Vulnerable Plaque

Pathophysiology, Detection, and Intervention

VP:

A Local Problem or Systemic Disease

Angioplasty Summit TCT Asia Pacific 2007
Wednesday, April 25 ~ Friday, April 27, 2007
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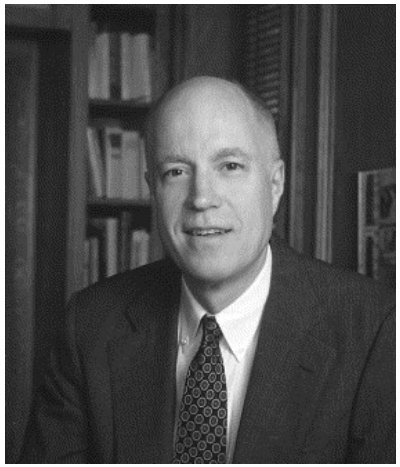
Diffuse Extent of Coronary Atherosclerosis in Fatal Coronary Artery Disease*

William C. Roberts, MD



Am J Cardiol 1990;65:2F-6F. Review

Diffuse Extent of Coronary Atherosclerosis in Fatal Coronary Artery Disease*

William C. Roberts, MD

In 4 subsets of patients with coronary artery disease, the amounts of narrowing of the 4 major epicardial coronary arteries were compared (left main, left anterior descending, left circumflex and right) by atherosclerotic plaques. Among 129 patients studied at necropsy, an average of 2.7 of the 4 arteries were narrowed >75% in cross-sectional area at some point; in control subjects, narrowing was seen in an average of 0.7 arteries. Patients with unstable angina pectoris had a greater incidence of narrowing (3.2 arteries) than did patients with sudden coronary death (2.8), acute myocardial infarction (MI) (2.7) or healed MI (2.3). Each of the 4 major arteries was divided into segments 5 mm in length, and histologic sections were prepared and stained by the Movat method. A total of 6,461 segments were analyzed from the 129 patients and 1,849 from the 40 controls. In the 129 patients, 35% of the 5-mm segments were narrowed 75 to 100% in cross-sectional area (compared with 3% in control subjects). The group with unstable angina had the highest percentage (48%) of severely narrowed segments compared with the groups with sudden coronary death (36%), acute (34%) and healed MI (31%). Only 8% of the 6,461 segments were narrowed ≤25% in cross-sectional area, and virtually none of the 6,461 segments was normal; thus, 92% of the coronary segments were narrowed >25% in cross-sectional area by atherosclerotic plaque alone. Among patients with fatal coronary artery disease studied at necropsy, therefore, the atherosclerotic process is severe and diffuse in the major epicardial coronary arteries.

(Am J Cardiol 1990;65:2F–6F)

Artherosclerotic coronary artery disease (CAD) is the most common cause of death in the Western world. In the United States, 1 person dies every minute because of atherosclerotic CAD, and approximately 6 million persons have symptomatic myocardial ischemia due to this disease. Furthermore, approximately 250,000 coronary artery bypass grafting procedures and a similar number of coronary angioplasties were performed in the United States in 1988.

The evidence is now overwhelming that atherosclerosis is caused by elevated cholesterol levels; the higher the level of total blood cholesterol (specifically low-density lipoprotein cholesterol), the greater the risk of developing symptomatic CAD, the greater the chance of having fatal CAD, and the greater the extent of the atherosclerotic plaques. Conversely, lowering total blood cholesterol decreases the risk of symptomatic or fatal CAD and increases the likelihood that some atherosclerotic plaques will actually become smaller (i.e., regress). Although the coronary arteries have been examined by visual inspection at necropsy for more than 100 years, only recently has the extent of the atherosclerotic process in patients with symptomatic or fatal CAD become appreciated. This article reviews the status of the major epicardial coronary arteries in various subsets of patients with fatal atherosclerotic CAD. A similar review has appeared previously.[1]

NUMBER OF SEVERELY NARROWED MAJOR EPICARDIAL CORONARY ARTERIES

The most common method of describing the severity of CAD in patients with clinical evidence of myocardial ischemia is by the number of major epicardial coronary arteries narrowed >50% in luminal diameter, as determined on angiography. Thus, patients are categorized as having either 1-, 2-, or 3-vessel or "left main" CAD.

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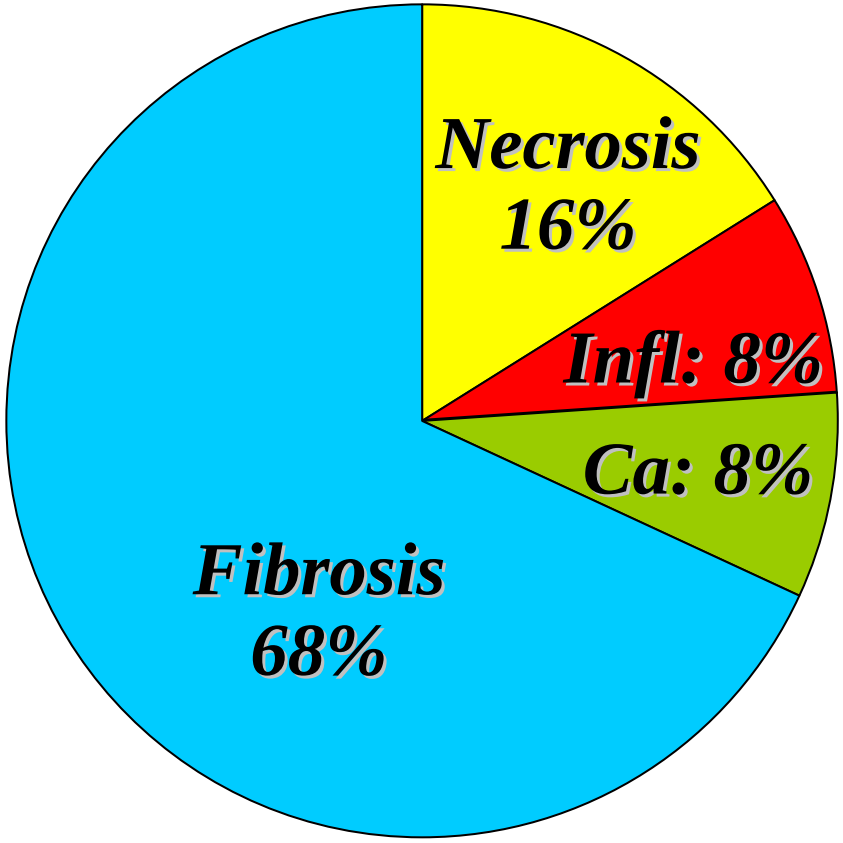
Atherosclerosis: chronic smoldering inflammation
plaque composition

