Research Center for Ischemic Heart disease, The Korea Ministry of Health and Welfare

Moderators: *Ik-Kyung Jang*
Seung-Jung Park

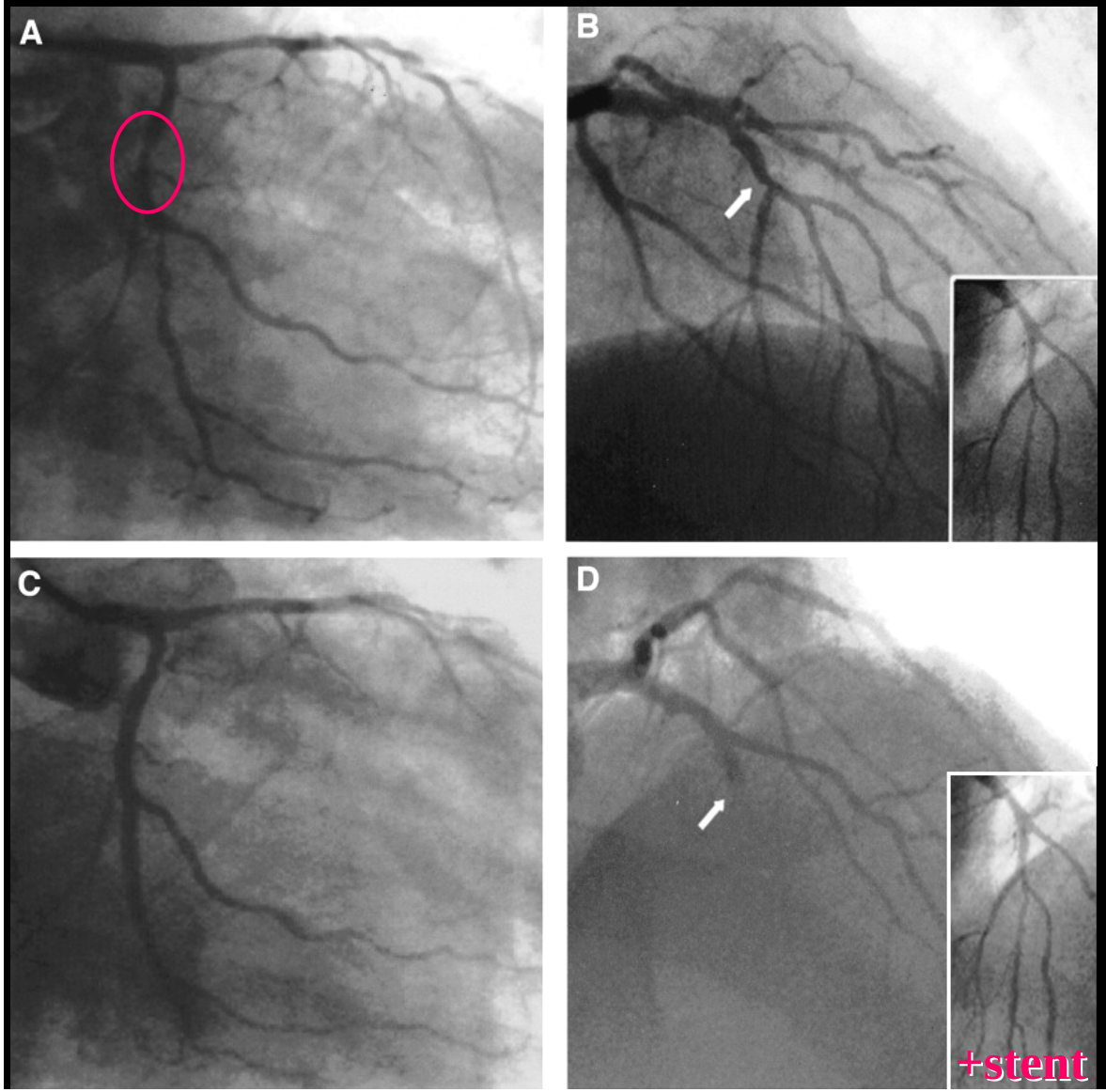
Pathogenesis and Pathologic Features of Vulnerable Plaque

Erling Falk, Seoul, April 28, 2006

58-year-old man with recent inferolateral MI

A,C: LCx culprit → stenting

B: LAD 50% stenosis *nonsignificant*



D, 1 hour later:

LAD occlusion & AMI → stenting

Romagnoli et al. Circulation 2006;113:e61-2

Culprit Lesion Seen 1 Hour Before Occlusion

Limits of Coronary Angiography in Detecting Vulnerable Plaques

Enrico Romagnoli, MD; Francesco Burzotta, MD, PhD; Floriana Giannico, MD; Filippo Crea, MD

A 58-year-old man with recent inferolateral myocardial infarction was admitted to our critical care unit after an episode of typical chest pain. At hospital admission, the physical examination was normal, and an ECG performed after the resolution of symptoms showed signs of the previous myocardial infarction and a mild (0.5 mm) up-slowing ST-segment elevation in leads V_3 through V_6, with resolution in the following ECGs. Blood samples revealed raised troponin levels. Coronary angiography showed subocclusive stenosis of the mid left circumflex (LCx) artery (Figure, A). Furthermore, the left anterior descending (LAD) artery exhibited a 50% uncomplicated stenosis (Figure, B). The LCx stenosis was treated by stent implantation with optimal angiographic results (Figure, C). An hour after the procedure, the patient suffered from increasing chest pain, refractory to endovenous nitrates and associated with ST-segment elevation in precordial leads. Urgent coronary angiography showed total occlusion of the LAD at the site of the previously noted nonsignificant stenosis (Figure, D). A drug-eluting stent was then deployed with optimal angiographic results (Figure, E). This case provided the opportunity to assess coronary anatomy at angiography immediately before an acute occlusion, highlighting the limitations of the "luminogram" provided by coronary angiography. It also confirms that the mechanism responsible for the transition from stable to unstable coronary syndromes does not operate at the site of a single plaque but affects the whole coronary circulation.

Circulation 2006;113:e61-2

Vulnerable plaques

- ***definition***
- ***pathogenesis***
- ***pathologic features***

MINI-REVIEW:
EXPERT OPINIONS

Circulation 2003
107:2068-71

Is There a Vulnerable Plaque?

Attilio Maseri, MD; Valentin Fuster, MD, PhD

The identification of potential triggers of acute coronary syndromes (ACS) represented by unstable angina (UA), myocardial infarction (MI) (preceded or not by UA), and sudden coronary death (SCD) is a rapidly growing area of research.

Issues of Nomenclature

1 Coronary plaque disruption and subsequent thrombosis is the major recognized pathogenetic component of 2 "unstable plaques," which characterize the transition from stable coronary artery disease (CAD) to ACS. However, in the presence of unstable or even stable plaques, a thrombogenic state or "high-risk blood" may contribute, at least in some cases, to the development of ACS.[1] Furthermore, thrombosis is also an integral component of the chronic atherothrombotic progression of atherosclerosis.

Although the observation that plaque disruption leads to ACS goes back a number of decades, the notion of 3 "vulnerable plaques" was first developed a little over a decade ago on the basis of post-mortem observations in patients with ACS.[2] 4 At the site of culprit coronary lesions, a rupture was often found at the shoulder of atheromatous plaques with a large pultaceous lipid core and a thin fibrous cap. Such rupture was originally thought to be the result of localized mechanical shear stress forces.[3] However, on the basis of emerging evidence of a prevalent inflammatory component in ACS, inflammatory mechanisms of plaque instability began to receive considerable attention.[4]

The acquisition of knowledge does not necessarily makes things more comprehensible, but rather often adds novel complexities. Yet, when confronted with a pressing issue, such as predicting major future adverse events, there is a natural inclination to accept generalizations not yet justified by available data.

The intriguing concept of a vulnerable plaque, as a potential short-term precursor of unstable plaques, derives from the theoretical possibility of identifying those coronary atherosclerotic plaques that might become unstable and thus trigger ACS. The notion of vulnerable plaques is already stimulating the development of imaging and other techniques for their detection before they become unstable, and eventually for their passivation. However, efforts to detect vulnerable plaques require a clearer definition of this concept. In particular, it should be clarified whether vulnerable or 5 high-risk coronary plaques may (1) become unstable because of a structural or an inflammatory vulnerability or because of other yet unknown causes; (2) be present simultaneously in multiple coronary arteries; (3) remain vulnerable for weeks, months, or years; and (4) be also fibrotic, without a lipid-rich core and thin fibrous cap, thus, better fulfilling the generic term high-risk plaque rather than the traditional term vulnerable plaque, which tends to imply the presence of a soft lipid core.

To define more precisely the concept of vulnerable or high-risk plaques as potential precursors of the unstable lesions that may trigger ACS, it is useful to consider the 6 distinctive structural and functional features of the culprit unstable coronary plaques and the distinctive clinical presentation of ACS.

Distinctive Structural and Functional Features of Unstable Coronary Plaques

The most obvious features that distinguish patients with ACS from those with stable CAD are (1) complex coronary 7 stenoses; (2) coronary plaque fissures; (3) fresh thrombi; and (4) plaque inflammation. Such findings, being both common and plausible pathogenetic mechanisms, led to the widely accepted unifying paradigm that instability is the conse-

Nomenclature

1. Plaque disruption
2. Unstable plaque
3. Vulnerable plaque
4. Plaque rupture
5. High-risk plaque
6. Culprit plaque
7. Plaque fissure

Next page:

8. Plaque erosion

Terminology for high-risk and vulnerable coronary artery plaques

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

Johannes A. Schaar*, James E. Muller, Erling Falk, Renu Virmani, Valentin Fuster, Patrick W. Serruys, Antonio Colombo, Christodoulos Stefanadis, S. Ward Casscells, Pedro R. Moreno, Attilio Maseri, Anton F.W. van der Steen

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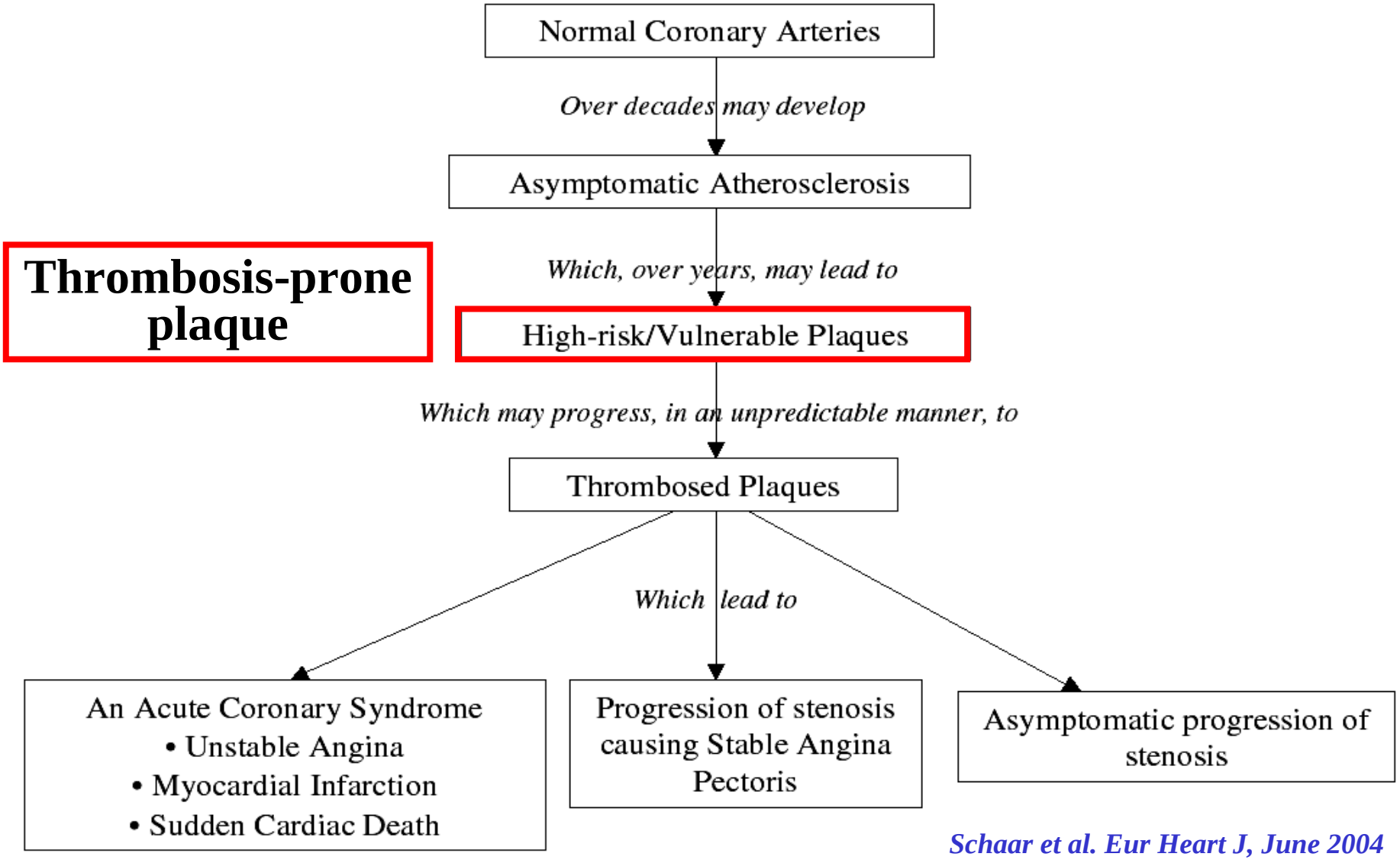
KEYWORDS
Vulnerable plaque;
High-risk plaque;
Acute coronary syndrome;
Terminology

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.

Development of atherosclerosis and progression to thrombosis and clinical events



Thrombosis-prone plaque

Schaar et al. Eur Heart J, June 2004

Vulnerable plaques

- *definition*
- *pathogenesis*
- *pathologic features*

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

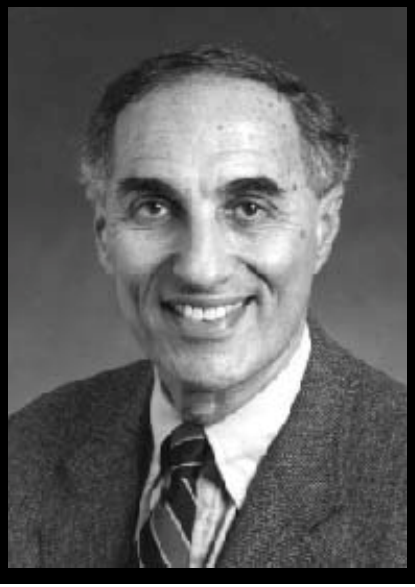
ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D.

ATHEROSCLEROSIS is an inflammatory disease. Because high plasma concentrations of cholesterol, in particular those of low-density lipoprotein (LDL) cholesterol, are one of the prin-

FACTORS THAT INDUCE AND PROMOTE INFLAMMATION OR ATHEROGENESIS

Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis.[6] The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; if unabated and excessive, this process will result in an advanced, complicated lesion. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL; free radicals caused by cigarette smoking, hypertension, and diabetes mellitus; genetic alterations; elevated plasma homocysteine concentrations;



† Seattle, March 18, 1999

N Engl J Med 1999 Jan;340:115-26

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Inflammation, Atherosclerosis, and Coronary Artery Disease

Göran K. Hansson, M.D., Ph.D.

RECENT RESEARCH HAS SHOWN THAT INFLAMMATION PLAYS A KEY ROLE in coronary artery disease (CAD) and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. This review highlights the role of inflammation in the pathogenesis of atherosclerotic CAD. It will recount the evidence that atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree.

A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate CAD by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and eastern Europe and the rising incidence of obesity and diabetes in the Western world.[1] Cardiovascular diseases cause 38 percent of all deaths in North America and are the most common cause of death in European men under 65 years of age and the second most common cause in women. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.

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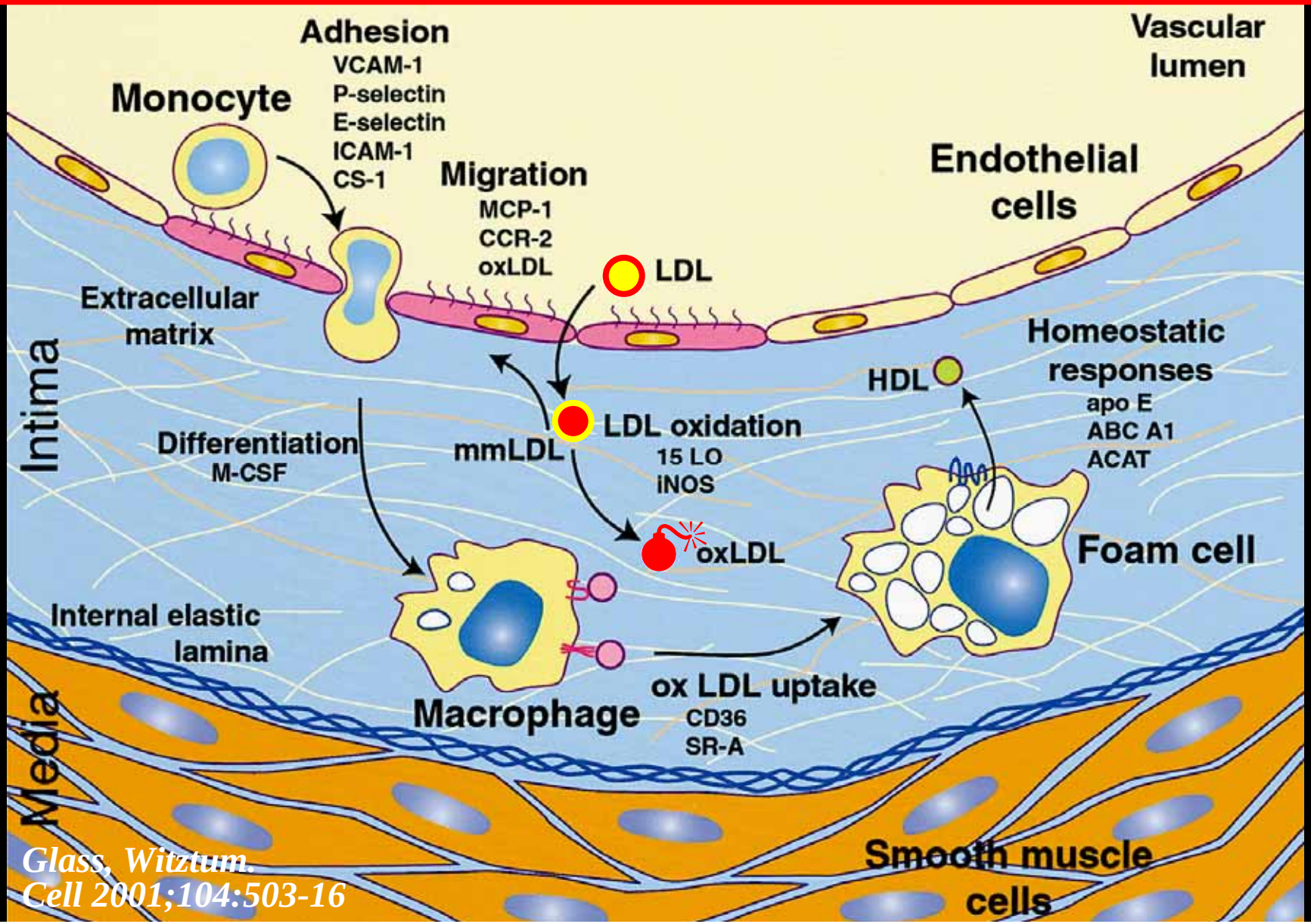
N Engl J Med 2005;352:1685-95.