Plaques causing >75% stenosis by histology



Roberts et al (Falk. JACC 2006;47:C7-12)

Mechanisms of Disease

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

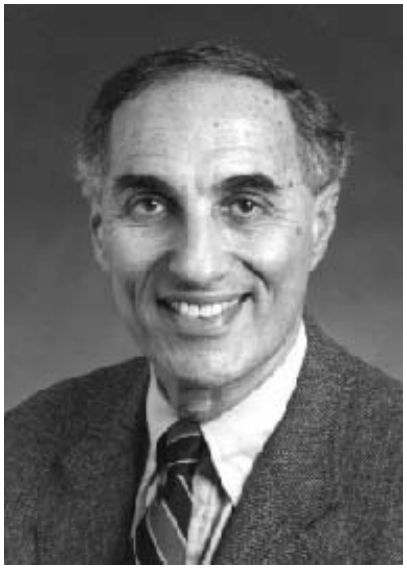
ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

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.

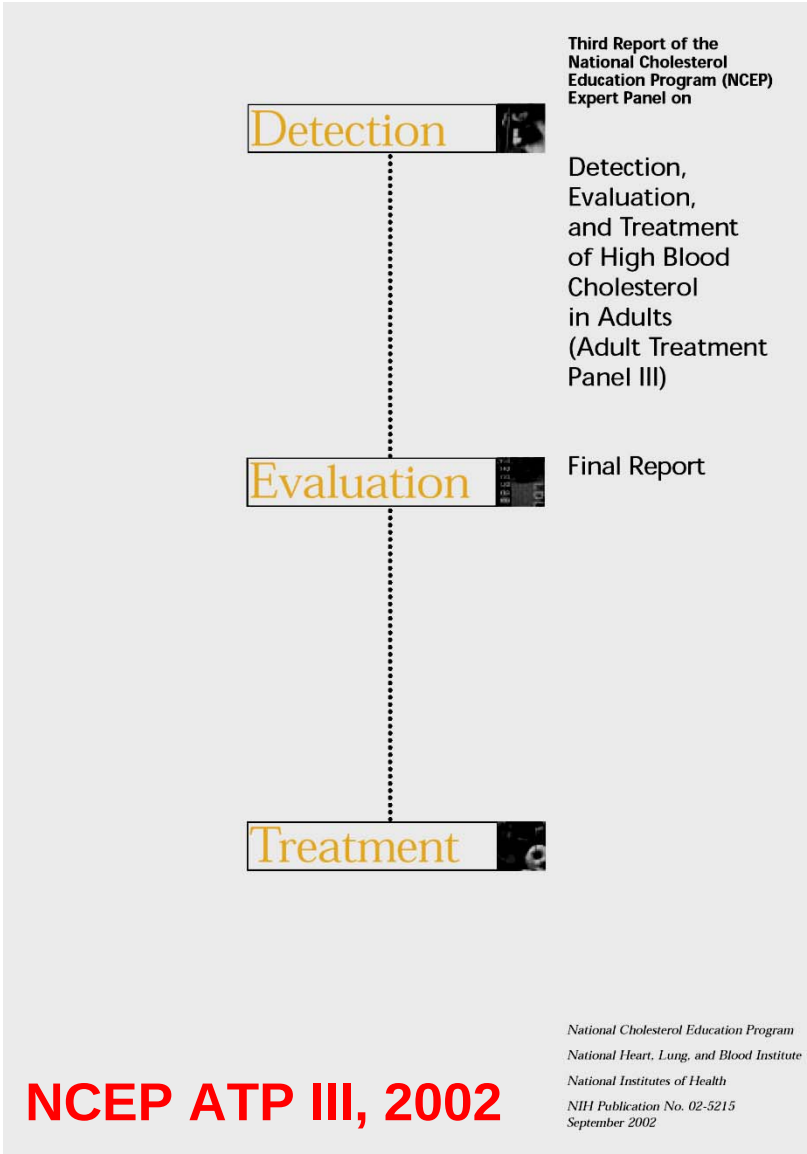
A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate CAD by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing 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.

From the Karolinska Institute, Center for Molecular Medicine, Department of Medicine, Karolinska University Hospital, Stockholm. Address reprint requests to Dr. Hansson at the Center for Molecular Medicine, L8:03, Karolinska University Hospital, SE-17176 Stockholm, Sweden, or at goran.hansson@cmm.ki.se.

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

NEJM 2005
352:1685-95

Non-coronary atherosclerosis
CHD risk equivalent

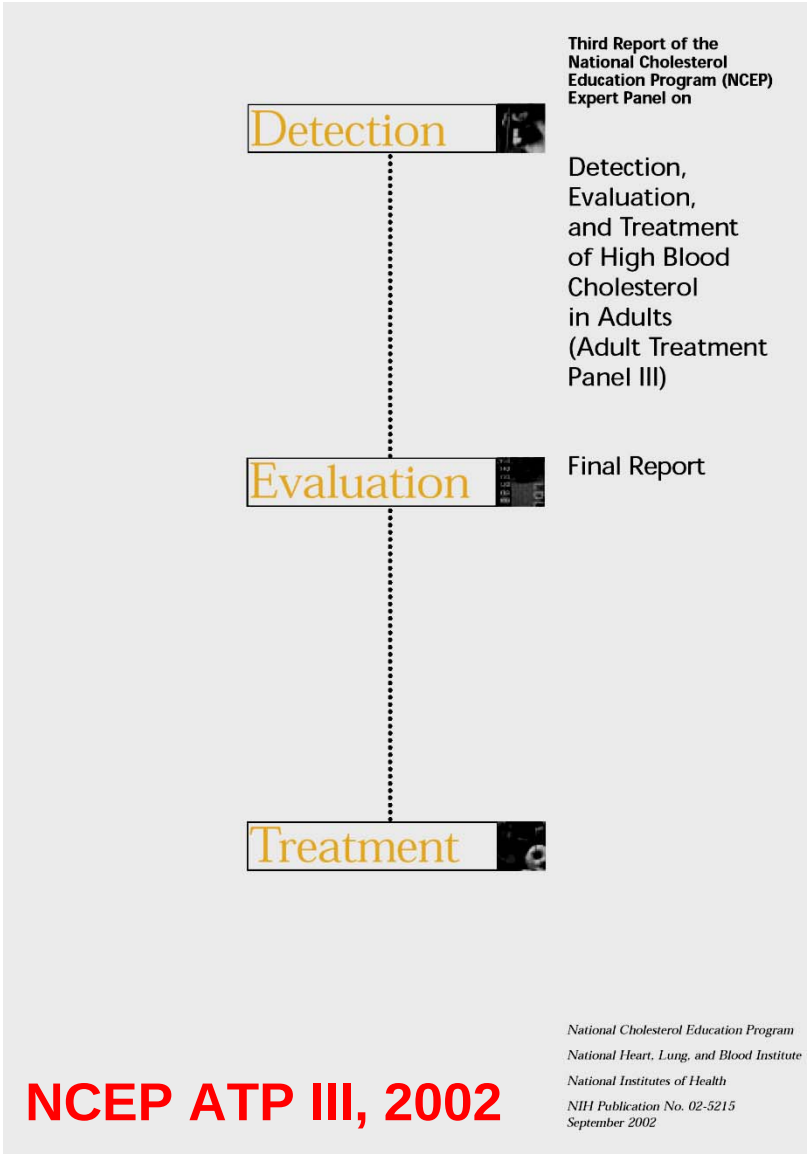


NCEP ATP III, 2002

Evidence statement: Clinical forms of non-coronary atherosclerosis carry a risk for clinical CHD approximately equal to that of established CHD and hence constitute a CHD risk equivalent (C1). These conditions include peripheral arterial disease, carotid artery disease (transient ischemic attack or stroke of carotid origin, or >50% stenosis on angiography or ultrasound), and abdominal aortic aneurysm.

Recommendation: Persons with clinical forms of non-coronary atherosclerosis should have the same LDL-cholesterol goal (<100 mg/dL) as those for persons with established CHD and should be managed similarly (see Section IV.1).

Non-coronary atherosclerosis
CHD risk equivalent



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AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update

Endorsed by the National Heart, Lung, and Blood Institute

Sidney C. Smith, Jr, MD; Jerilyn Allen, RN, ScD; Steven N. Blair, PED; Robert O. Bonow, MD; Lawrence M. Brass, MD†; Gregg C. Fonarow, MD; Scott M. Grundy, MD, PhD; Loren Hiratzka, MD; Daniel Jones, MD; Harlan M. Krumholz, MD; Lori Mosca, MD, PhD, MPH; Richard C. Pasternak, MD*; Thomas Pearson, MD, MPH, PhD; Marc A. Pfeffer, MD, PhD; Kathryn A. Taubert, PhD

Since the 2001 update of the American Heart Association (AHA)/American College of Cardiology (ACC) consensus statement on secondary prevention,[1] important evidence from clinical trials has emerged that further supports and broadens the merits of aggressive risk-reduction therapies for patients with established coronary and other atherosclerotic vascular disease, including peripheral arterial disease, atherosclerotic aortic disease, and carotid artery disease. This growing body of evidence confirms that aggressive comprehensive risk factor management improves survival, reduces recurrent events and the need for interventional procedures, and improves quality of life for these patients.

Compelling evidence from recent clinical trials and revised practice guidelines provided the impetus for this update of the 2001 recommendations with evidence-based results (Table 1). Classification of Recommendations and Level of Evidence are expressed in ACC/AHA format, as detailed in Tables 2 and 3. Recommendations made herein are based largely on major practice guidelines from the National Institutes of Health and ACC/AHA. In many cases, these practice guidelines were supplemented by research findings published after the publication of the primary reference(s). Thus, the development of the present statement involved a process of partial adaptation of other guideline statements and reports and supplemental literature searches.[2–32] (For specific search criteria, see the Appendix.) The findings from additional lipid reduction trials[33–37] involving more than 50 000 patients resulted in new optional therapeutic targets, which were outlined in the 2004 update of the National Heart, Lung, and Blood Institute's Adult Treatment Panel (ATP) III report.[6] These changes defined optional lower target cholesterol levels for very high-risk coronary heart disease (CHD) patients, especially those with acute coronary syndromes, and expanded indications for drug treatment. Subsequent to the 2004 update of ATP III, 2 additional trials[8,9] demonstrated cardiovascular benefit for lipid lowering significantly below current cholesterol goal levels for those with chronic CHD. These new trials allow for alterations in guidelines, such that low-density lipoprotein cholesterol (LDL-C) should be <100 mg/dL for all patients with CHD and other clinical forms of atherosclerotic disease, but in addition, it is reasonable to treat to LDL-C <70 mg/dL in such patients. When the

Acute coronary syndrome
very high risk

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Scott M. Grundy; James I. Cleeman; C. Noel Bairey Merz; H. Bryan Brewer, Jr; Luther T. Clark; Donald B. Hunninghake*; Richard C. Pasternak; Sidney C. Smith, Jr; Neil J. Stone; for the Coordinating Committee of the National Cholesterol Education Program

Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association

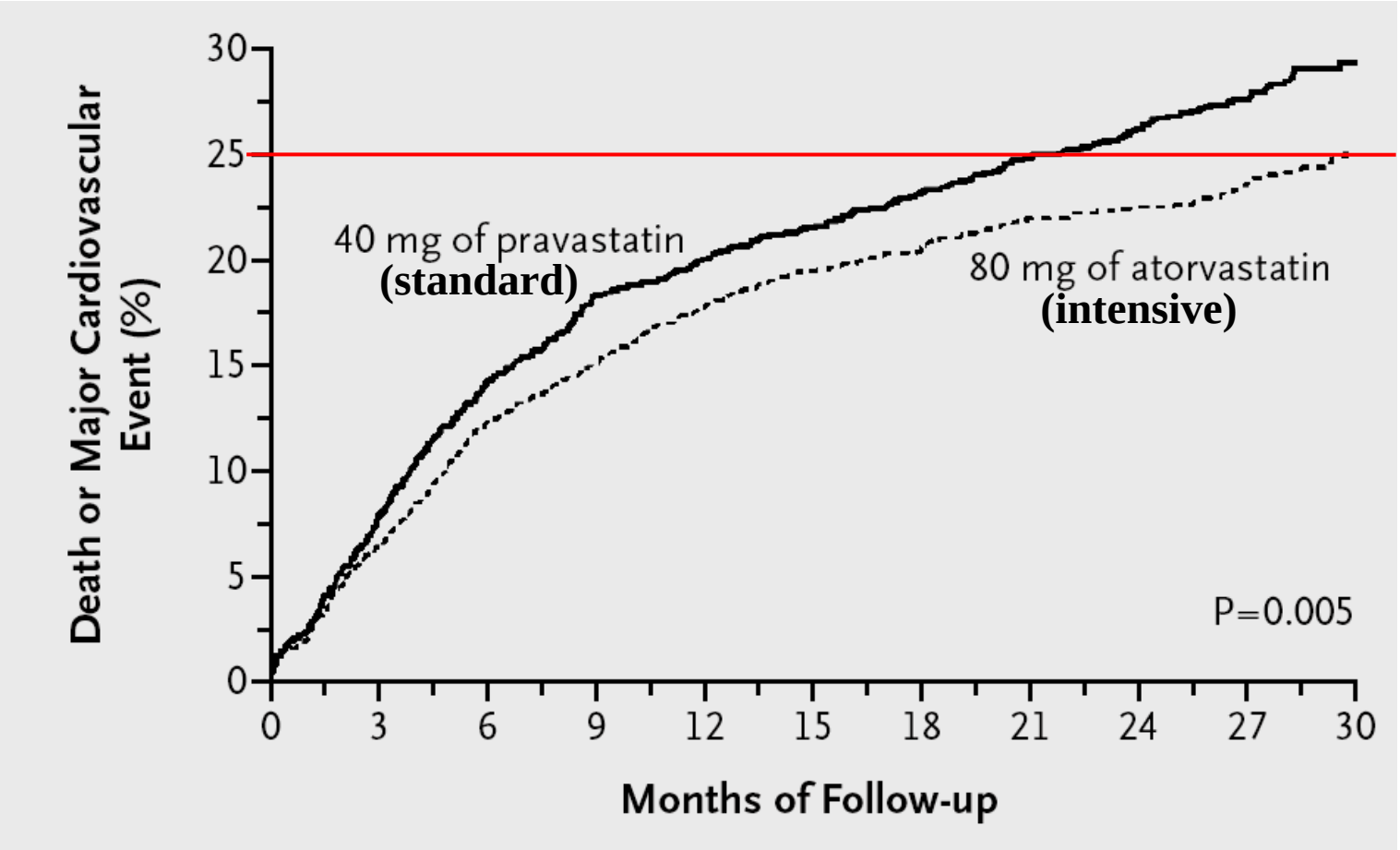
Abstract—The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program issued an evidence-based set of guidelines on cholesterol management in 2001. Since the publication of ATP III, 5 major clinical trials of statin therapy with clinical end points have been published. These trials addressed issues that were not examined in previous clinical trials of cholesterol-lowering therapy. The present document reviews the results of these recent trials and assesses their implications for cholesterol management. Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. The trials confirm the benefit of cholesterol-lowering therapy in high-risk patients and support the ATP III treatment goal of low-density lipoprotein cholesterol (LDL-C) <100 mg/dL. They support the inclusion of patients with diabetes in the high-risk category and confirm the benefits of LDL-lowering therapy in these patients. They further confirm that older persons benefit from therapeutic lowering of LDL-C. The major recommendations for modifications to footnote the ATP III treatment algorithm are the following. In high-risk persons, the recommended LDL-C goal is <100 mg/dL, but when risk is very high, an LDL-C goal of <70 mg/dL is a therapeutic option, ie, a reasonable clinical strategy, on the basis of available clinical trial evidence. This therapeutic option extends also to patients at very high risk who have a baseline LDL-C <100 mg/dL. Moreover, when a high-risk patient has high

Circulation 2004;110:227-239

Despite profound lipid lowering in ACS

¼ come back with a new event within 30 m

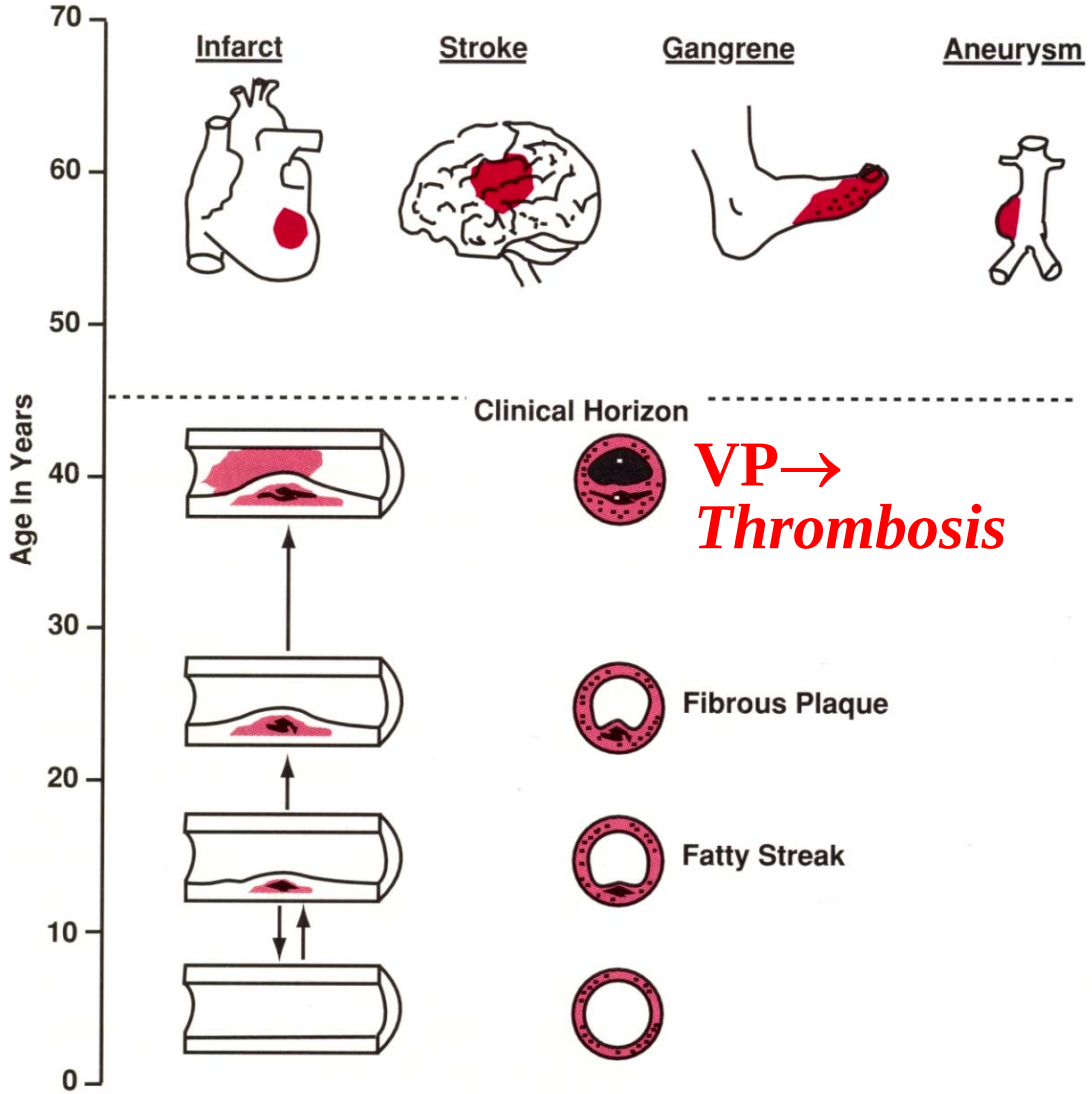
PROVE IT – TIMI 22: statin after stabilized ACS