NEJM 2005
352:1685-95

Atherogenesis: inflammation fueled by lipid

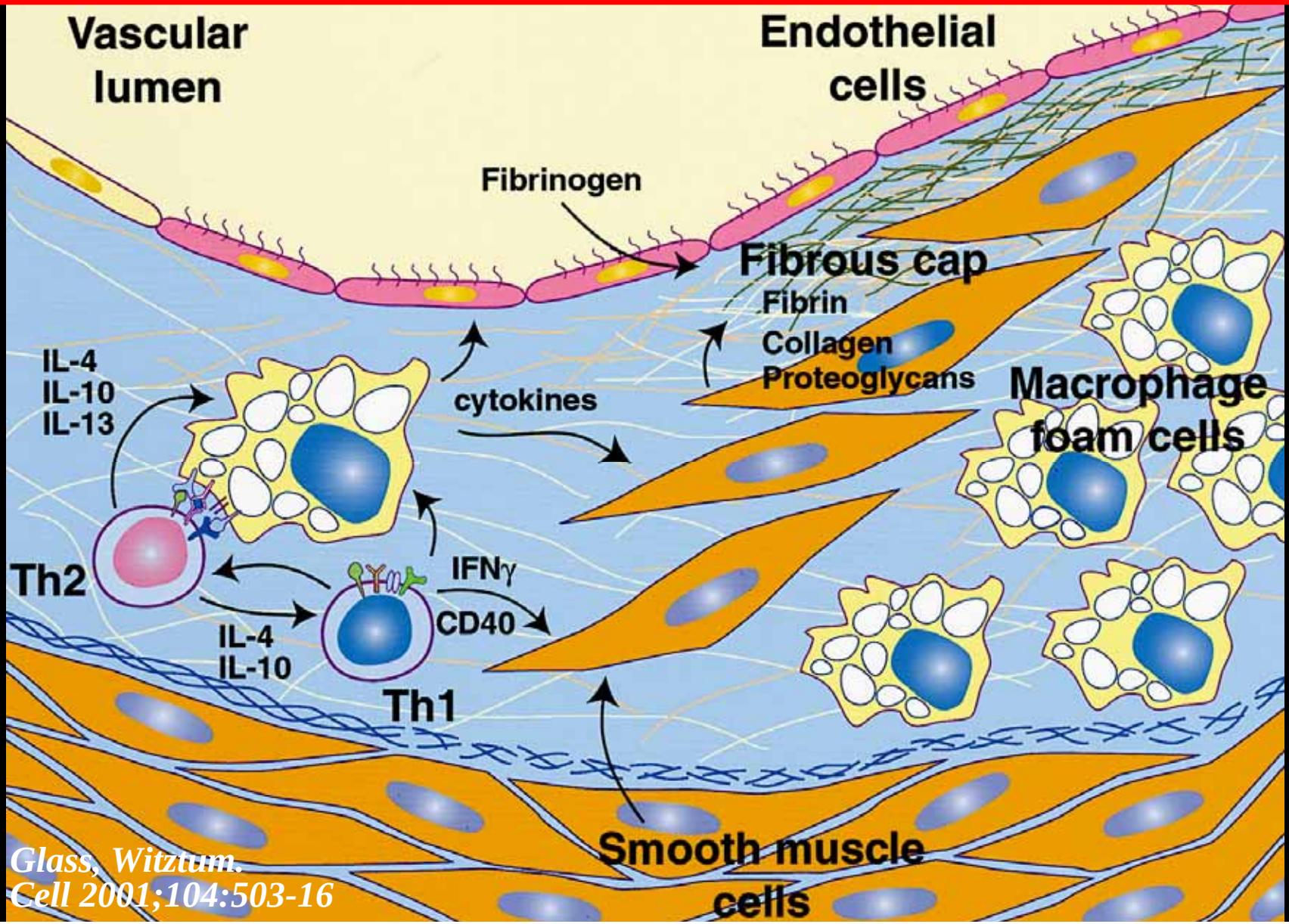
macrophage recruitment



Glass, Witztum. Cell 2001;104:503-16

Atherogenesis: inflammation fueled by lipid

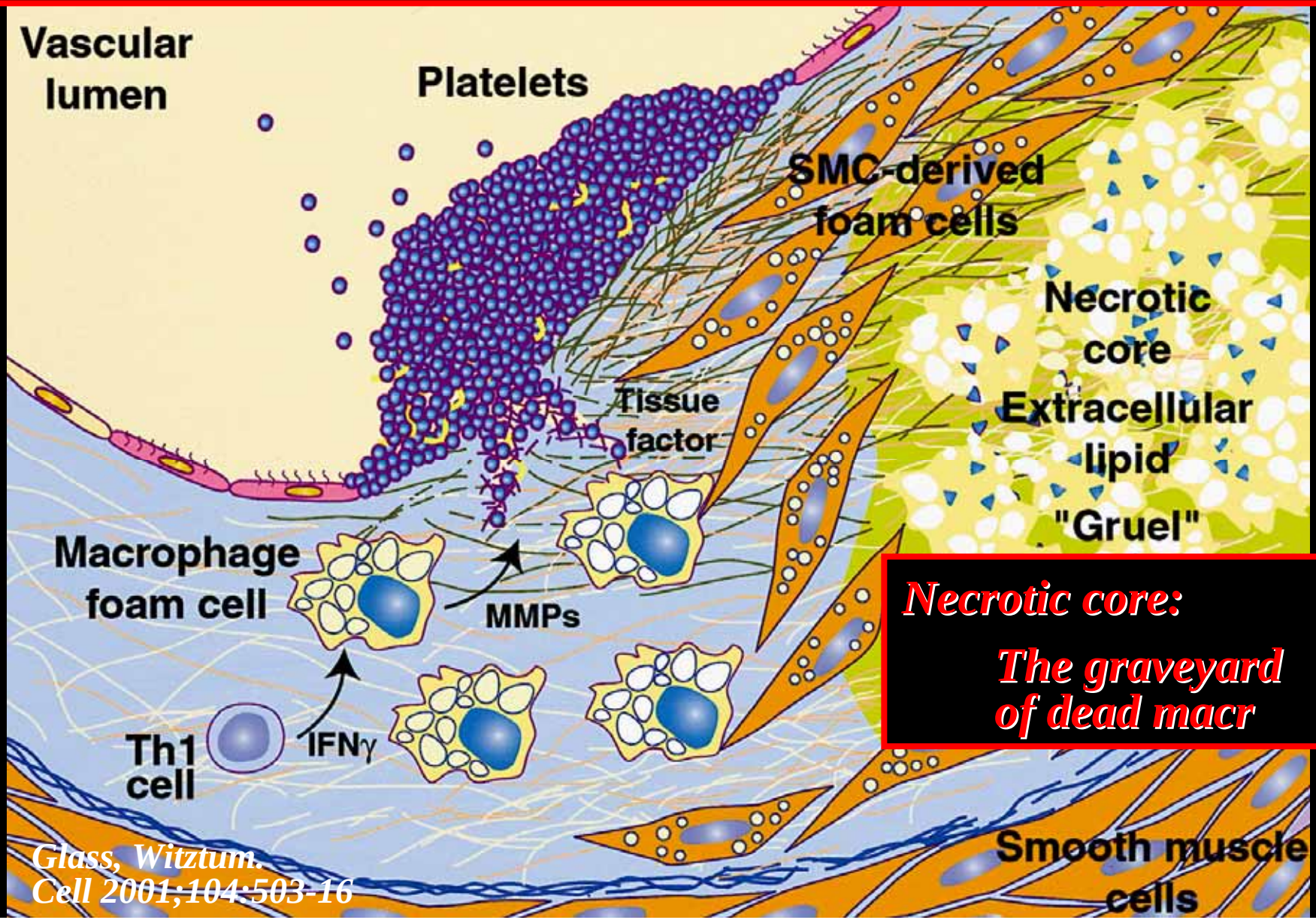
chr. inflammatory – immuno – proliferative disease



Glass, Witztum. Cell 2001;104:503-16

Athero-thrombosis: plaque rupture ~75%

necrotic core, thin fibrous cap, inflammation

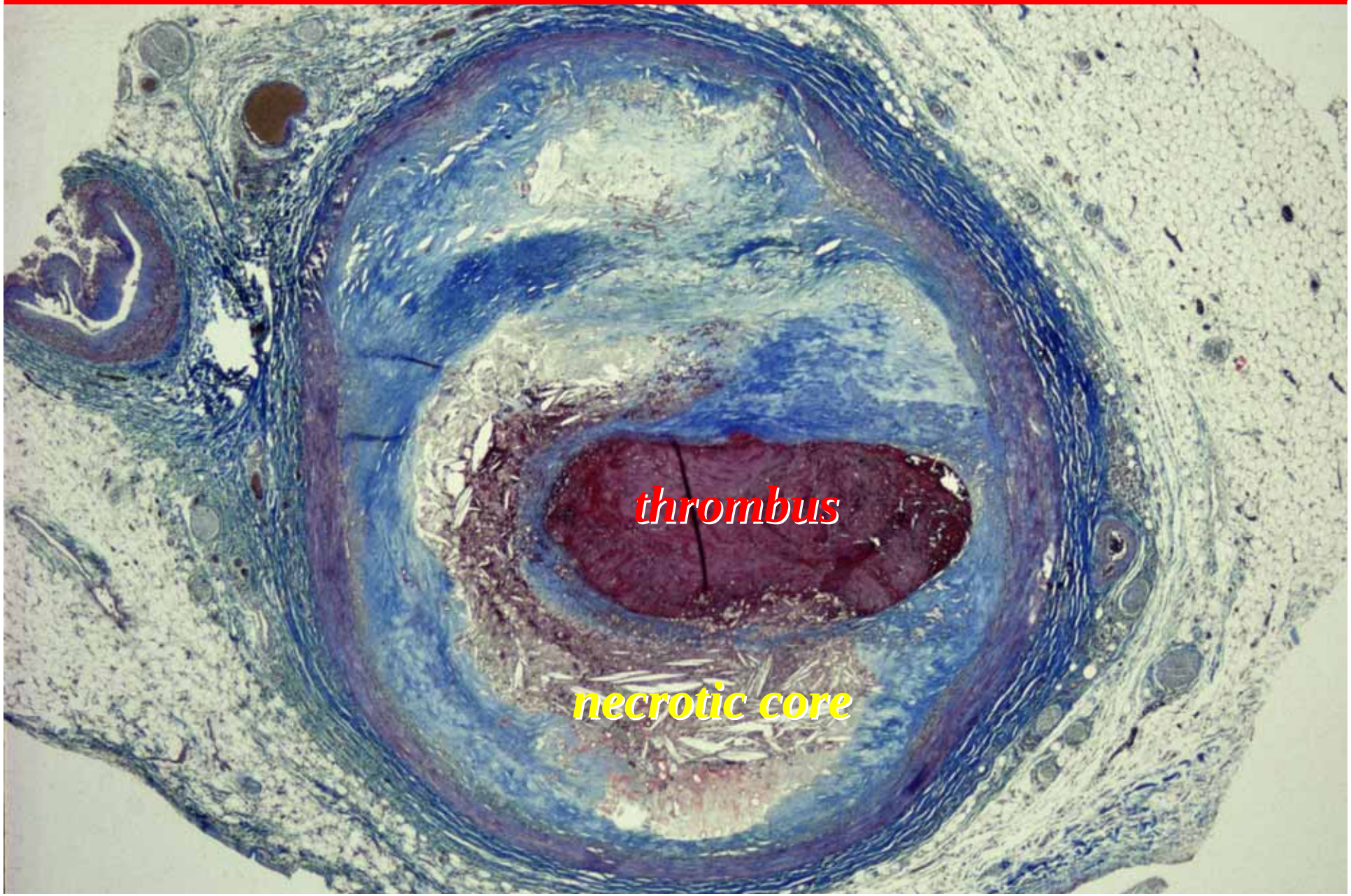


Necrotic core:

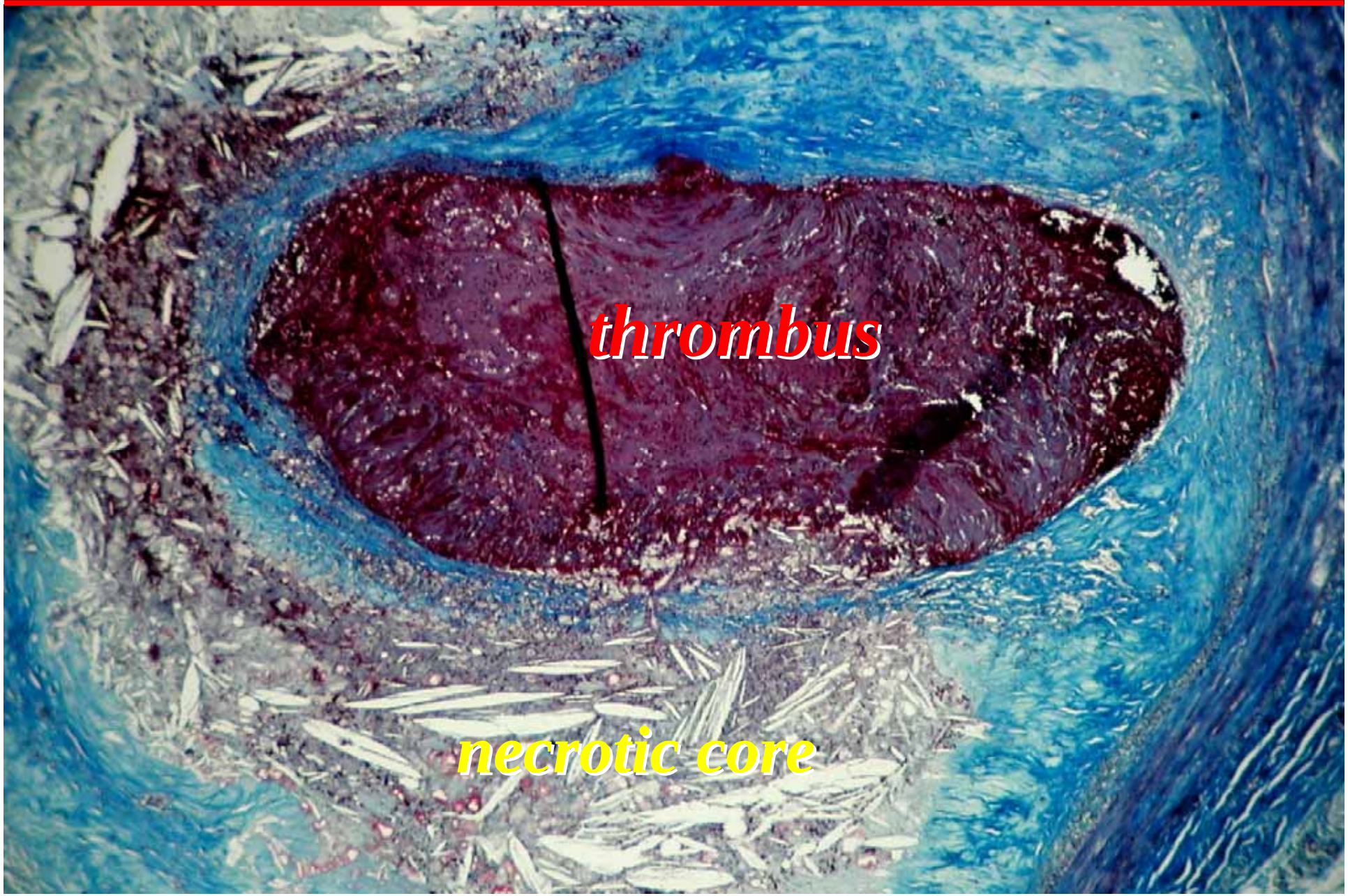
The graveyard of dead macr

Glass, Witztum. Cell 2001;104:503-16

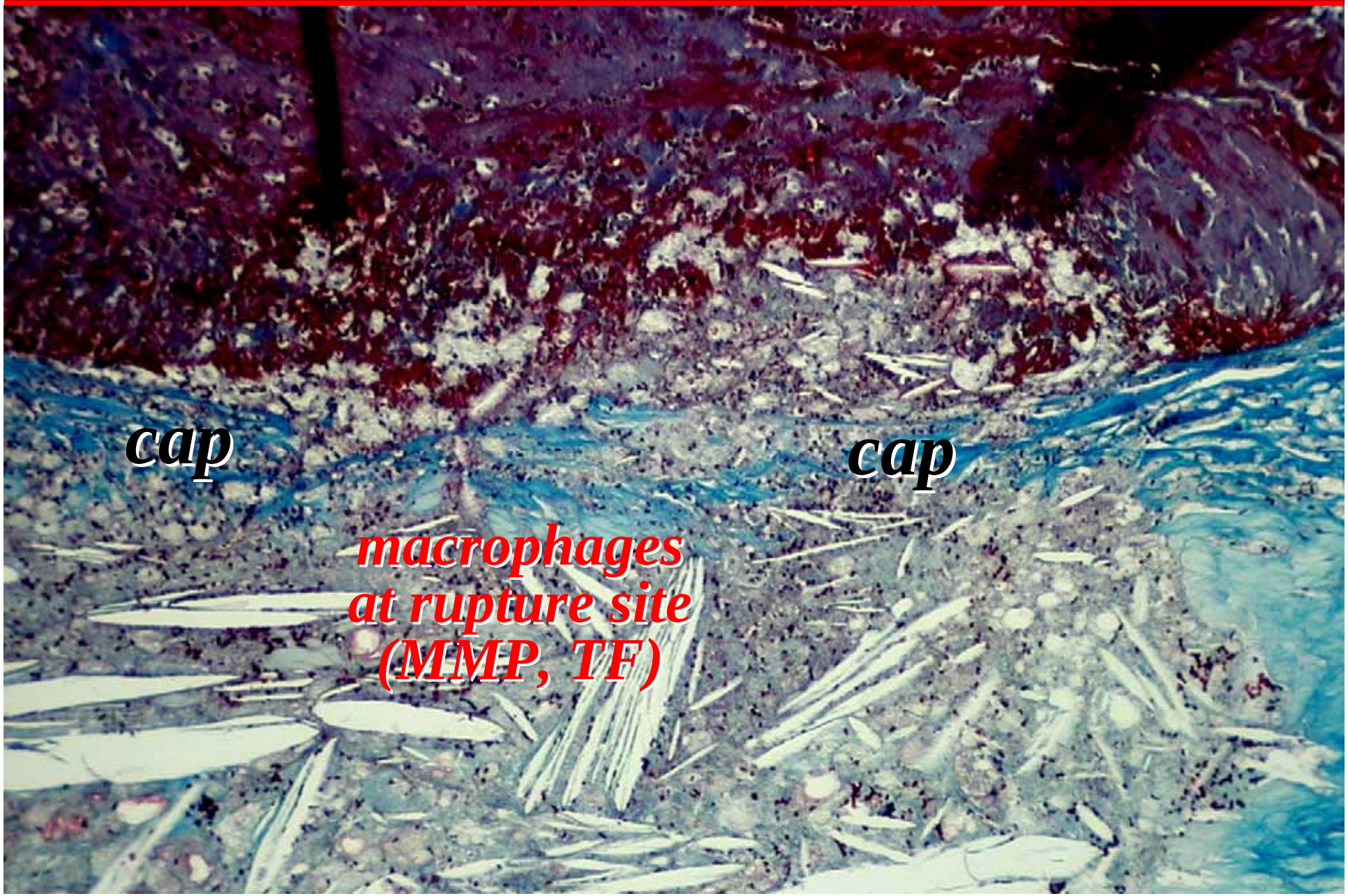
Plaque rupture: role of macrophages



Plaque rupture: role of macrophages



Plaque rupture: role of macrophages



1460 thrombosed coronary plaques

plaque rupture

Patients		Age	n	Rupture	Study
Hospital,	?	?	19	19 = 100%	Chapman-1965
Hospital,	?	?	17	17 = 100%	Constantinides-1966
Hospital,	AMI+SCD	58 y	40	39 = 98%	Friedman-1966
Hospital,	AMI	62 y	88	71 = 81%	Bouch-1970
Hospital,	AMI	66 y	91	68 = 75%	Sinapius-1972
Coroner,	SCD	53 y	20	19 = 95%	Friedman-1973
Hospital,	AMI	67 y	76	69 = 91%	Horie-1978
Hospital,	AMI	67 y	49	40 = 82%	Falk-1983
Coroner,	SCD	<65 y	32	26 = 81%	Tracy-1985
Med.exam,	SCD	<70 y	61	39 = 64%	El Fawal-1987
Hospital,	AMI		83	52 = 63%	Yutani-1987
Coroner,	SCD?	?	85	71 = 84%	Richardson-1989
Hospital,	AMI	63 y	20	12 = 60%	van der Wal-1994
Coroner,	SCD (all?)	?	202	143 = 71%	Davies-1997, update
Hospital,	AMI	69 y	291	218 = 75%	Arbustini-1999
Hospital,	AMI	61 y	61	56 = 92%	Shi-1999
Hospital,	AMI	69 y	100	81 = 81%	Kojima-2000
Med.exam,	SCD	48 y	125	74 = 59%	Virmani-2000, update
			1460	1114 = **76%**	**Worldwide**

Plaque Rupture → Fatal Thrombosis

acute MI ≈ sudden death

Patients		Age	n	Rupture	Study
Hospital,	?	?	19	19 = 100%	Chapman-1965
Hospital,	?	?	17	17 = 100%	Constantinides-1966
Hospital,	AMI+SCD	58 y	40	39 = 98%	Friedman-1966
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Hospital,	AMI	61 y	61	56 = 92%	Shi-1999
Hospital,	AMI	69 y	100	81 = 81%	Kojima-2000
			935	742 = 79%	Acute MI
Coroner,	SCD	53 y	20	19 = 95%	Friedman-1973
Coroner,	SCD	<65 y	32	26 = 81%	Tracy-1985
Med.exam,	SCD	<70 y	61	39 = 64%	El Fawal-1987
Coroner,	SCD?	?	85	71 = 84%	Richardson-1989
Coroner,	SCD (all?)	?	202	143 = 71%	Davies-1997, update
Med.exam,	SCD	48 y	125	74 = 59%	Virmani-2000, update
			525	372 = 71%	Sudden death

Plaque Rupture → Fatal Thrombosis

Europe ≈ Asia ≈ USA

Patients		Age	n	Rupture	Study
Hospital,	AMI	62 y	88	71 = 81%	Bouch-1970
Hospital,	AMI	66 y	91	68 = 75%	Sinapius-1972
Hospital,	AMI	67 y	49	40 = 82%	Falk-1983
Med.exam,	SCD	<70 y	61	39 = 64%	El Fawal-1987
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Hospital,	AMI	63 y	20	12 = 60%	van der Wal-1994
Coroner,	SCD (all?)	?	202	143 = 71%	Davies-1997, update
Hospital,	AMI	69 y	291	218 = 75%	Arbustini-1999
			887	662 = **75%**	**Europe**
Hospital,	AMI	67 y	76	69 = 91%	Horie-1978
Hospital,	AMI		83	52 = 63%	Yutani-1987
Hospital,	AMI	61 y	61	56 = 92%	Shi-1999
Hospital,	AMI	69 y	100	81 = 81%	Kojima-2000
			320	258 = **81%**	**Asia**
Hospital,	?	?	19	19 = 100%	Chapman-1965
Hospital,	?	?	17	17 = 100%	Constantinides-1966
Hospital,	AMI+SCD	58 y	40	39 = 98%	Friedman-1966
Coroner,	SCD	53 y	20	19 = 95%	Friedman-1973
Coroner,	SCD	<65 y	32	26 = 81%	Tracy-1985
Med.exam,	SCD	48 y	125	74 = 59%	Virmani-2000, update
			253	194 = **77%**	**USA**

Plaque Rupture → Fatal Thrombosis

age

Patients		Age	n	Rupture	Study
Hospital,	?	?	19	19 = 100%	Chapman-1965
Hospital,	?	?	17	17 = 100%	Constantinides-1966
Hospital,	AMI		83	52 = 63%	Yutani-1987
Coroner,	SCD?	?	85	71 = 84%	Richardson-1989
Coroner,	SCD (all?)	?	202	143 = 71%	Davies-1997, update
			406	302 = **74%**	**Age unknown**
Hospital,	AMI	62 y	88	71 = 81%	Bouch-1970
Hospital,	AMI	66 y	91	68 = 75%	Sinapius-1972
Hospital,	AMI	67 y	76	69 = 91%	Horie-1978
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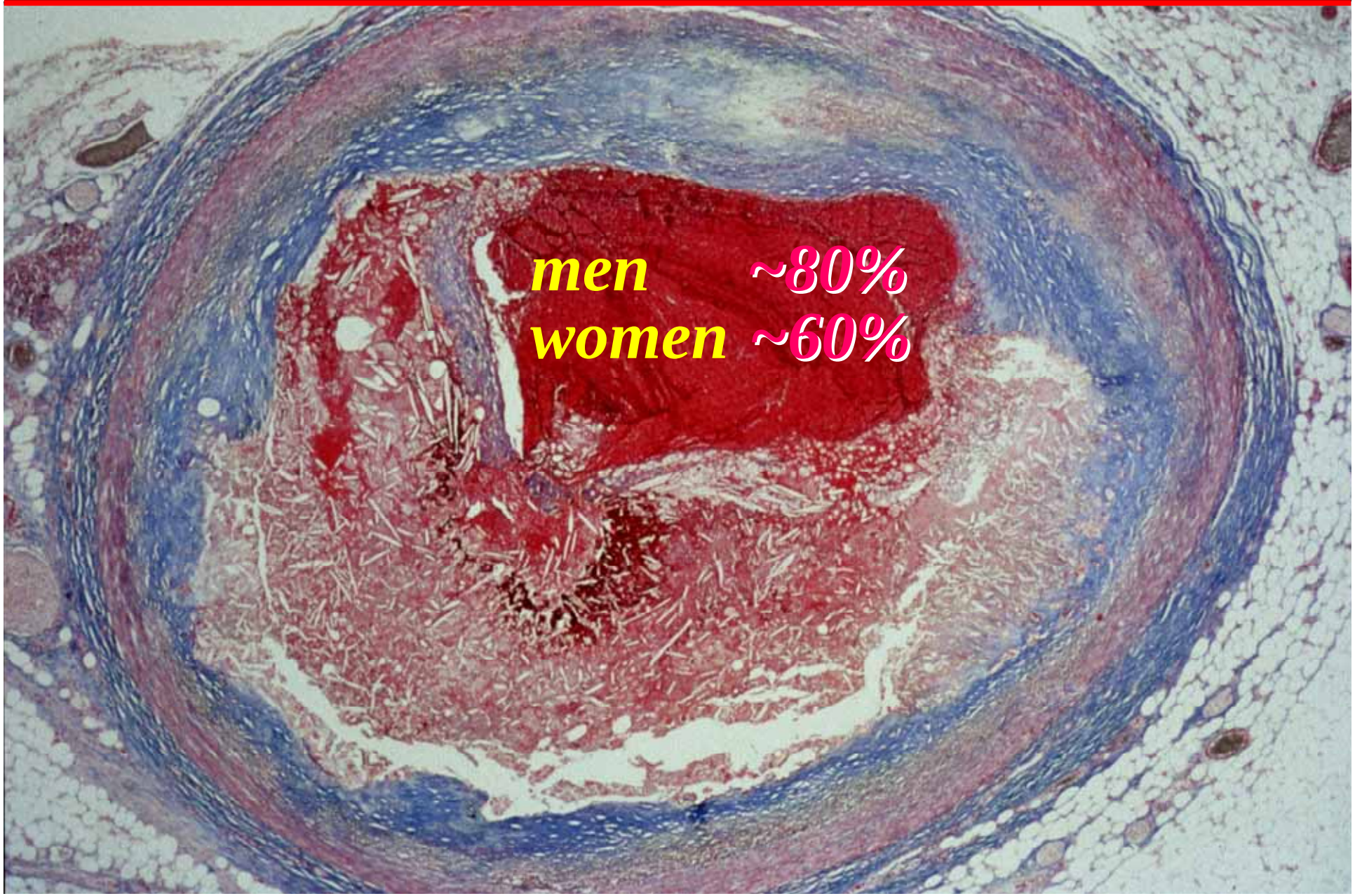
Hospital,	AMI	69 y	100	81 = 81%	Kojima-2000
			837	654 = **78%**	**>60 years**
Coroner,	SCD	<65 y	32	26 = 81%	Tracy-1985
Hospital,	AMI+SCD	58 y	40	39 = 98%	Friedman-1966
Coroner,	SCD	53 y	20	19 = 95%	Friedman-1973
Med.exam,	SCD	48 y	125	74 = 59%	Virmani-2000, update
			217	158 = **73%**	**<60 years**

Plaque Rupture → Fatal Thrombosis

sex

Sex	n	Rupture	Study	p
Male	37	32 = 86%	Falk-1983	
	134	113 = 84%	Davies-1997	
	184	151 = 82%	Arbustini-1999	.0004
	74	63 = 85%	Kojima-2000	.08 → .4
	94	64 = 68%	Virmani-2000, update	
	523	423 = **81%**		
Female	12	8 = 67%	Falk-1983	
	27	16 = 59%	Davies-1997	
	107	67 = 63%	Arbustini-1999	
	26	18 = 69%	Kojima-2000	
	31	10 = 32%	Virmani-2000, update	
	203	119 = **59%**		

Plaque Rupture → Coronary Thrombosis

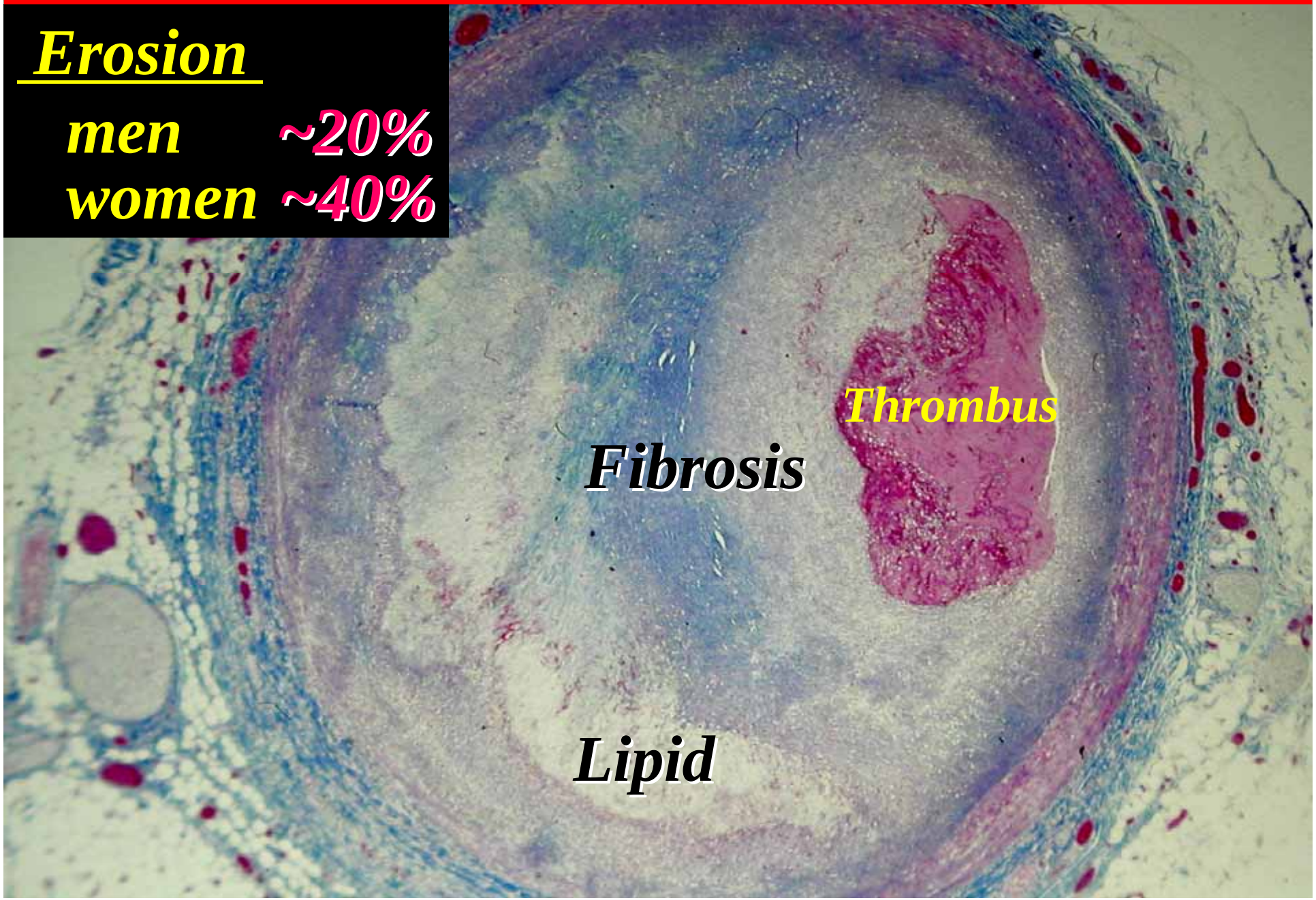


Thrombosis not caused by plaque rupture

Erosion

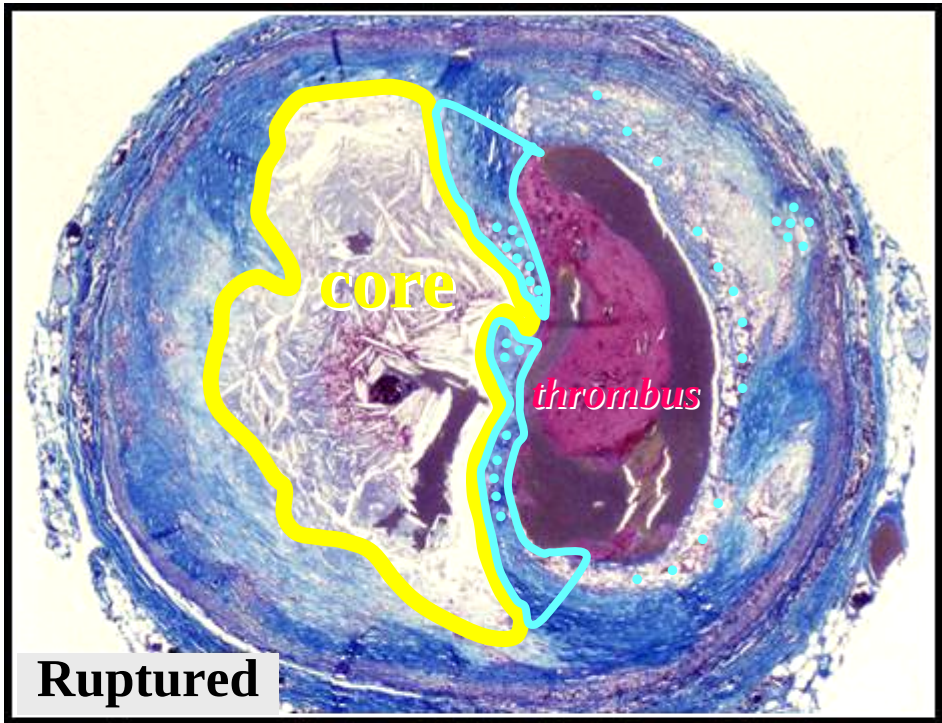
men ~20%

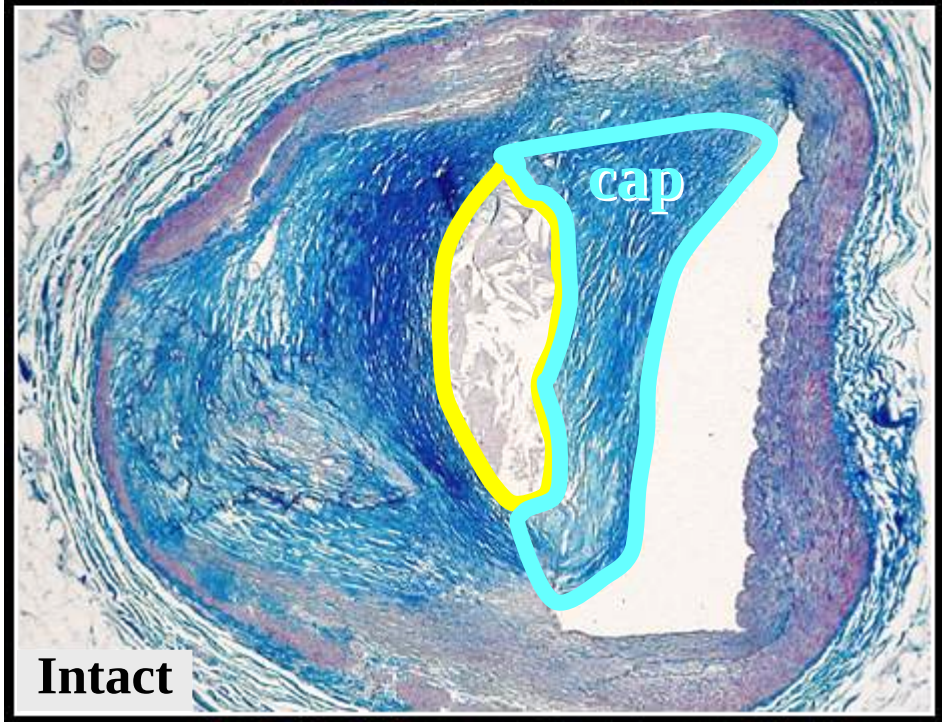
women ~40%



Vulnerable plaques

- ***definition***
- ***pathogenesis***
- ***pathologic features***





Coronary Atherosclerosis

ruptured vs intact plaque

- **Necrotic core↑**
  - **~34% of plaque area***
  - **~3.8 mm^2 & ~9 mm long***
- **Fibrous cap**
  - **thinkness↓, ~23 μm (95% <65 μm)***
  - **macrophages↑, *~26% of cap****

Macrophages in plaque

- **Plaque area ~11 mm^2**
- **Macr area ~ 0.14 mm^{2*}**

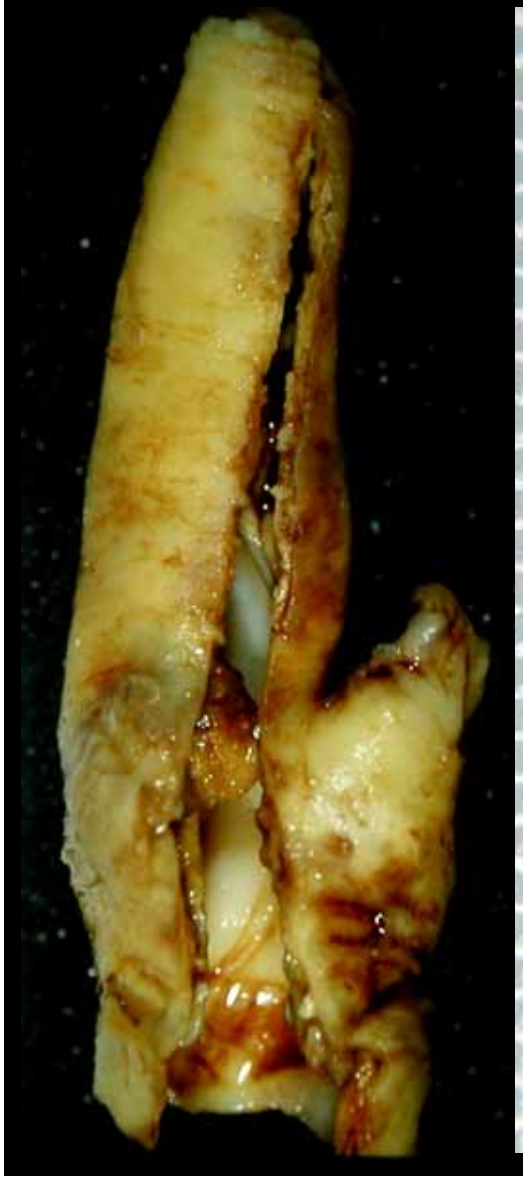
<2% of plaque area

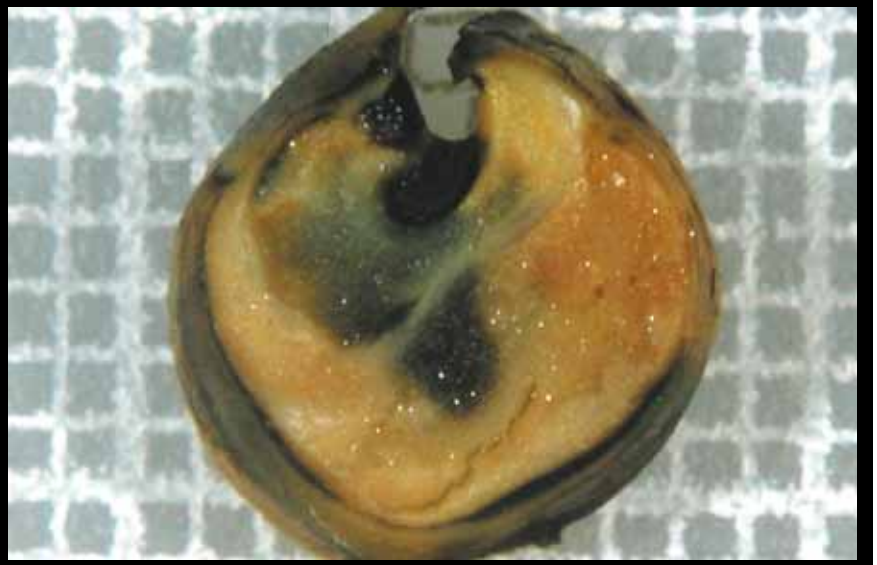
**TCFA, Kolodgie, ..., Virmani. NEJM 2003;349:2316-25*

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

Carotid Atherosclerosis & Stroke

endarterectomy specimen





Carotid Plaque → Stroke ~ CAD → AMI

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

Luigi Giusto Spagnoli, MD
Alessandro Mauriello, MD
Giuseppe Sangiorgi, MD
Stefano Fratoni, MD
Elena Bonanno, MD
Robert S. Schwartz, MD
David G. Piepgras, MD
Raimondo Pistolese, MD
Arnaldo Ippoliti, MD
David R. Holmes, Jr, MD

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

Carotid Plaque → Stroke ~ CAD → AMI

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

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

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

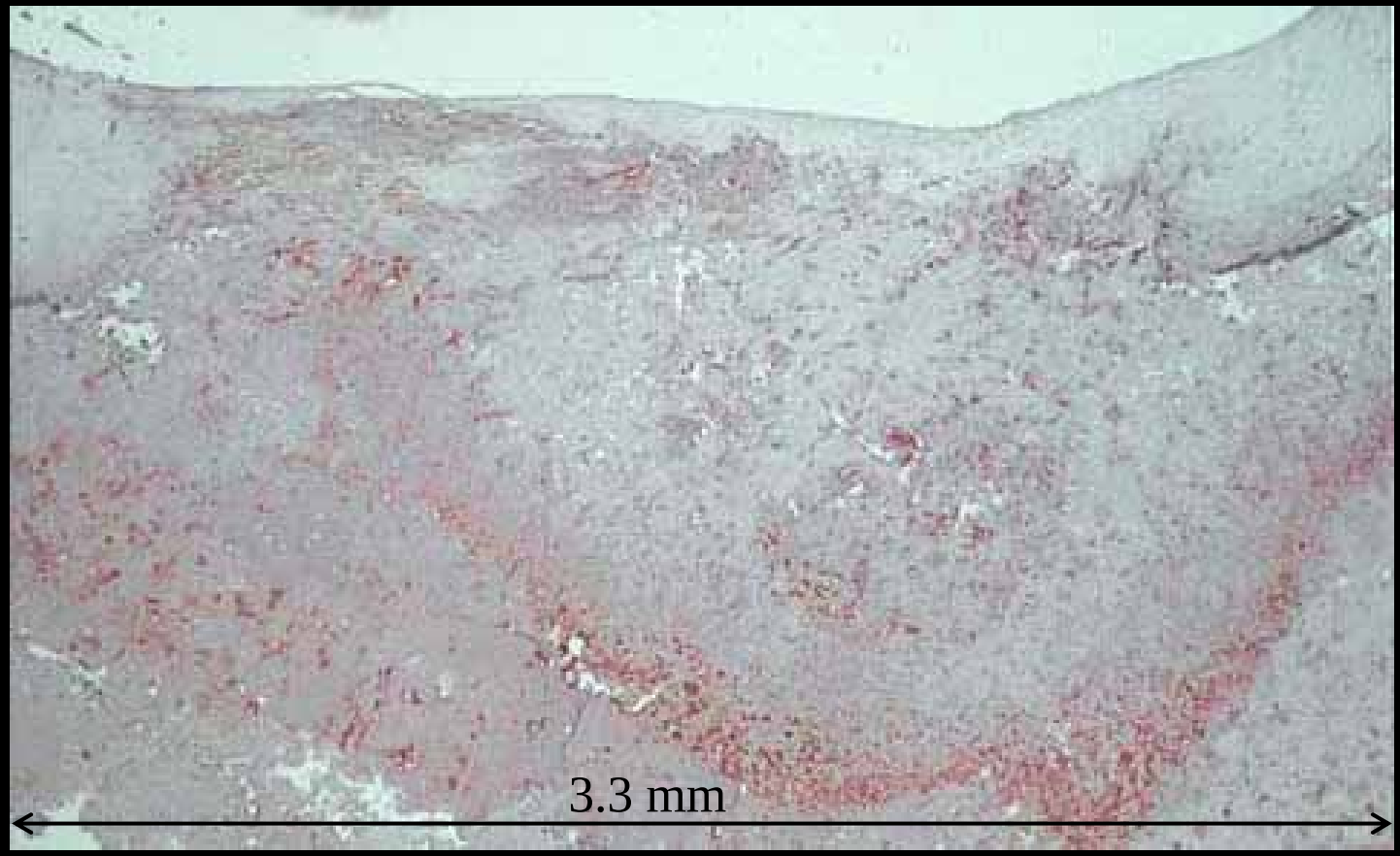
Marie-Louise M. Grønholdt, MD, PhD,[a] Børge G. Nordestgaard, MD, DMSc,[b] Jacob Bentzon,[c] Britt M. Wiebe, MD,[d] Ji Zhou, MD,[c] Erling Falk, MD, DMSc,[c] and Henrik Sillesen, MD, DMSc,[e]
Copenhagen and Aarhus, Denmark

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

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

J Vasc Surg 2002;35:137-45



Macrophages red (CD68+): ~1% to 1.8%

Gene expression in carotid plaques

Expression Profiling Identifies Smooth Muscle Cell Diversity Within Human Intima and Plaque Fibrous Cap

Loss of RGS5 Distinguishes the Cap

Lawrence D. Adams, Randolph L. Geary, Jing Li, Anthony Rossini, Stephen M. Schwartz

Background—The fibrous cap of the atherosclerotic lesion is believed to be critical to stability because disruption of the cap is the final event leading to plaque rupture. We have, therefore, used expression arrays to define the phenotype of the cap and other plaque components.

Methods and Results—To identify unique expression programs able to distinguish the smooth muscle of the cap from other plaque smooth muscle cells, RNA profiles were determined in human carotid artery media, nonatherosclerotic adjacent intima, fibrous cap of advanced atherosclerotic plaques, and whole advanced plaque with cDNA arrays covering 21 000 or 26 000 Unigene clusters. The molecular signature of each tissue was dominated by a core gene-set with differential expression of <1% of clusters assayed.

Conclusions—Both intima and cap expressed novel genes not previously associated with SMC pathology. If the cap is derived from a unique subpopulation, this pattern is the signature of that particular set of cells. The loss of RGS5 in the fibrous cap is of particular interest because of its role in vessel development and physiology. (***Arterioscler Thromb Vasc Biol*. 2006;26:319-325.**)

of breast cancer growth and metastasis.[37] Our data also show a paucity of inflammatory genes in the intima and cap versus the media. We suspect this is a product of arrays measuring total expression from the adjacent nonatherosclerotic intima and that the whole fibrous caps versus looking at whole plaque using in situ or IHC, which would pick up small areas of inflammation and inflammatory gene expression in these two tissues.

Our data on whole plaque should be viewed with caution because of the complexity of plaque tissue. For example, some genes previously reported as characteristic of atherosclerotic plaque were inconsistent in this analysis. For example, CD68, a commonly used marker for the plaque macrophage,[38] as well as osteopontin and eotaxin, genes known as plaque markers,[39,40] were upregulated in some but not all plaques. These data may result from the fact that we were

Adams et al. ATVB 2006;26:319-25

Table VII. Array data for genes known to be expressed in plaque tissue from the literature.

Genes	total positive plaques	plaque 1	plaque 2	plaque 3	plaque 4	plaque 5
OPN	3	+	-	+	-	+
CD40	not present on filter					
TGFβ	0	-	-	-	-	-
PAI-I	0	-	-	-	-	-
CD68	0	-	-	-	-	-
TNFα	2	-	-	+	-	+
IL-1	0	-	-	-	-	-
MCP-1	1	+	-	-	-	-
IL-8	0	-	-	-	-	-
CD3	0	-	-	-	-	-
CD11b	0	-	-	-	-	-
CD34	0	-	-	-	-	-
CD14	0	-	-	-	-	-
Eotaxin	0	-	-	-	-	-

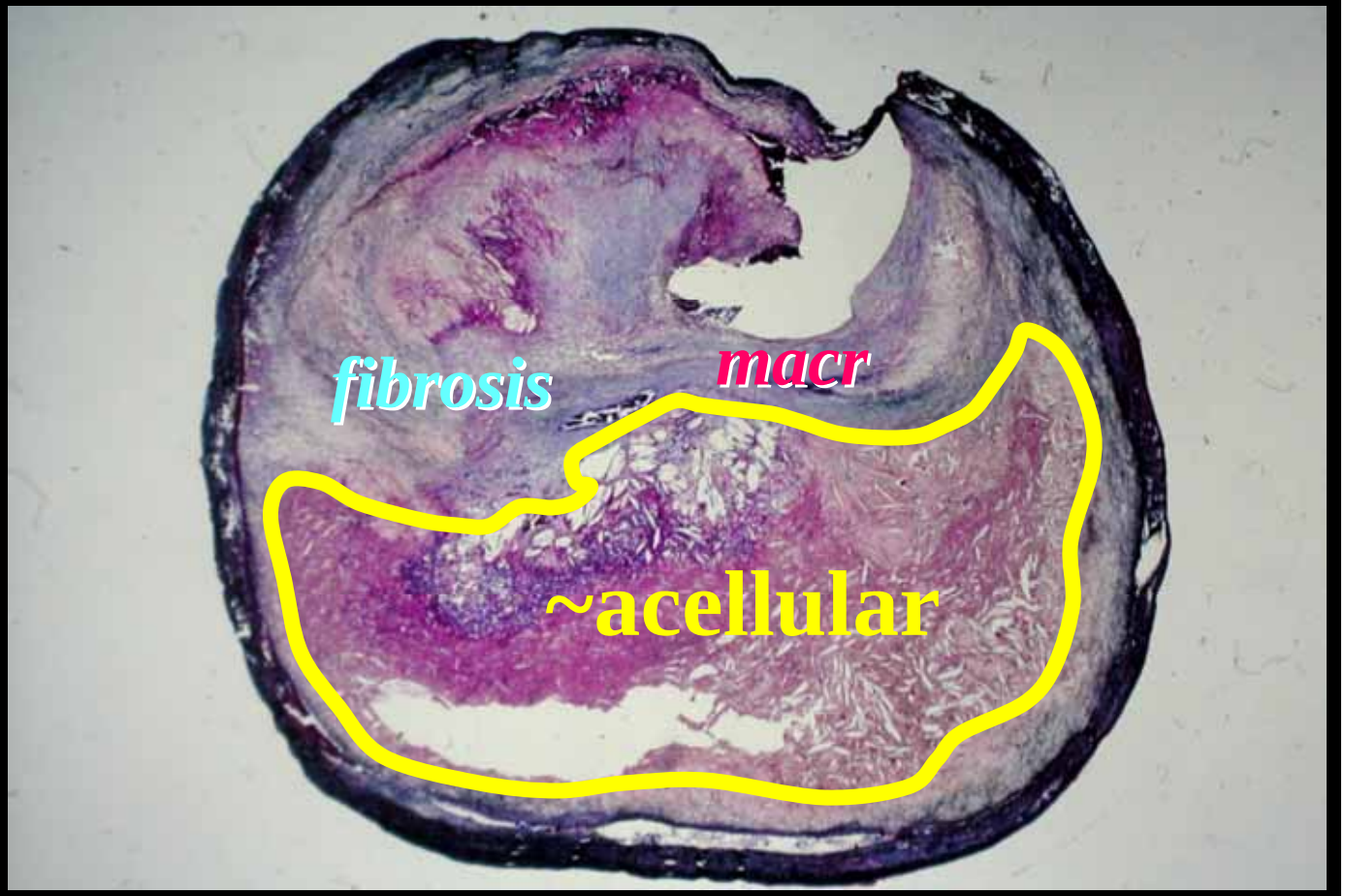
Adams et al. ATVB 2006;26:319-25

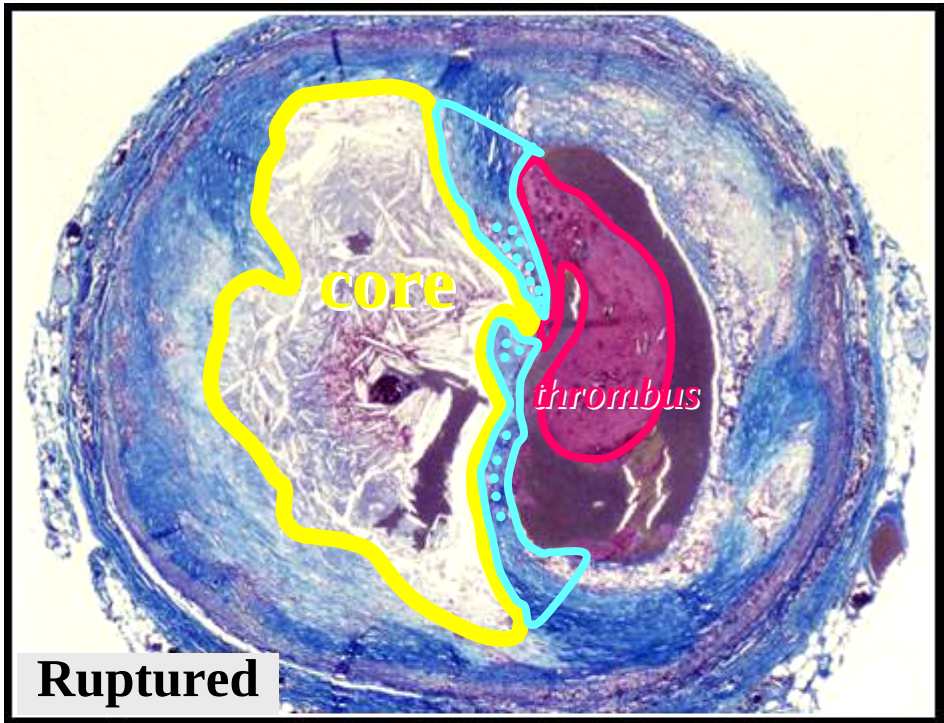
plaques. These data may result from the fact that we were arraying whole plaque, and looking at overall levels of genes and macrophage RNA may be just a small overall percentage of the total sample. In situ and IHC studies can detect small areas of inflammation and are better methods for fine detail analysis compared with array analysis of whole samples; microscopic-aided laser dissection, however, could be used to isolate inflammation-rich plaque regions for array analysis in the future. This variability suggests that more detailed studies of plaque to plaque, or even intraplaque variation, will be useful. Recently, for example, Faber et al used subtraction suppression hybridization to identify two genes whose expression was unique to ruptured plaques.[8] We would have discarded these genes as inconsistent in the present study, because they were not expressed universally in all plaques.