Cannon et al. NEJM 2004:350:1495-504

Atherosclerosis

systemic disease with focal manifestations



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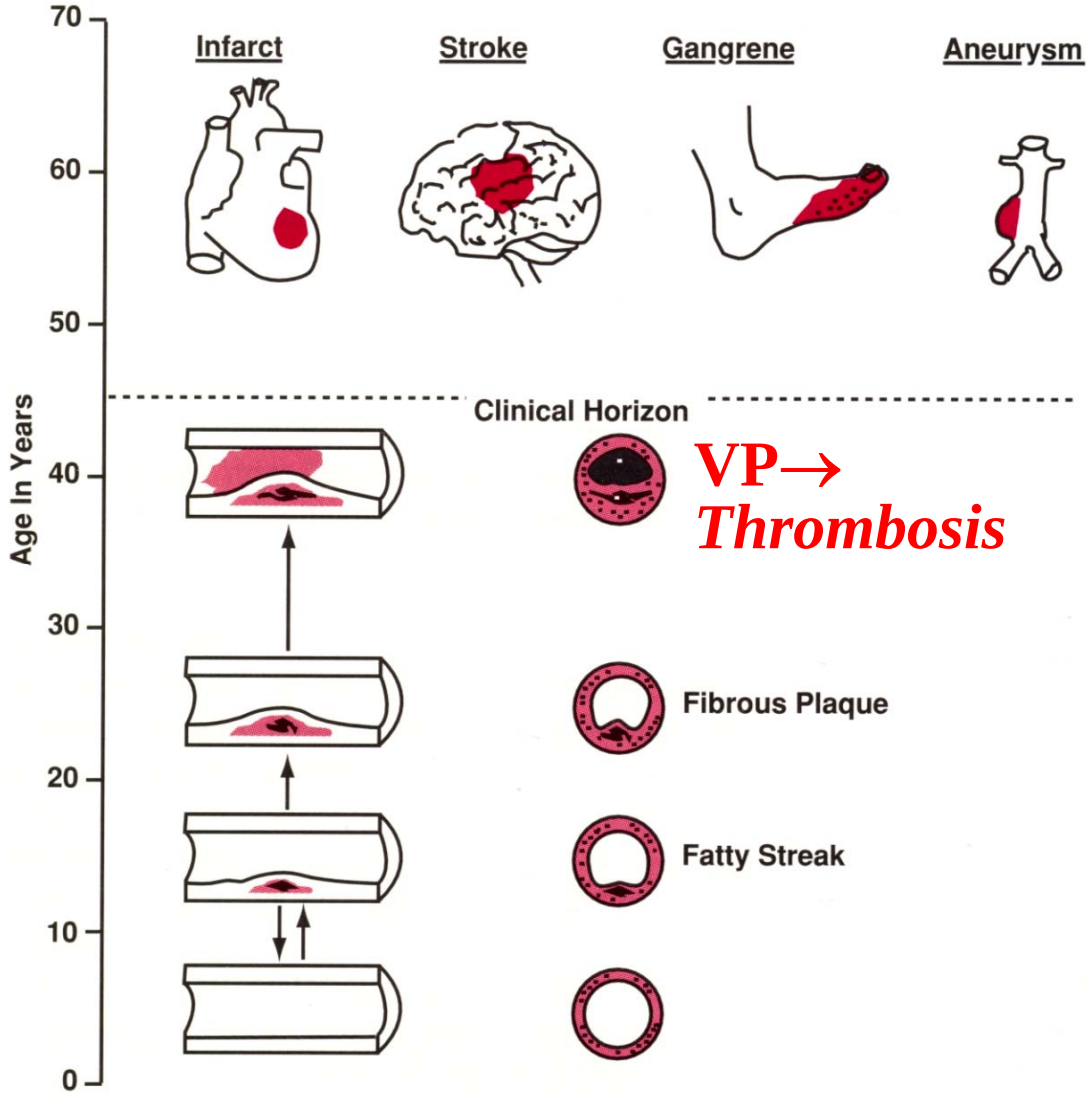

VP/culprit

One?

Few?

Many?

Atherosclerosis: Disease Biology Affecting the Coronary Vasculature

Peter Libby, MD

The concept of the vulnerable plaque has generated much interest and stimulated a quest to develop diagnostic modalities to identify potentially unstable atherosclerotic plaques. However, accumulating clinical data now suggest that multiple vulnerable plaques coexist in a single coronary tree and that inflammation is a critical determinant of the stability of plaques. Inflammatory mediators, such as cytokines, can influence several biologic processes that regulate stability of the plaque's fibrous cap and its resistance to rupture. Thus, the quest for strategies to identify and target treatment to a single culprit lesion seriously underestimates the complexity of the clinical biology of thrombosis in atherosclerotic arteries. For the optimum management of our patients, we must now also consider the vulnerable artery, the vulnerable arterial bed, and ultimately, the vulnerable patient. Treatment of vulnerable patients should include measures to stabilize plaques and to lessen the thrombotic consequences of plaque disruptions. (Am J Cardiol 2006;98[suppl]:3Q–9Q)

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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)

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CONCLUSIONS

Fatal AMI is characterized by diffuse coronary instability and is not associated with a single vulnerable plaque.

Mauriello et al. JACC 2005;45:1585-93

Plaque rupture (14/16 thrombi = 87.5%) → ✞ AMI

<2 TCFA per patient

Table 2. Distribution of the Various Plaque Types in the Three Groups of Patients

Plaque Types	CS of Patients Without Stable Angina Who Died of Noncardiac Causes (CTRL Group) N = 304 CS (%)	CS of Patients With Stable Angina Who Died of Noncardiac Causes (SA Group) N = 109 CS (%)	**16 patients** CS of Patients Who Died of AMI (AMI Group) N = 544 CS (%)
Culprit plaques with thrombosis	0	0	16 (3.0)
Associated with cap rupture	0	0	14 (2.6)
Associated with cap erosion	0	0	2 (0.4)
Vulnerable plaques	13 (4.3)	4 (3.7)	109 (20.0)
Thin fibrous-cap atheromata	3 (1.0)	0	31 (5.7)
Superficial calcified nodule	8 (2.6)	4 (3.7)	31 (5.7)
Plaques with stenosis >90%	2 (0.7)	0	47 (8.6)
Stable plaques	291 (95.7)	105 (96.3)	419 (77.0)

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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) © 2005 by the American College of Cardiology Foundation

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.