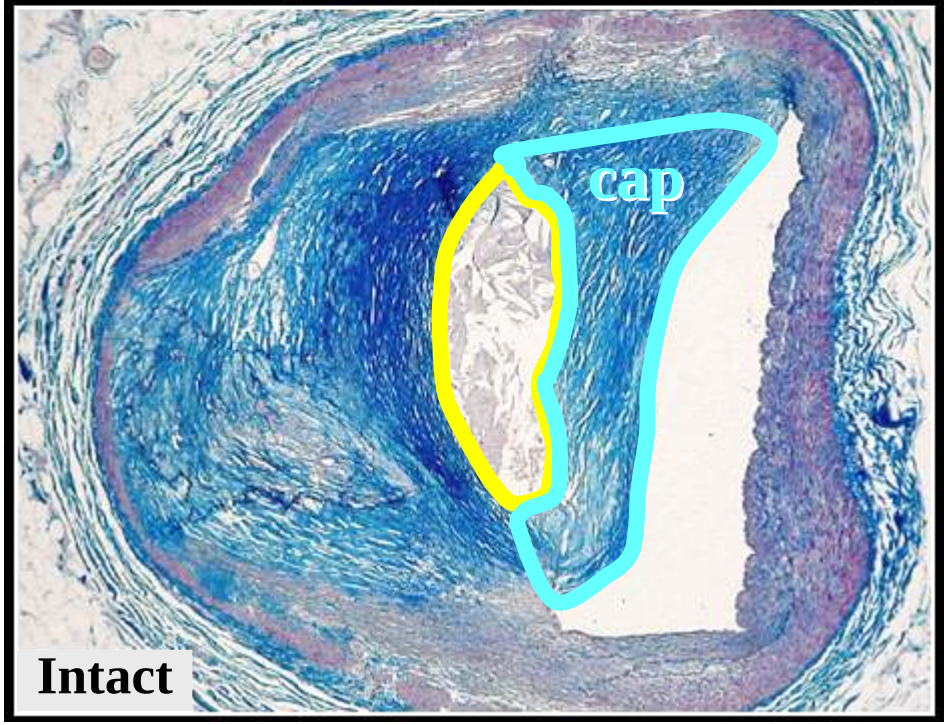
Adams et al. ATVB 2006;26:319-25

Symptomatic Carotid Atherosclerosis

macrophage density: <2-3%







Coronary Atherosclerosis

ruptured vs intact plaque

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  - **~34% of plaque area***
  - **~3.8 mm^2 & ~9 mm long***
- **Fibrous cap**
  - **thinkness↓, ~23 μm (95% <65 μm)***
  - **macrophages↑, ~26% of cap***
  - **smooth muscle cells↓ (apoptosis)**
  - **thrombus↑**
- **Expansive remodeling↑**

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

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.

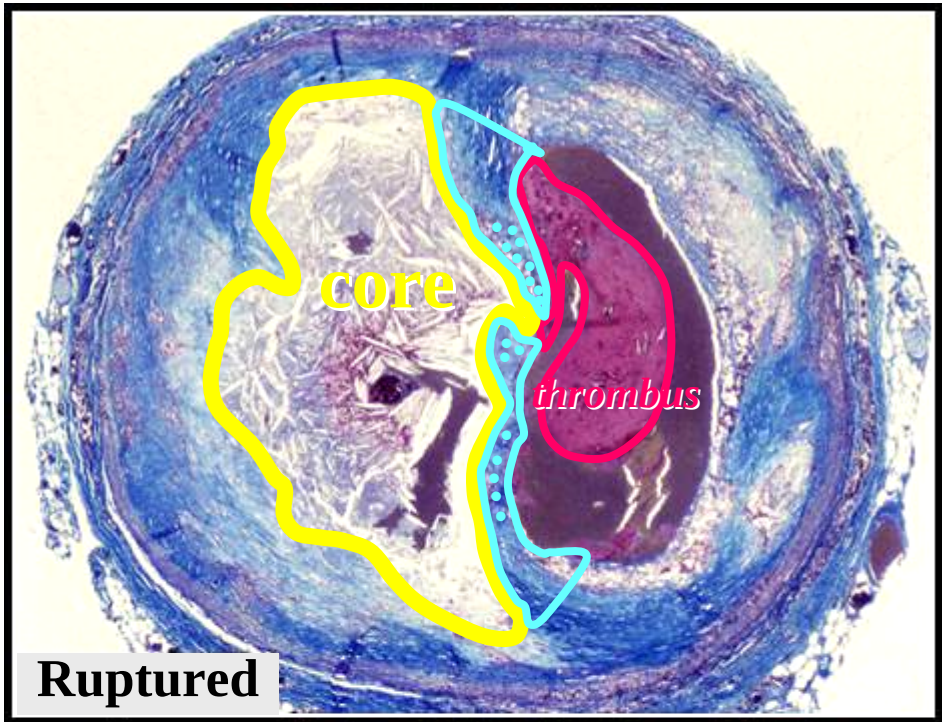
Conclusion. Intraindividually, pathohistologic markers previously reported to be related to plaque vulnerability were associated with a larger plaque area and vessel area. In addition, inflammation of the cap and shoulder of the plaque was a common finding in the atherosclerotic femoral artery.

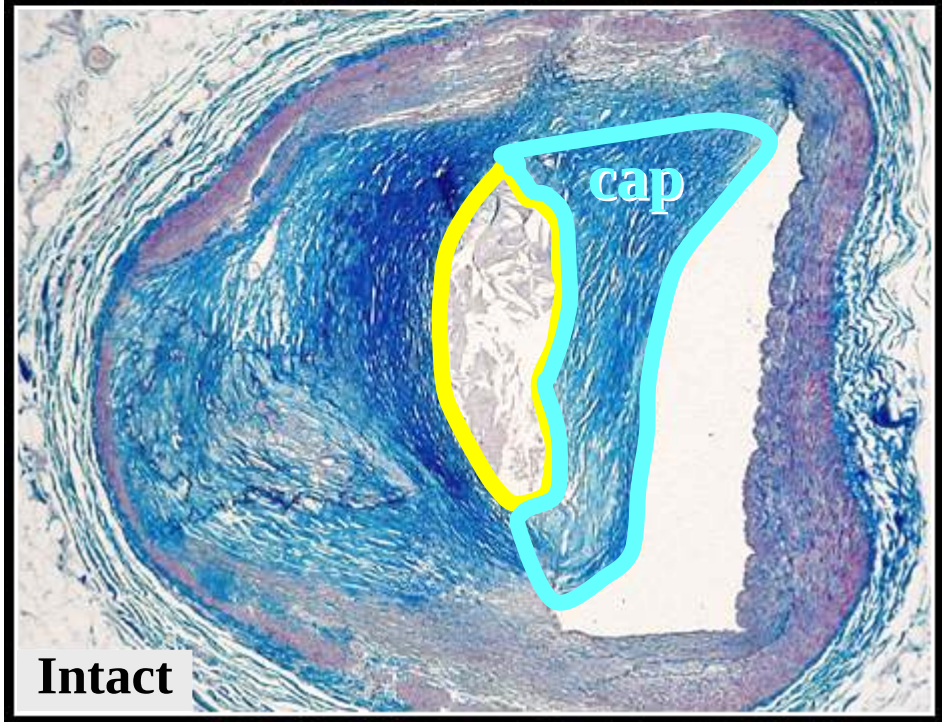
(J Am Coll Cardiol 1998;32:655–62)

Gregg W. Stone, TCT Asia Pacific

Satellite Lecture, April 26, 2006

“What we do in the cath. lab.
do not prevent heart attack or death”





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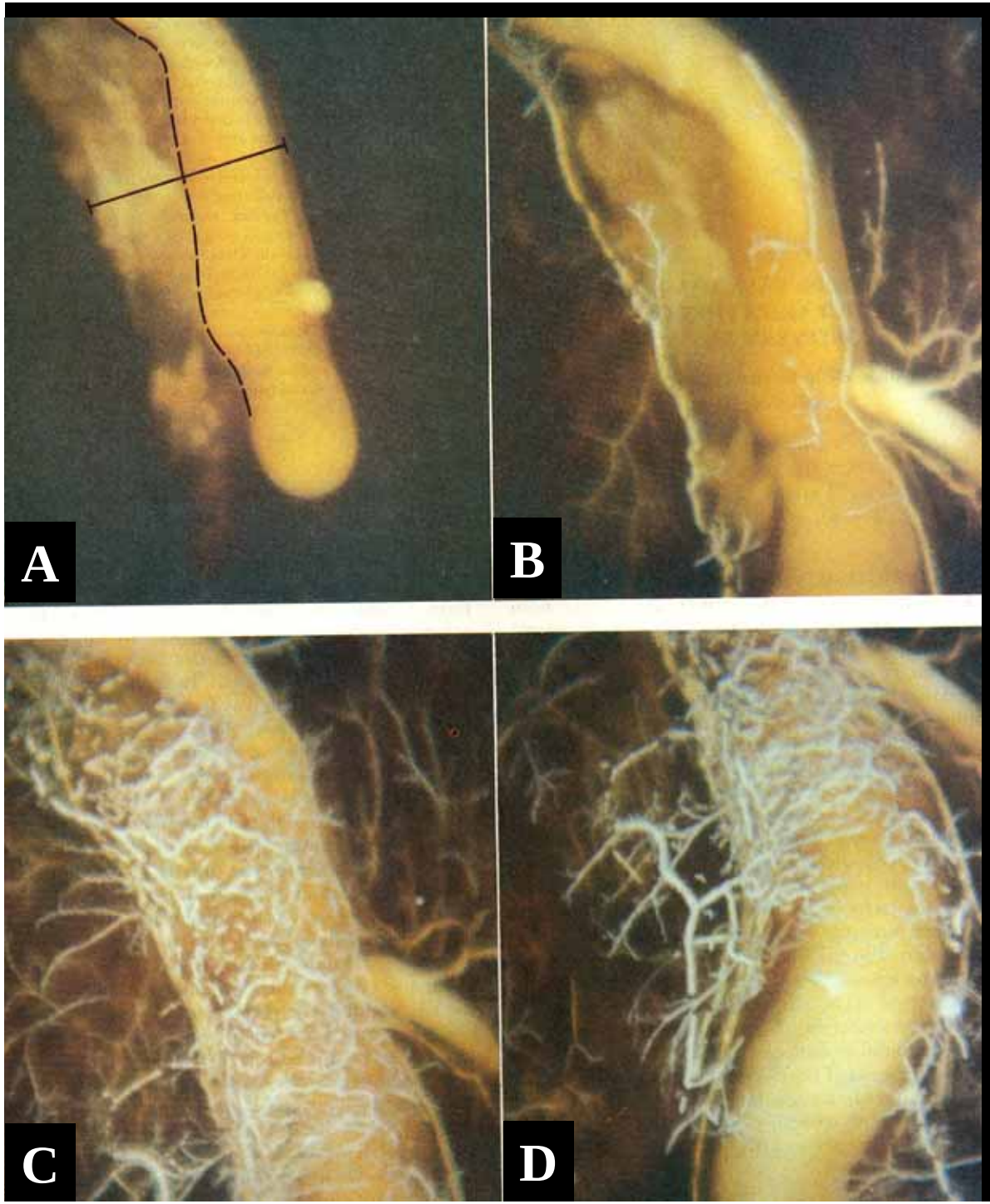
- **Expansive remodeling↑**
- **Angiogenesis↑**

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

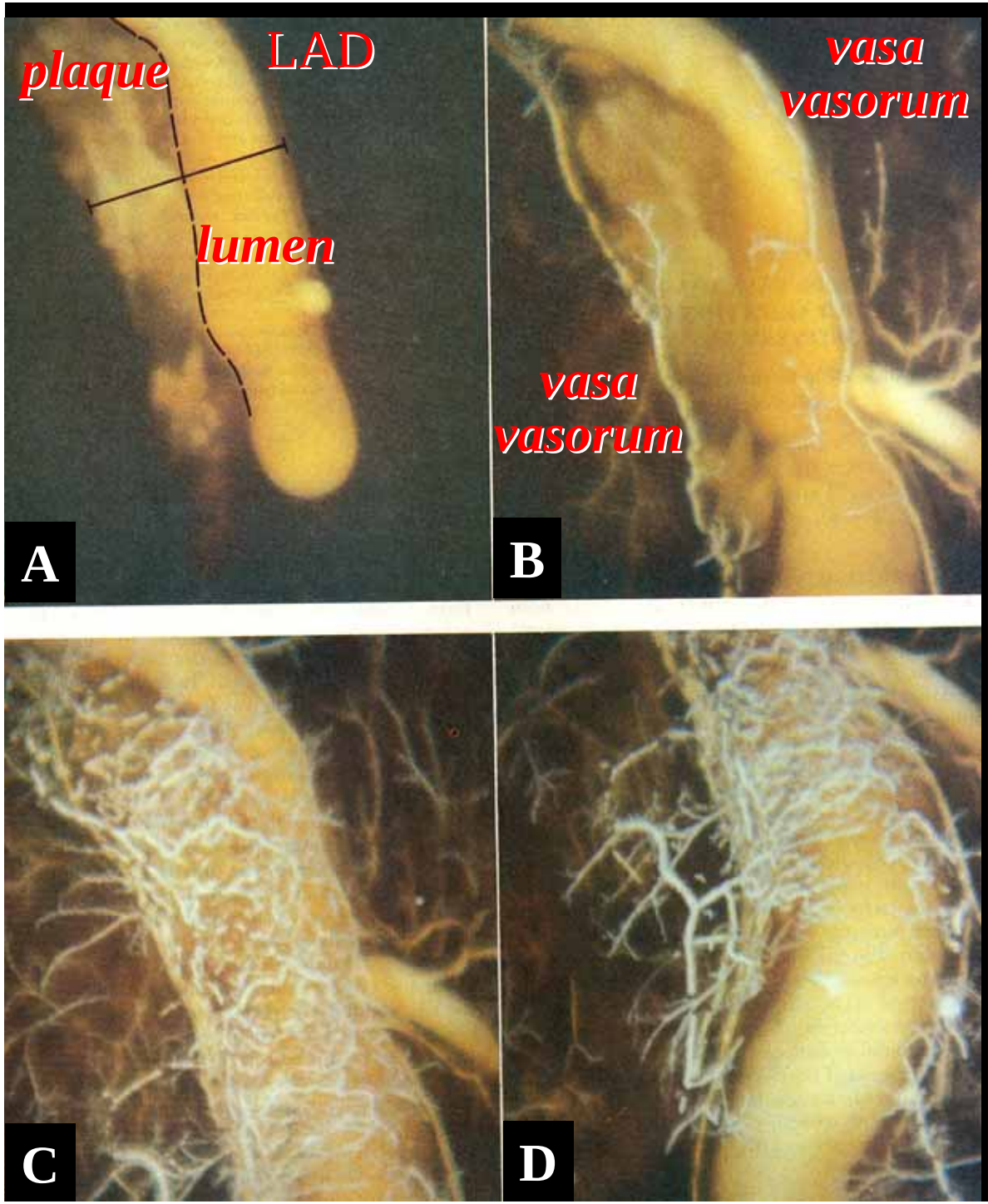


Barger et al.

Visualization of vasa vasorum and neovascularization **of atherosclerotic coronary arteries by cinematography of *silicone injection* in cleared human hearts.**

Vasa vasorum were rarely seen in normal arteries.
In contrast, ….

NEJM 1984;310:175-7

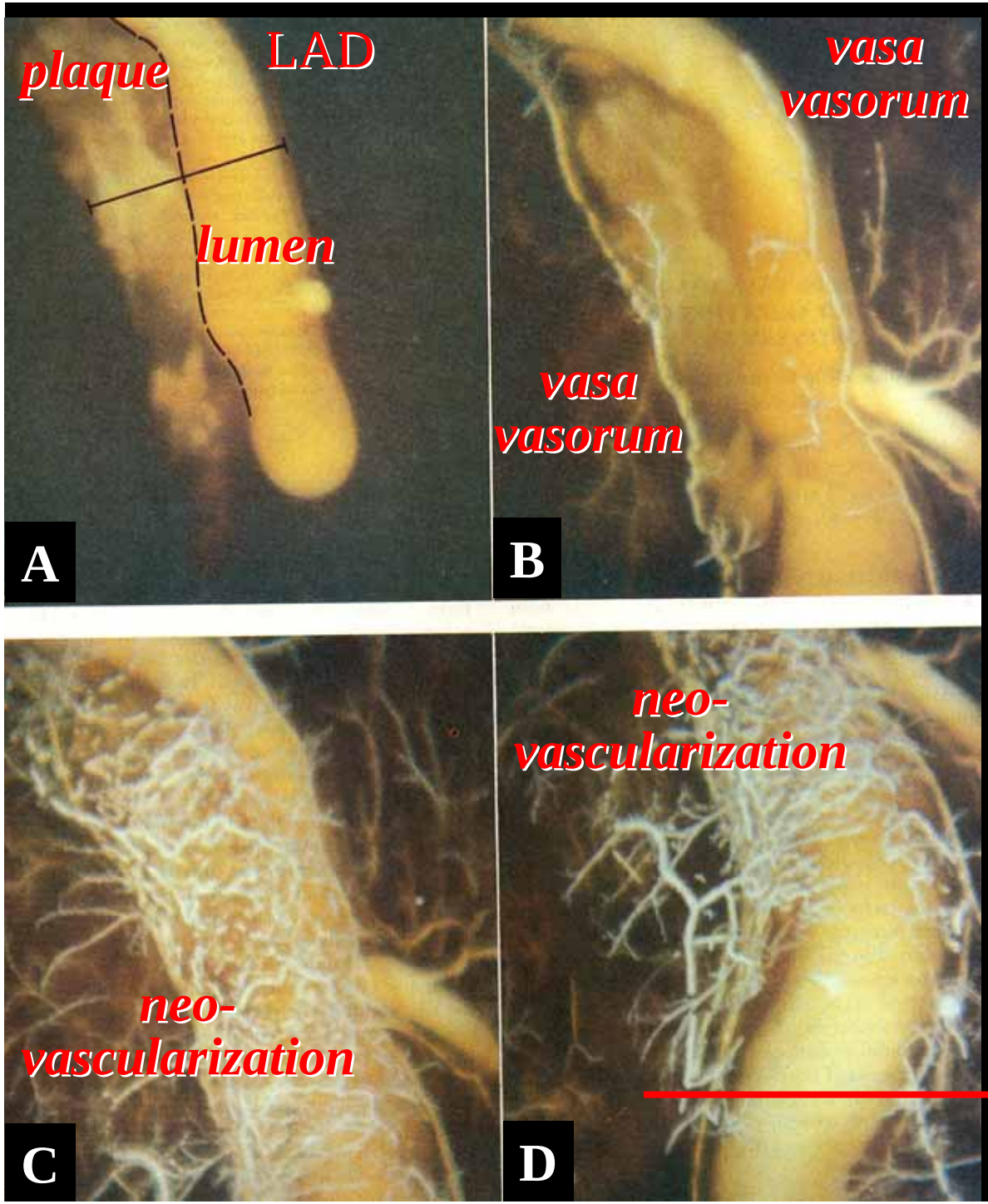


Barger et al.

Panel B, later:

Long, parallel vasa vasorum in the adventitia.

NEJM 1984;310:175-7



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

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☆

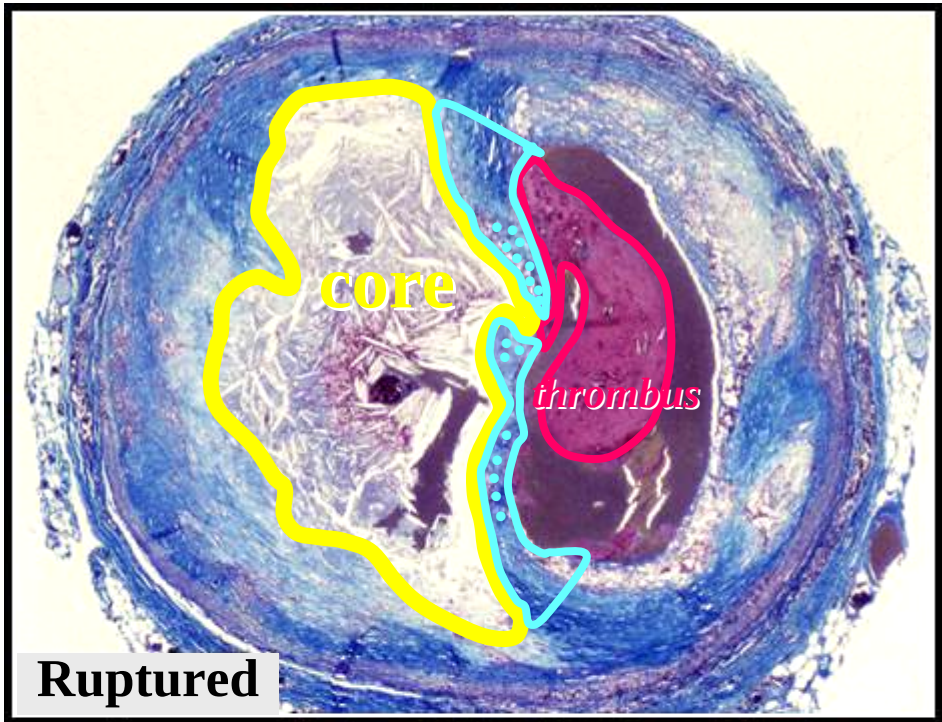
Toshiaki Nakano MD[a,b], Yutaka Nakashima MD, PhD[a], Yoshikazu Yonemitsu MD, PhD, FAHA[a,*], Shinji Sumiyoshi MD[a], Young-Xiang Chen PhD[a], Yuri Akishima MD[c], Toshiharu Ishii MD, PhD[c], Mitsuo Iida MD, PhD[b], Katsuo Sueishi MD, PhD[a]

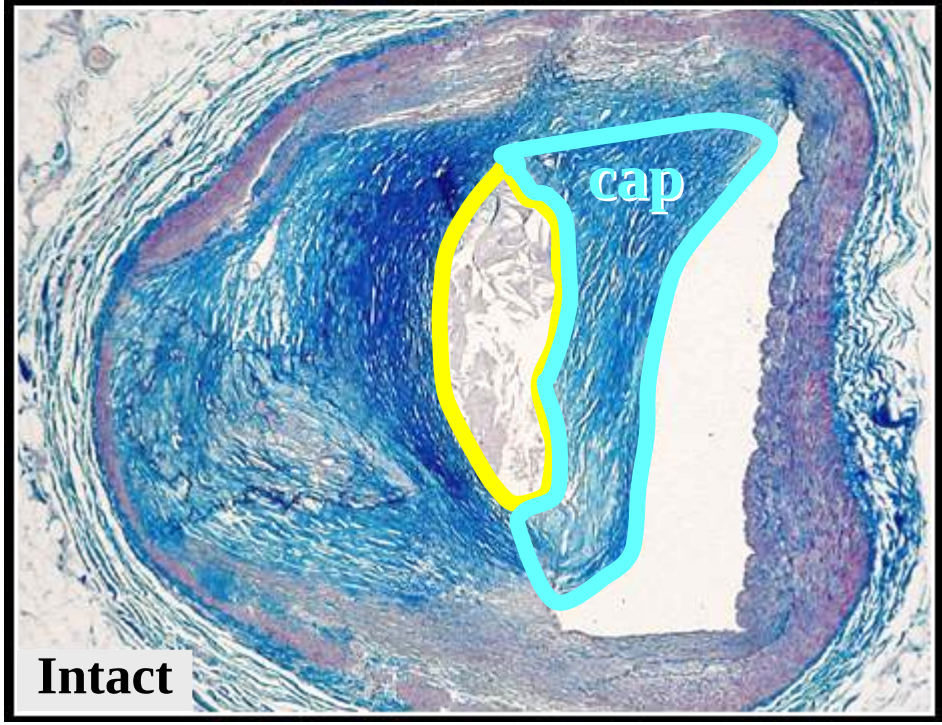
[a]*Division of Pathophysiological and Experimental Pathology, Department of Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[b]*Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[c]*Department 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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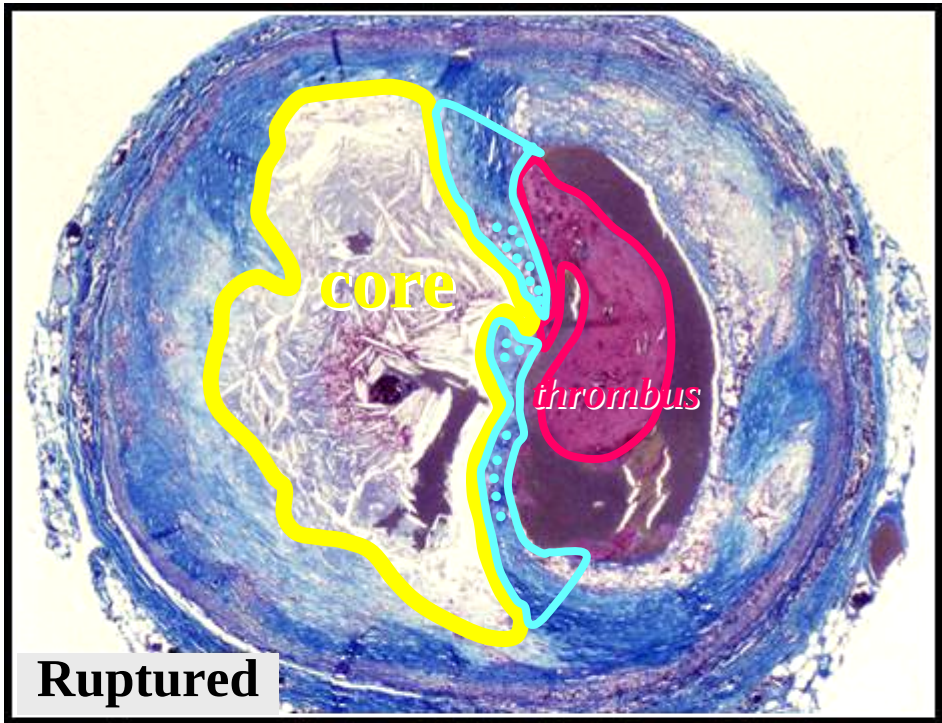
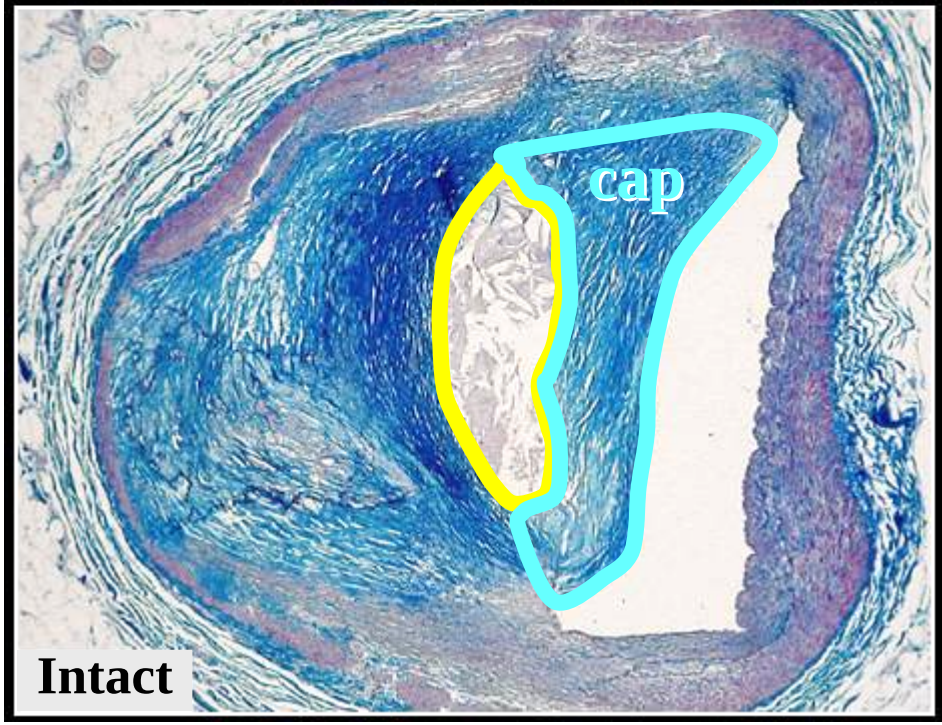
- **Expansive remodeling↑**
- **Angiogenesis↑**
  - intraplaque hemorrhage

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





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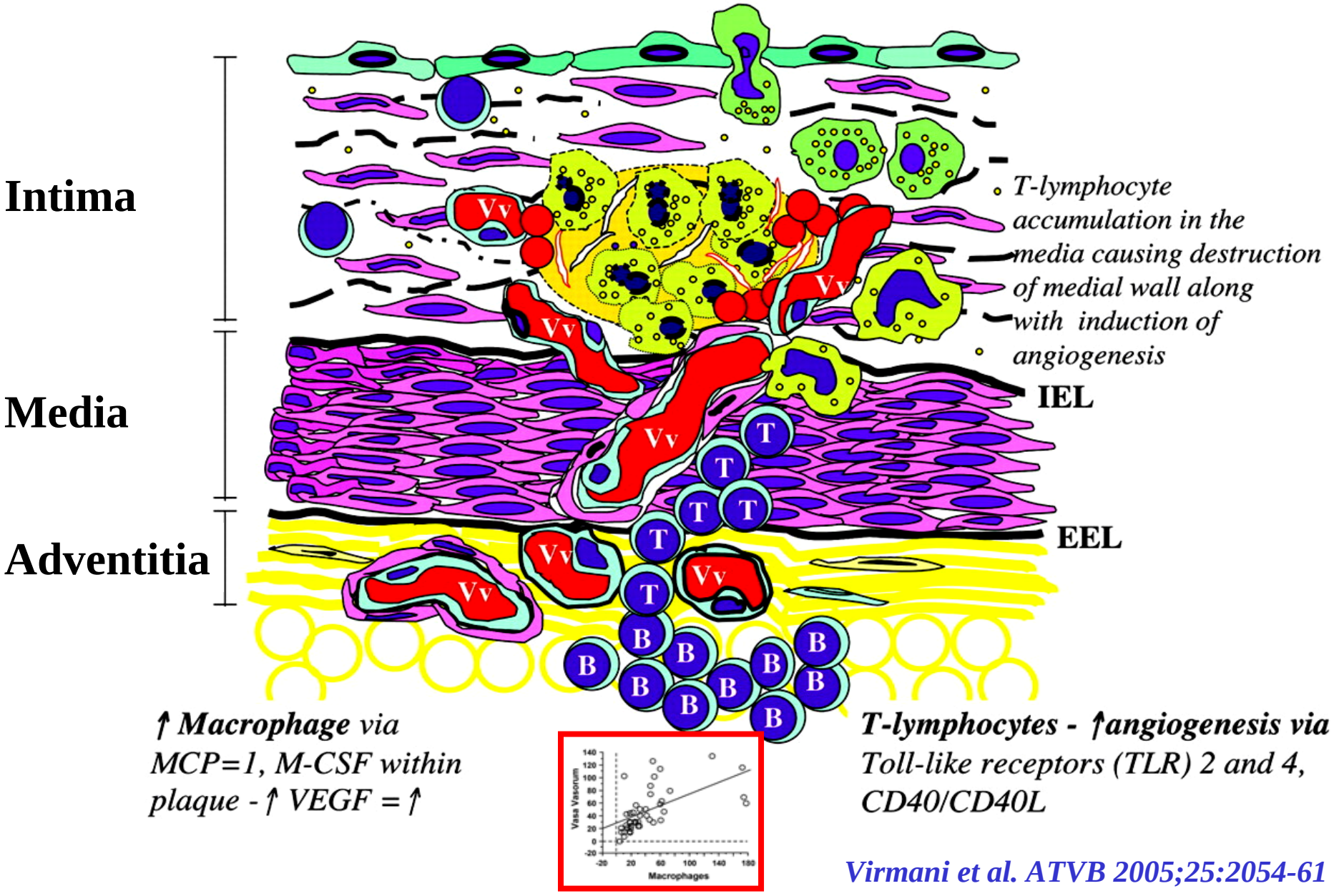
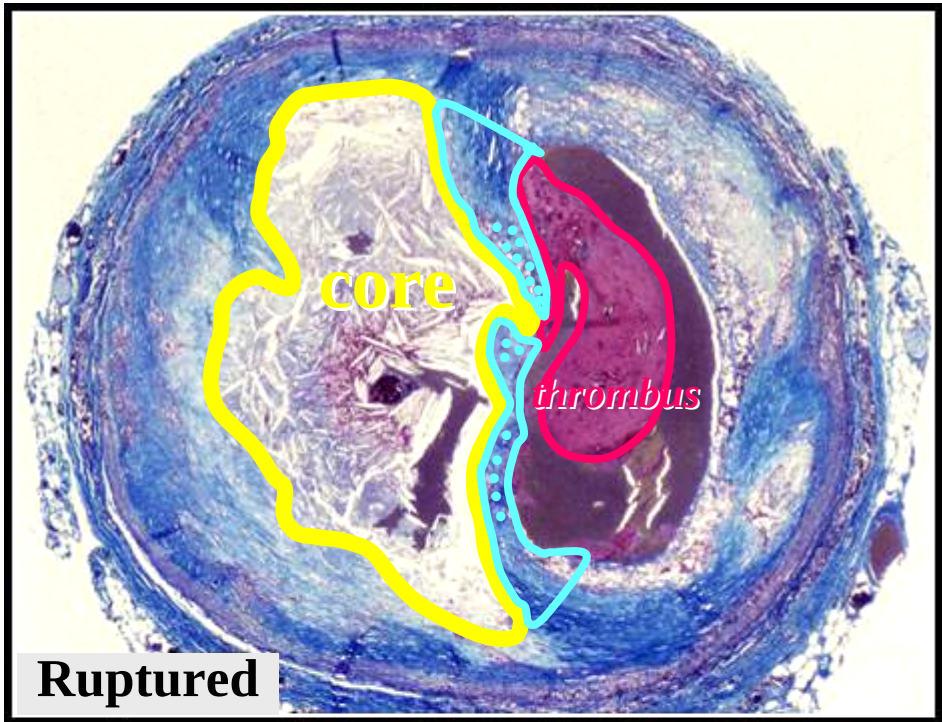
- **Angiogenesis↑**
  - **intraplaque hemorrhage**
- **Perivascular inflammation**