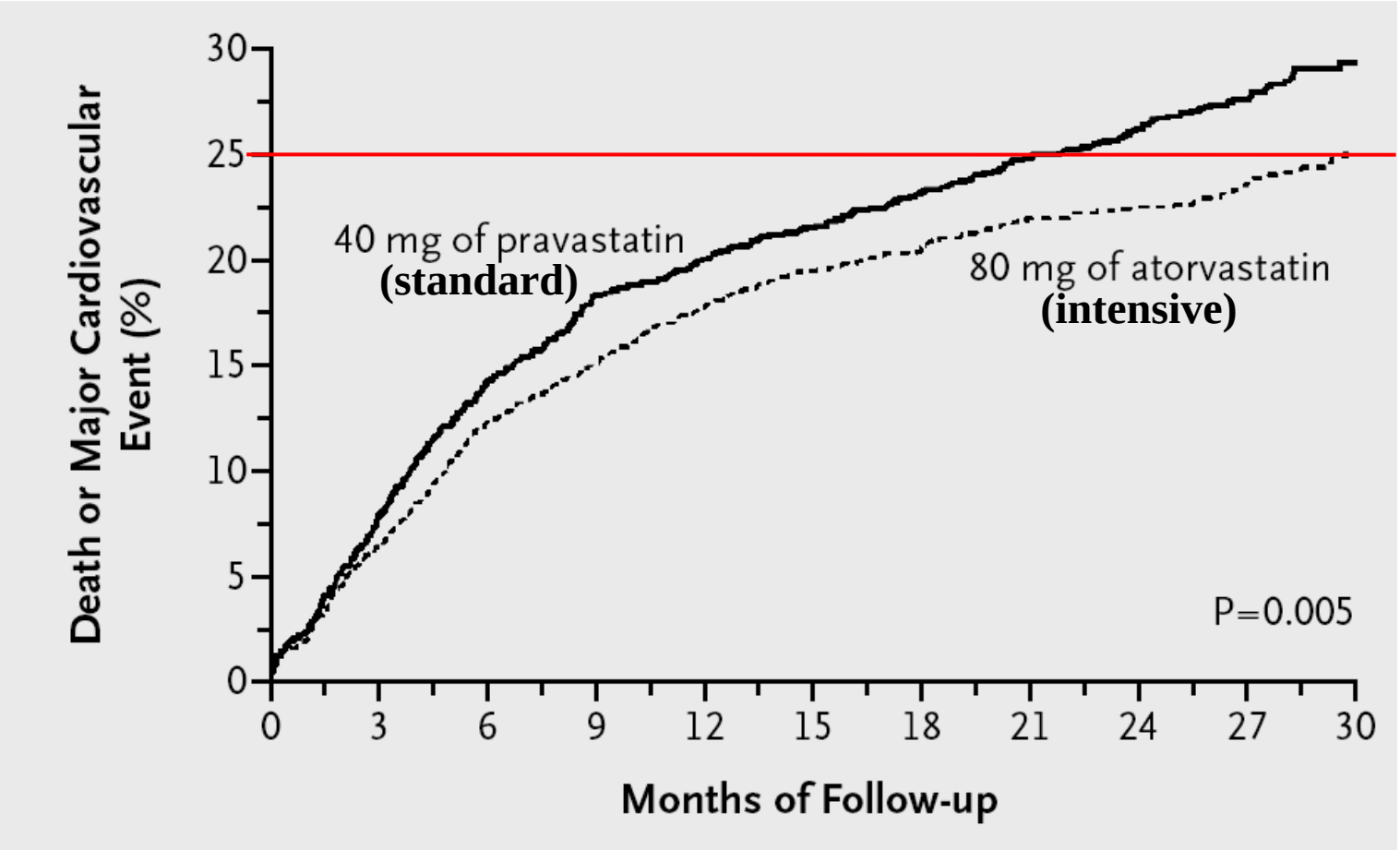
CONCLUSIONS This histopathologic study found that both vulnerable and stable coronary plaques of patients dying of AMI are diffusely infiltrated by inflammatory cells. (J Am Coll Cardiol 2005;45: 1585–93) © 2005 by the American College of Cardiology Foundation

<2 TCFA per patient

Despite profound lipid lowering in ACS

¼ come back with a new event within 30 m

PROVE IT – TIMI 22: statin after stabilized ACS



Cannon et al. NEJM 2004:350:1495-504

Plaque rupture in fatal CAD
2-3 per patient, including culprit

	Ruptured Plaques	
	total	+thrombus
47 patients[1]	103	40
83 patients[2]	211	102

[1] Falk E. Br Heart J 1983;50:127-34
[2] Frink RJ. J Inv Cardiol 1994;6:173-85

Plaque rupture in non-cardiac death, n=129
relatively rare (vs CAD)

Atheroma-related disease		Plaque Rupture no thrombus	Plaque Rupture +thrombus
69 persons:	no	6 (9%)	0
60 persons:	+	10 (17%)	3 mural (5%)

Davies MJ et al. Eur Heart J 1989;10:203-8

The New England
Journal of Medicine

Volume 310 MAY 3, 1984 Number 18

THROMBOSIS AND ACUTE CORONARY-ARTERY LESIONS IN SUDDEN CARDIAC ISCHEMIC DEATH

MICHAEL JOHN DAVIES, M.D., AND ANTHONY THOMAS, M.B., B.S.

Abstract The nature of the pathologic lesion in sudden cardiac ischemic death is in dispute. Among 100 subjects who died of ischemic heart disease in less than six hours, coronary thrombi were found in 74. There was no difference in incidence between those who died in less than 15 minutes, those who died in 15 to 60 minutes, and those who died after one hour. Among 26 cases without an intraluminal thrombus, plaque fissuring was found in 21; thus, in only 5 cases was no acute arterial lesion demonstrated. No intraluminal thrombi were found in age-matched controls. Forty-eight of the 74 thrombi were found at sites of preexisting high-grade stenosis; 14 were found at points of previous stenosis of less than 50 per cent of the diameter of the lumen. Forty-seven per cent of the thrombi were found in the right coronary artery. Only 30 per cent were found in the left anterior descending coronary artery. The pathologic process in sudden ischemic death involves a rapidly evolving coronary-artery lesion in which plaque fissuring and resultant thrombus formation are present. These findings have implications for the prevention of sudden cardiac death by antithrombotic therapy. (N Engl J Med 1984; 310:1137-40.)