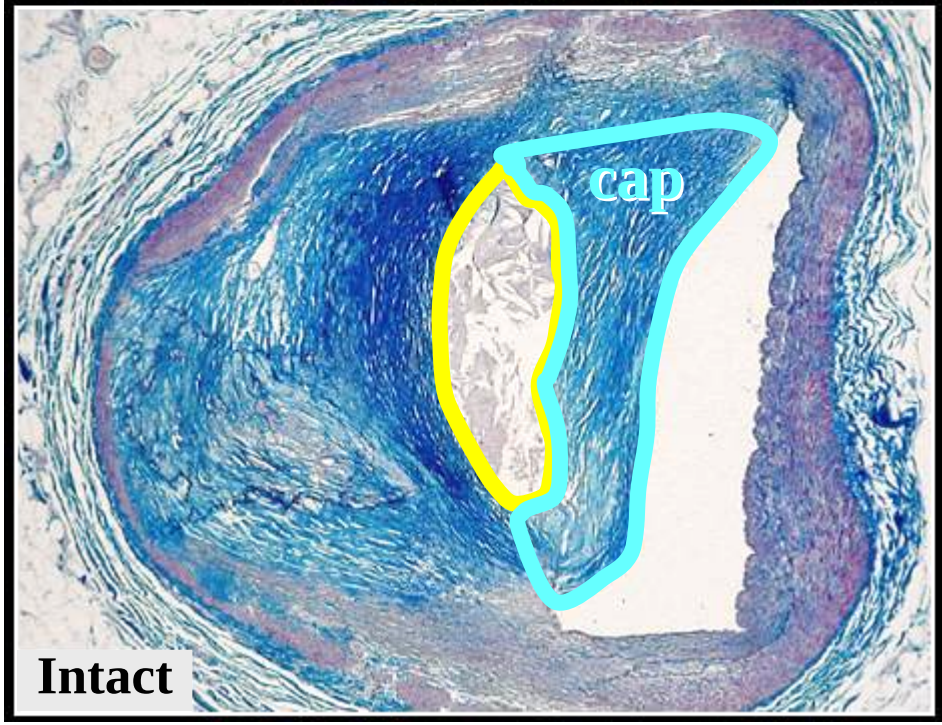
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

Mechanisms of coordinated angiogenesis and inflammation in the progressive enlargement of the necrotic core



Virmani et al. ATVB 2005;25:2054-61





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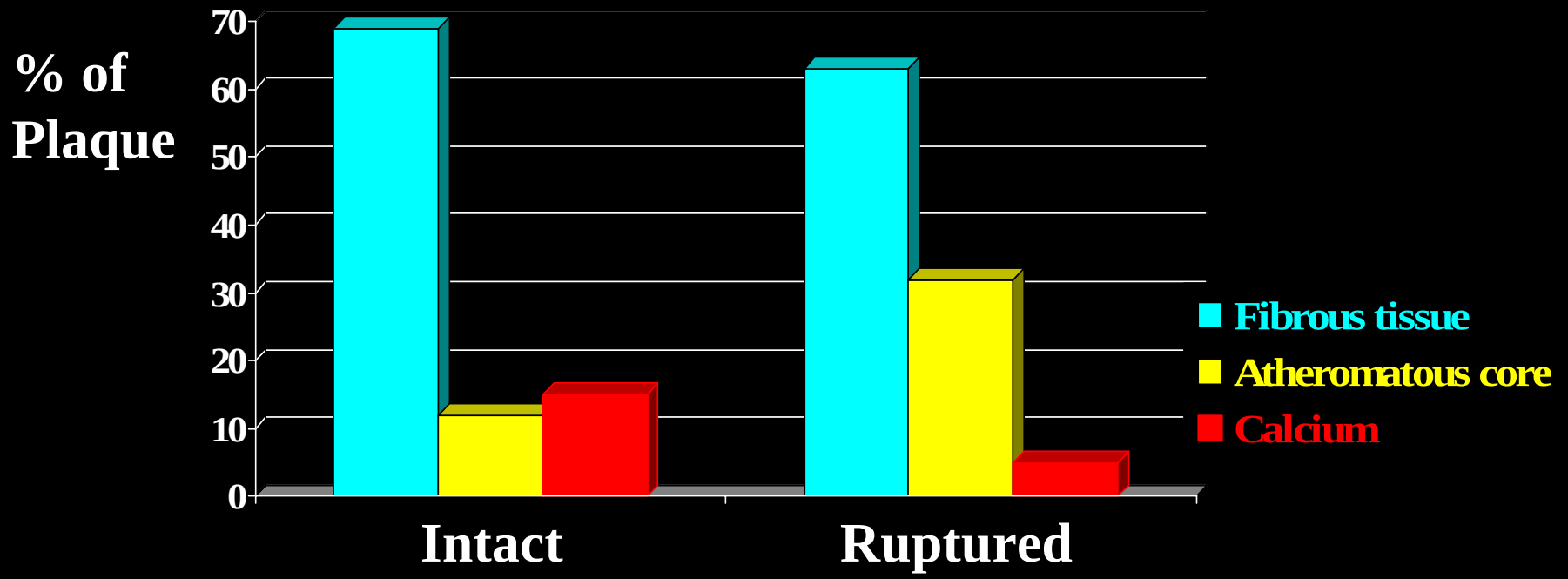
- **Angiogenesis↑**
  - **intraplaque hemorrhage**
- **Perivascular inflammation**
- **Calcification↓ & *spotty***

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

Coronary Plaque Vulnerability

calcium stabilizes plaques?

Infarct-Related Coronary Arteries: Composition of Stenosis >75%



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.)

Plaque heterogeneity

Plaque heterogeneity among patients
dissimilar syndromes

Macrophage Infiltration in Acute Coronary Syndromes

Implications for Plaque Rupture

Pedro R. Moreno, MD; Erling Falk, MD; Igor F. Palacios, MD; John B. Newell, BA; Valentín Fuster, MD, PhD; John T. Fallon, MD, PhD

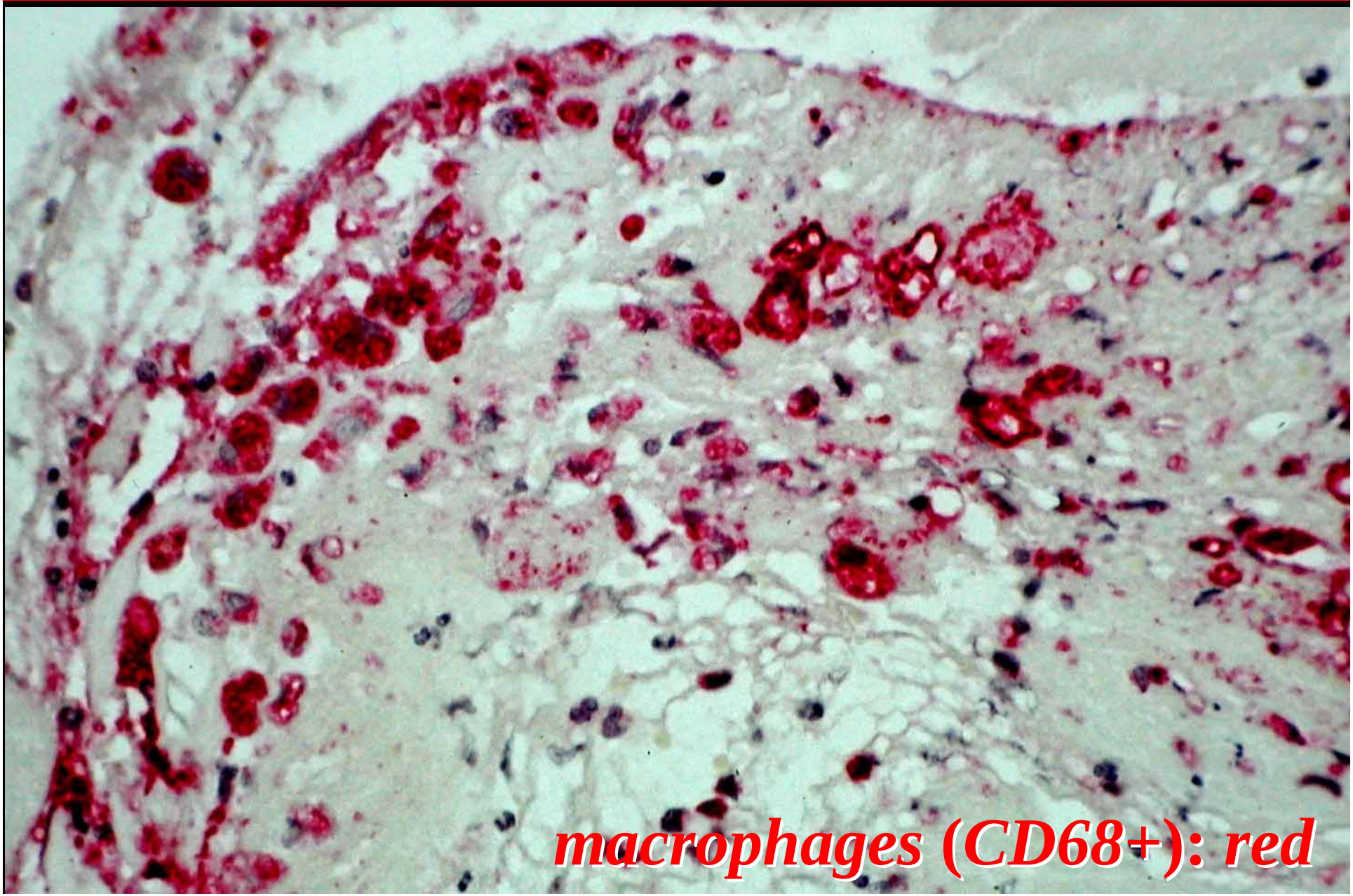
Background Rupture of atherosclerotic plaques is probably the most important mechanism underlying the sudden onset of acute coronary syndromes. Macrophages may release lytic enzymes that degrade the fibrous cap and therefore produce rupture of the atherosclerotic plaque. This study was designed to quantify macrophage content in coronary plaque tissue from patients with stable and unstable coronary syndromes.

Methods and Results Hematoxylin and eosin and immunostaining with anti-human macrophage monoclonal antibody (PG-M1) were performed. Computerized planimetry was used to analyze 26 atherectomy specimens comprising 524 pieces of tissue from 8 patients with chronic stable angina, 8 patients with unstable angina, and 10 patients with non–Q-wave myocardial infarction. Total plaque area was 417±87 $mm^2 \times 10^{-2}$ in patients with stable angina, 601±157 $mm^2 \times 10^{-2}$ in patients with unstable angina, and 499±87 $mm^2 \times 10^{-2}$ in patients with non–Q-wave myocardial infarction (P=NS). The macrophage-rich area was larger in plaques from patients with unstable angina (61±18 $mm^2 \times 10^{-2}$) and non–Q-wave myocardial infarction (87±32 $mm^2 \times 10^{-2}$) than in plaques from patients with stable angina (14±5 $mm^2 \times 10^{-2}$) (P=.024). The percentage of the total plaque area occupied by macrophages was also larger in patients with unstable angina (13.3±5.6%) and non–Q-wave myocardial infarction (14.6±4.6%) than in patients with stable angina (3.14±1%) (P=.018). Macrophage-rich sclerotic tissue was largest in patients with non–Q-wave myocardial infarction (67±30 $mm^2 \times 10^{-2}$) and unstable angina (55±19 $mm^2 \times 10^{-2}$) than in patients with stable angina (11.5±4.1 $mm^2 \times 10^{-2}$) (P=.046). Macrophage-rich atheromatous gruel was also largest in patients with non–Q-wave myocardial infarction (15±4 $mm^2 \times 10^{-2}$) than in patients with unstable angina (3.3±1.7 $mm^2 \times 10^{-2}$) or stable angina (2.4±1.2 $mm^2 \times 10^{-2}$) (P=.026).

Conclusions Macrophage-rich areas are more frequently found in patients with unstable angina and non–Q-wave myocardial infarction. This suggests that macrophages are a marker of unstable atherosclerotic plaques and may play a significant role in the pathophysiology of acute coronary syndromes. (***Circulation*. 1994;90:775-778.**)

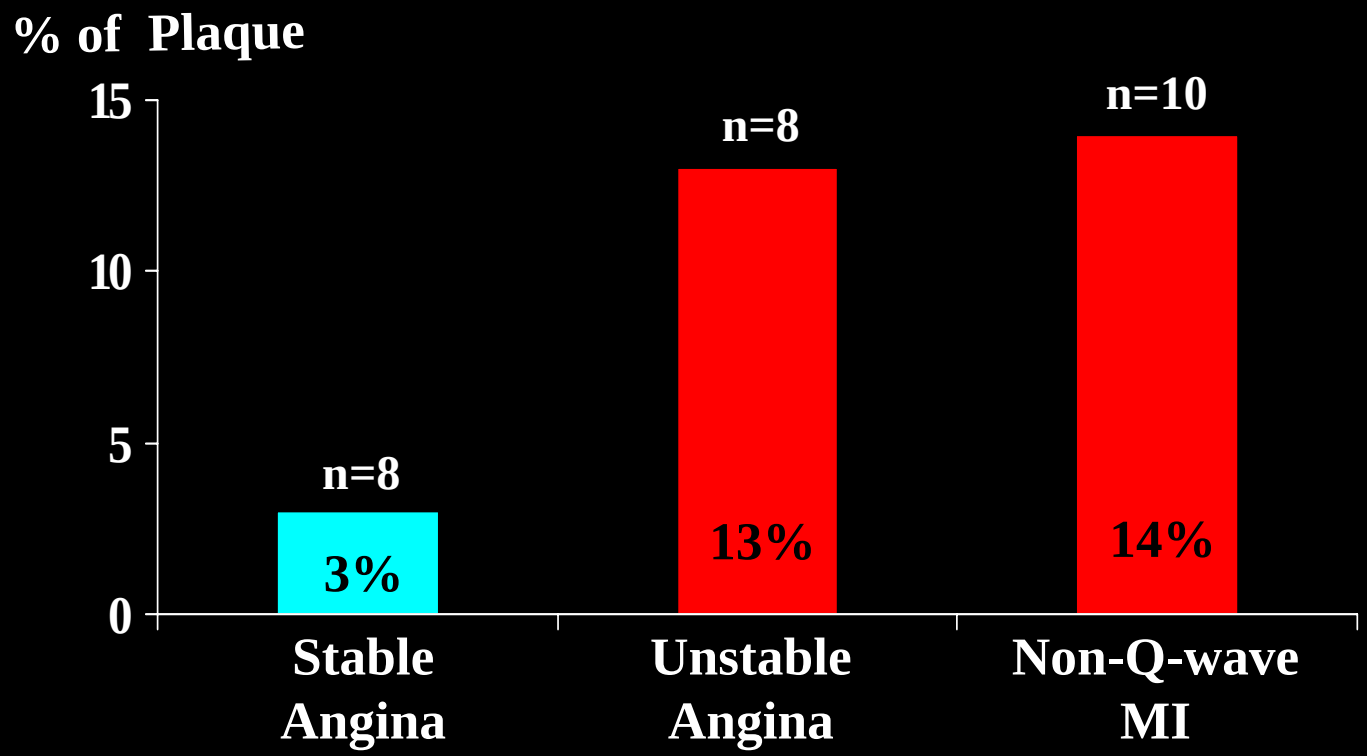
Key Words • plaques • myocardial infarction • angina • macrophages

Coronary atherectomy: non-ST↑ MI culprit



Coronary Plaque Inflammation
macrophage density

Macrophages in Culprit Lesion



Moreno, Falk, Palacios et al. Circulation 1994;90:775-8

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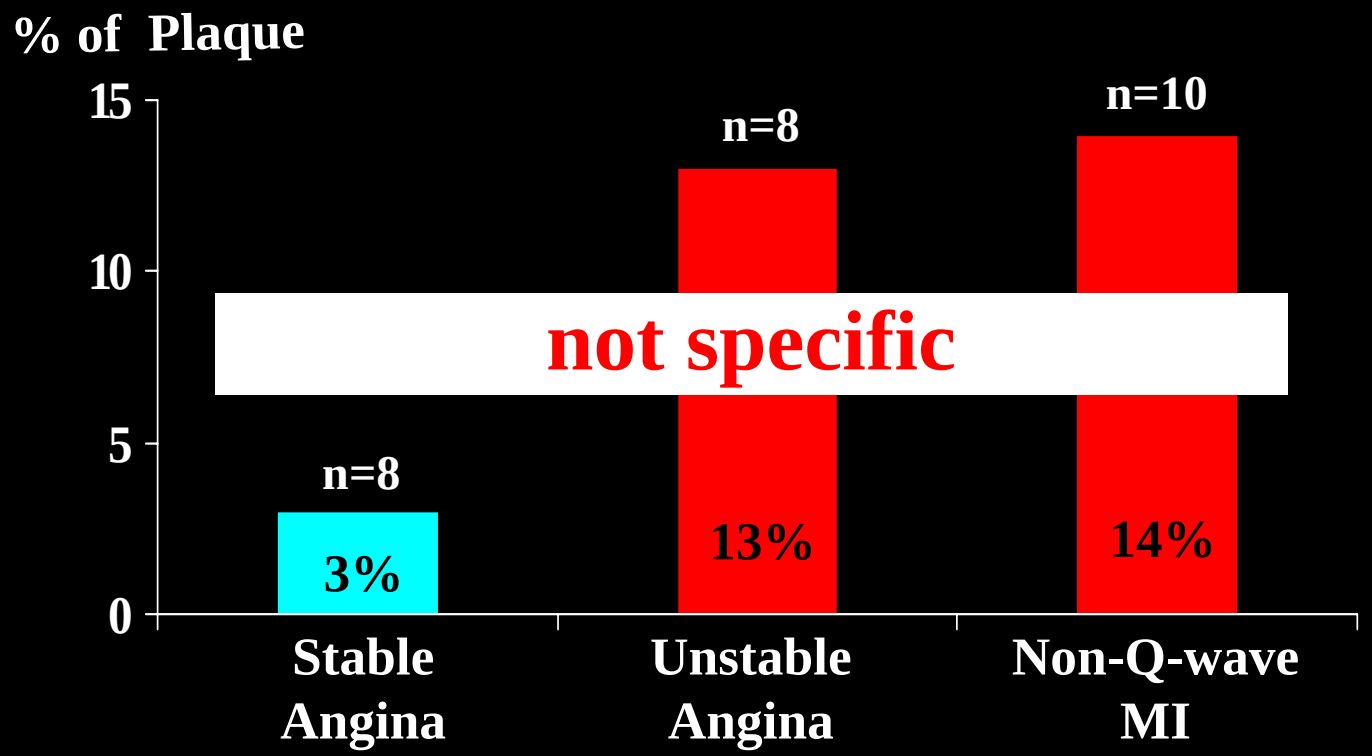