NEJM 1984;310:1137-40

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THROMBOSIS AND ACUTE CORONARY-ARTERY LESIONS IN SUDDEN CARDIAC ISCHEMIC DEATH

MICHAEL JOHN DAVIES, M.D., AND ANTHONY THOMAS, M.B., B.S.

- **115 thrombi in 74 patients**
- **103 (90%) of these had plaque fissuring**

NEJM 1984;310:1137-40

The thin-cap fibroatheroma: a type of vulnerable plaque

The major precursor lesion to acute coronary syndromes

Frank D. Kolodgie, PhD,* Allen P. Burke, MD,* Andrew Farb, MD,*
Herman K. Gold, MD,* Junying Yuan, PhD,† Jagat Narula, MD, PhD,‡
Aloke V. Finn, MD,§ and Renu Virmani, MD*

While the concept of plaque 'vulnerability' implies a propensity towards thrombosis, the term vulnerable was originally intended to provide a morphologic description consistent with plaques that are prone to rupture. It is now known that the etiology of coronary thrombi is diverse and can arise from entities of plaque erosion or calcified nodules. These findings have prompted the search for more definitive terminology to describe precursor lesions associated with rupture, now referred to as *thin-cap fibroatheromas*. This review focuses on the *thin-cap fibroatheroma*, as a specific cause of acute coronary syndromes. To put these issues into current perspective, we need to revisit some of the older literature describing plaque morphology in stable and unstable angina, acute myocardial infarction, and sudden coronary death. The morphology, frequency, and precise location of these *thin-cap fibroatheromas* are further discussed in detail. Potential mechanisms of fibrous cap thinning are also addressed, in particular emerging data, which suggests the role of cell death "apoptosis" in cap atrophy. Curr Opin Cardiol 2001, 16:285–292

Curr Opin Cardiol 2001;16:285-292

Plaque rupture is the initiating event in most acute coronary syndromes [1–8]. Morphologic observations at autopsy have identified specific plaque types associated with lesions prone to rupture, commonly referred to in the literature as 'vulnerable plaques'. Plaque rupture, however, is not the sole etiology of acute coronary thrombi. For this reason, the term 'vulnerable' evokes confusion because it implies a specific morphologic entity. In a recent modification to the American Heart Association Classification of atherosclerosis, we describe two additional plaque morphologies associated with acute coronary thrombi, namely, plaque erosion and the calcified nodule [9]. Clearly, other precursor lesions leading to alternative mechanisms of thrombi must also be considered under the title 'vulnerable', because of morphologic dissimilarities to those plaques eliciting rupture. Using descriptive terminology, we propose to call lesions that are at risk for rupture *thin-cap fibroatheromas* [9••]. This simplified classification is based on morpho-

Plaque rupture → ✞ CAD
~1.3 TCFA per patient

Table 3. Mean incidence of thin-cap fibroatheromas in culprit plaques

Culprit plaque	Lesions, *N*	Mean incidence of thin-cap fibroatheromas		
Acute rupture	47	1.3 ± 1.4		$P = 0.0001$
Acute MI	9 (19)	1.4 ± 1.3		
Healed MI	19 (40)	1.5 ± 1.6		
No MI	19 (40)	1.1 ± 1.1		
Healed rupture	36 (77)	1.6 ± 1.3	P = ns	
No healed rupture	11 (23)	0.9 ± 1.5		
Erosion	23	0.2 ± .52		
Stable	73	1.1 ± 1.3		
Acute MI	3 (4)	2.7 ± 0.6		
Healed MI	41 (56)	1.2 ± 1.5		
No MI	32 (44)	0.9 ± 1.2		
Healed rupture	49 (67)	1.4 ± 1.4	$P = 0.005$	
No healed rupture	24 (33)	0.5 ± 0.8		

Mean values are presented as ± standard deviation. The numbers in parentheses correspond to percentages. MI, myocardial infarction.

Kolodgie, …, Virmani. Curr Opin Cardiol 2001;16:285-292

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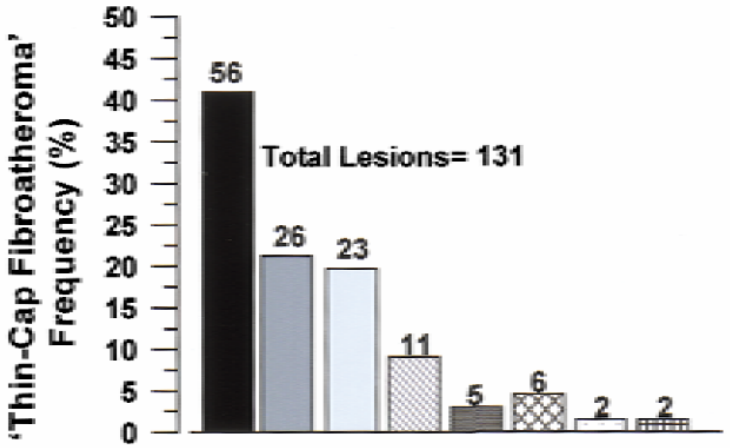
Mean values are presented as ± standard deviation. The numbers in parentheses correspond to percentages. MI, myocardial infarction.

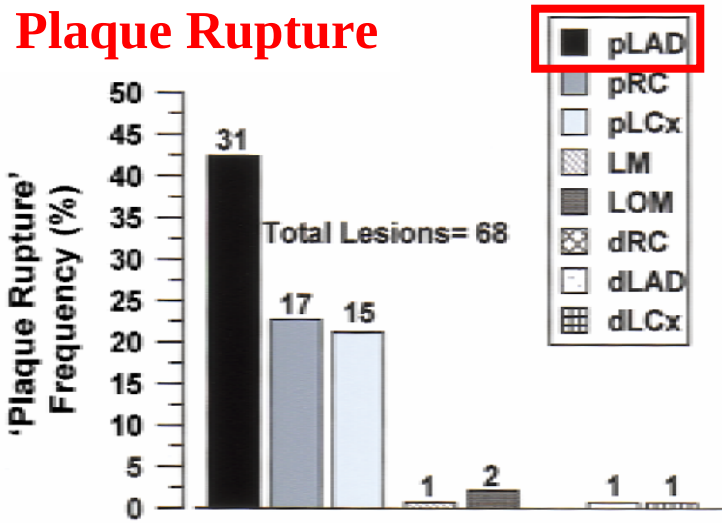
Kolodgie, …, Virmani. Curr Opin Cardiol 2001;16:285-292

Thin-cap fibroatheroma & rupture
prox LAD: "hot spot"