Moreno, Falk, Palacios et al. Circulation 1994;90:775-8

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 heterogeneity among patients
(dis)similar syndromes

Considerable overlap between

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

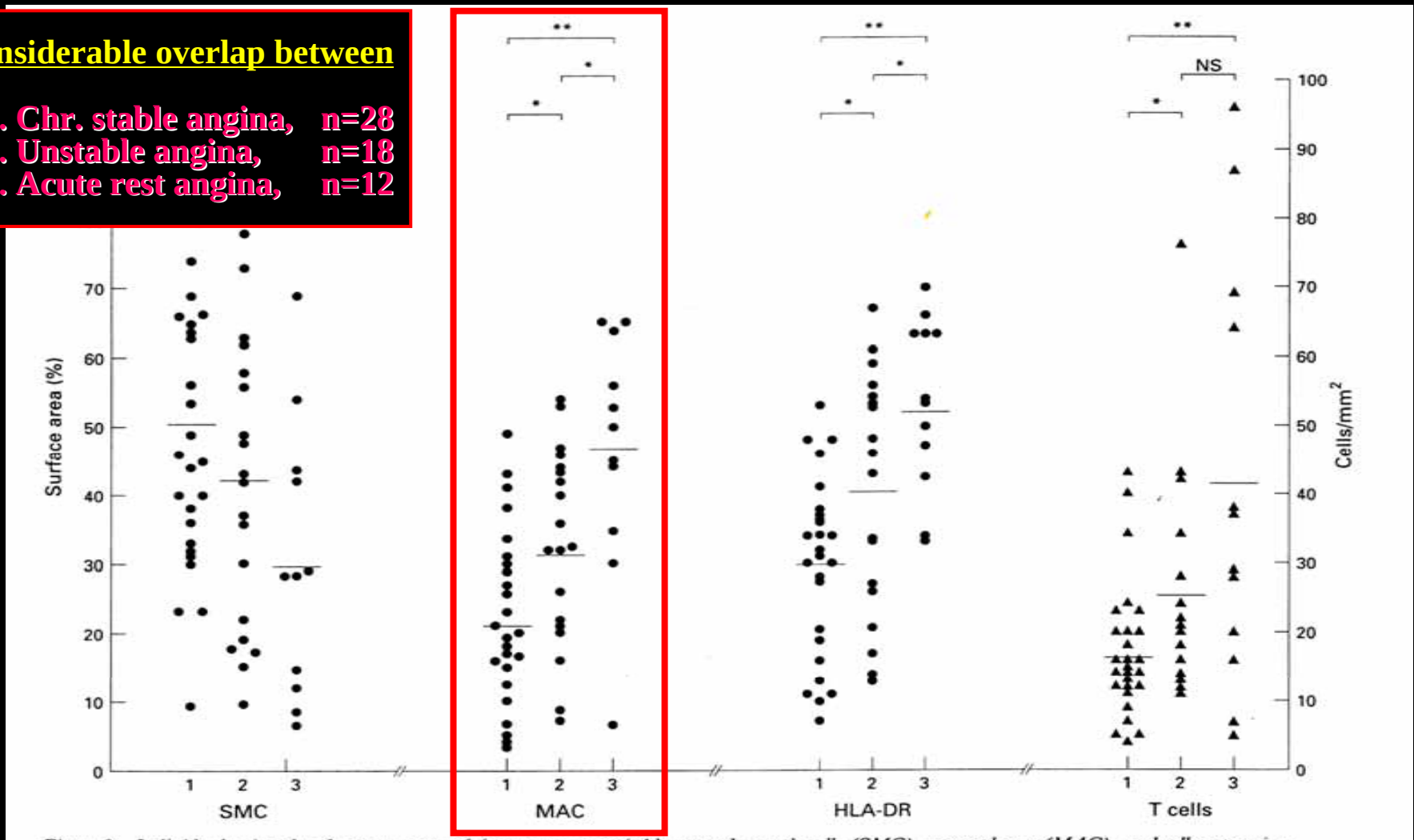
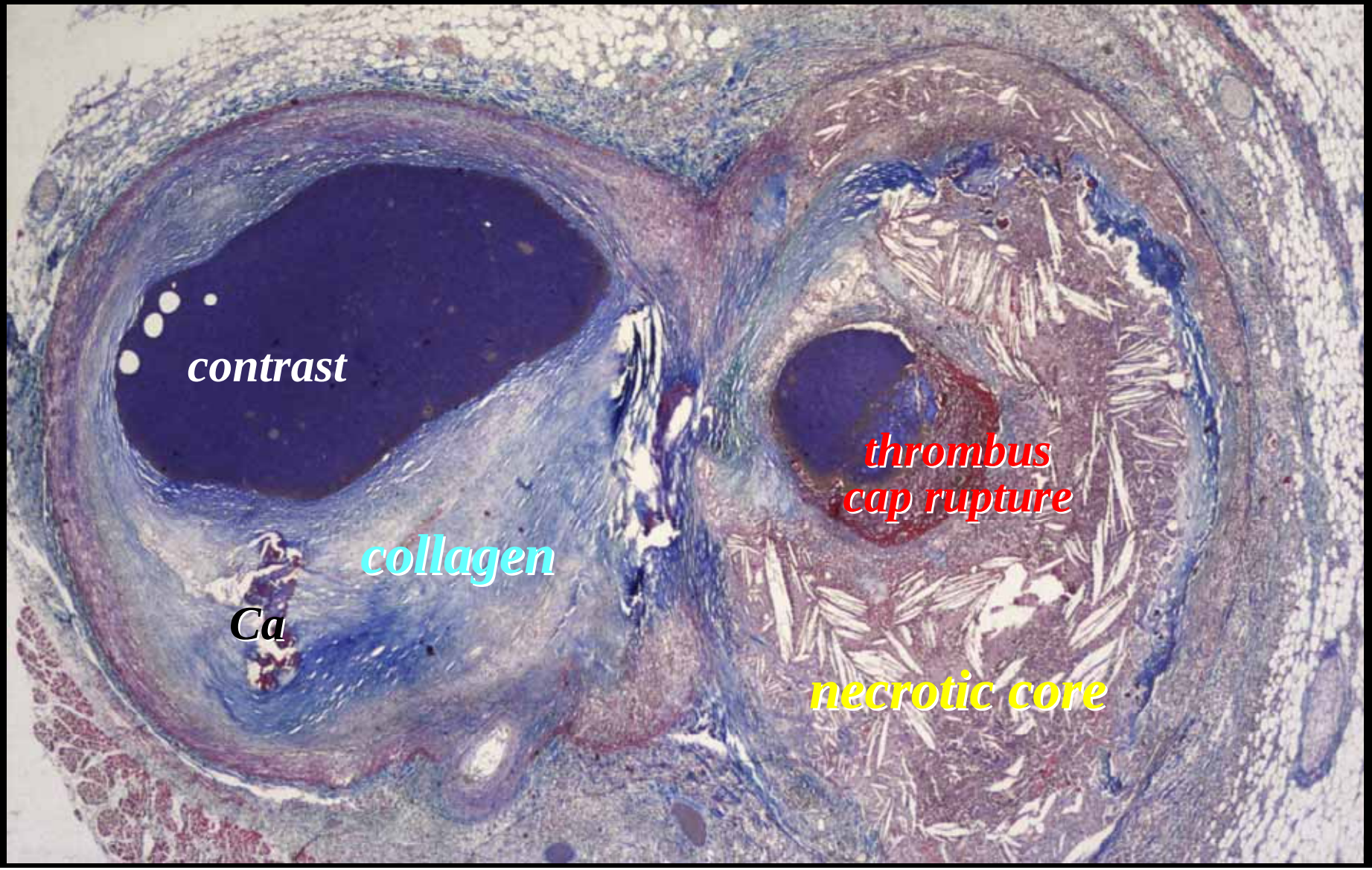


*Figure 2 Individual point plots for percentages of tissue areas occupied by smooth muscle cells (SMC), macrophages (MAC), and cells expressing HLA-DR (HLA-DR) and the number of T lymphocytes per mm² for each atherectomy specimen in the three patient groups. Note the considerable overlap between the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

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

Plaque heterogeneity within a person

plaques next to each other



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

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Giampiero Palmieri, MD,* Elena Bonanno, MD,* Lucia Anemona, MD,*
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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)

Vulnerable Plaque

A disaster waiting to happen

Atherosclerosis is a generalized disease with (multi)focal manifestations

Vulnerable Plaque

A disaster waiting to happen

Atherosclerosis is a generalized disease with (multi)focal manifestations

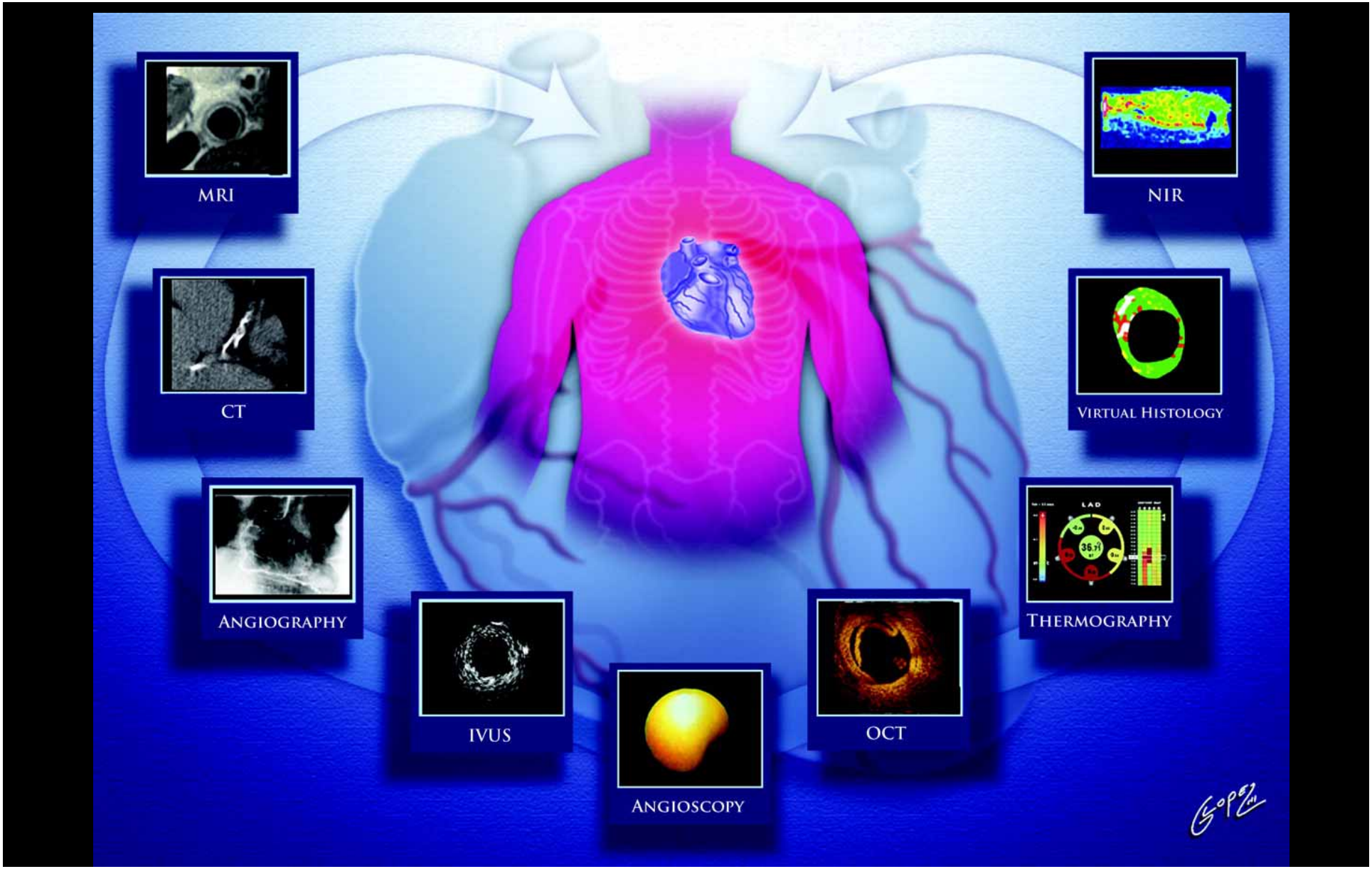
How many VP?

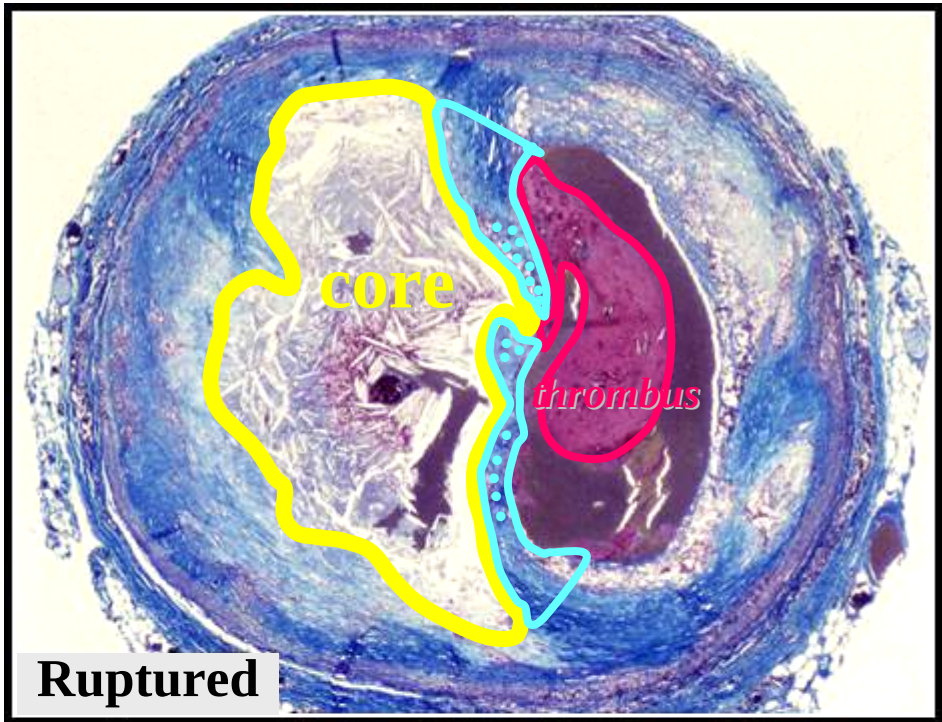
Can we find them?

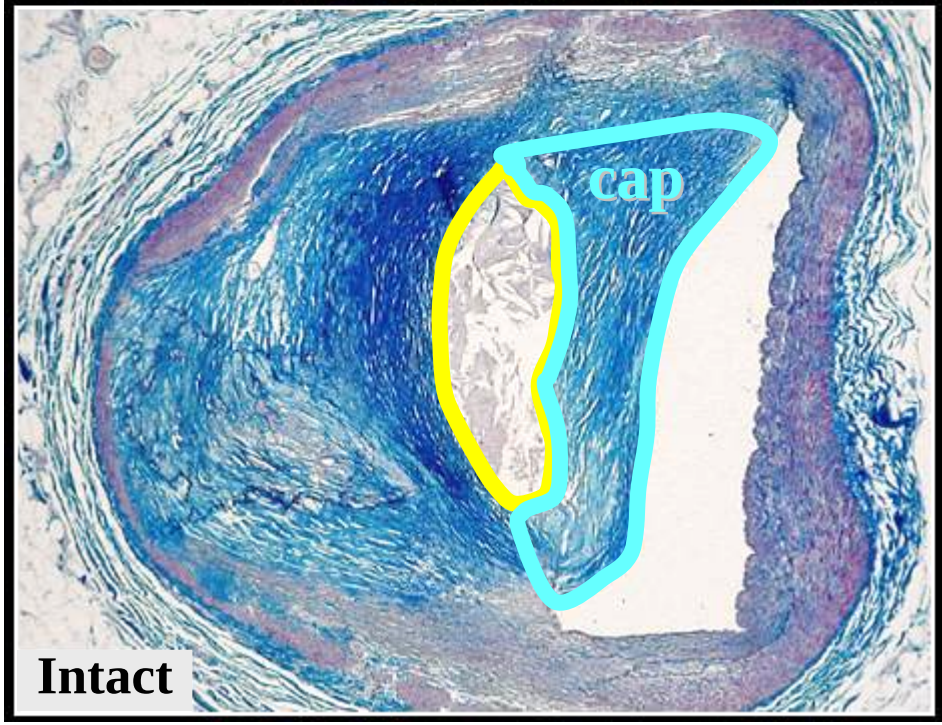
Can we treat them and prevent heart attack?

Finding Vulnerable Atherosclerotic Plaques

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







Coronary Atherosclerosis

targets for imaging

- **Necrotic core↑**
  - **~34% of plaque area***
  - **~3.8 mm^2 & ~9 mm long***
- **Fibrous cap**
  - **thinkness↓, ~23 μm (95% <65 μm)***
  - **macrophages↑, ~26% of cap***
  - **smooth muscle cells↓ (apoptosis)**
  - **thrombus↑**
- **Expansive remodeling↑**
- **Angiogenesis↑**
  - **intraplaque hemorrhage**
- **Perivascular inflammation**
- **Calcification↓ & *spotty***

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