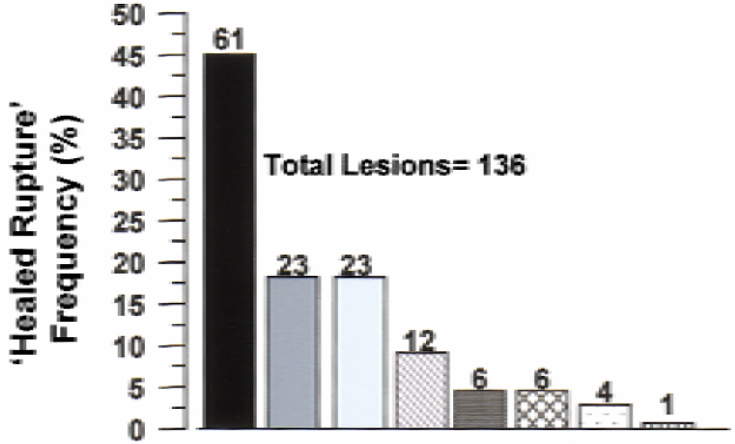
TCFA



Plaque Rupture



Healed Rupture



Kolodgie, …, Virmani. Curr Opin Cardiol 2001;16:285-292

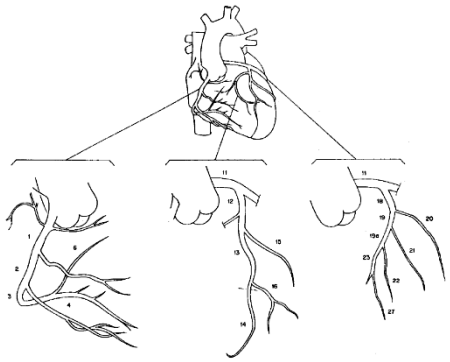
Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions

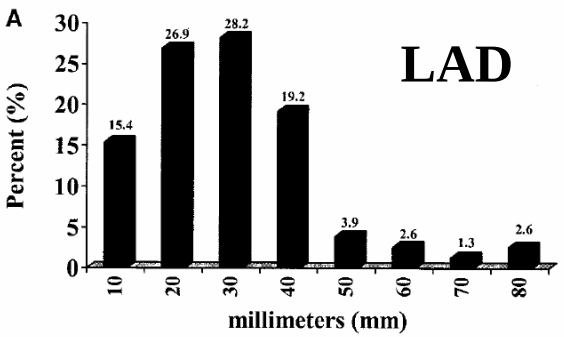
John C. Wang, MD, MSc; Sharon-Lise T. Normand, PhD;
Laura Mauri, MD, MSc; Richard E. Kuntz, MD, MSc

Background—Acute coronary occlusions leading to ST-segment elevation myocardial infarctions (STEMIs) are due primarily to rupture of atherosclerotic plaques. Present "vulnerable plaque" detection technology focuses on identifying individual plaques with no clear therapeutic plan beyond conventional risk factor reduction. We developed a spatial map of the distribution of acute coronary occlusions to test our hypothesis that plaque ruptures do not occur uniformly throughout the coronary tree.

Methods and Results—We analyzed 208 consecutive patients who presented to the Brigham and Women's Hospital with STEMI and mapped the location of the acute coronary occlusion. These occlusions were not uniformly distributed throughout each of the major epicardial coronary arteries but tended to cluster within the proximal third of each of the vessels (right coronary artery, $P=0.001$; left anterior descending artery, $P=0.003$; left circumflex artery, $P=0.001$). Furthermore, Poisson regression showed that for each 10-mm increase in distance from the ostium, the risk of an acute coronary occlusion was significantly decreased by 13% in the right coronary artery, 30% in the left anterior descending artery, and 26% in the left circumflex artery.

Conclusions—Acute coronary occlusions leading to STEMI tend to cluster in predictable "hot spots" within the proximal third of the coronary arteries. Identification of these high-risk zones for acute coronary occlusions will lead to future advances in vulnerable plaque detection technology and potentially locally directed preventive strategies. **(*Circulation*. 2004;110:278-284.)**





VP and ruptured plaques

"… relatively infrequent … limited, focal distribution…"

[251] Density and Distribution of Thin-Cap Fibroatheroma and Ruptured Plaque in Human Coronary Arteries -- A Pathologic Study

Pavan K Cheruvu, Harvard Medical Sch, Boston, MA; Aloke V Finn, Massachusetts General Hosp, Boston, MA; Craig Gardner, InfraReDx, Inc., Burlington, MA; Jay Caplan, InfraReDx, Burlington, MA; James A Goldstein, William Beaumont Hosp, Detroit, MI; Gregg W Stone, Lenox Hill Hosp and Cardiovascular Res Foundatoin, New York City, NY; Renu Virmani, CV Path, Gaithersburg, MD; James E Muller, InfraReDx, Inc., Burlington, MA

Background - Most cases of acute coronary syndrome and sudden death are believed to arise from rupture of a thin cap fibroatheroma (TCFA) with resultant intracoronary thrombosis. Although atherosclerosis is a diffuse disease, it is unclear whether plaques at high risk of rupture are focally or diffusely distributed. ***Methods and Results -*** To determine the frequency and extent of TCFA and ruptured plaque, we performed longitudinal sectioning of 148 human coronary arteries from 50 cardiac autopsy specimens (mean age 73 years, 64% male) taken from patients dying of cardiovascular (n=33), non-cardiovascular (13) and unknown (4) causes. A total of 3639 longitudinal segments of length 3 mm were sectioned in 148 coronary arteries, comprising 10.9 meters of total coronary tissue length. Overall, 23 TCFAs and 19 ruptured plaques were found (mean ± SD: 0.46 ± 0.95 and 0.38 ± 0.70 per heart, respectively), accounting for only 1.5% and 1.2%, respectively, of the total length of all coronary trees examined. The majority of TCFA and ruptured plaque localized in the proximal third of the major coronary arteries, and in 92% of cases these lesions clustered within 2 or fewer non-overlapping 20-mm segments. ***Conclusions -*** TCFA and ruptured plaques, the suspected precursor lesions of intracoronary thrombi, are relatively infrequent and have a limited, focal distribution in human coronary arteries, supporting ongoing research to pre-emptively identify and passivate vulnerable plaque.

AHA, Nov 2006; abstract 251

VP and ruptured plaques

"… relatively infrequent … limited, focal distribution…"

[251] Density and Distribution of Thin-Cap Fibroatheroma and Ruptured Plaque in Human Coronary Arteries -- A Pathologic Study

50 hearts (33 ✞ CVD)

- **TCFA, Vulnerable Plaque** **n=23 (0.46 per heart)**
- **Ruptured plaques** **n=19 (0.38 per heart)**

AHA, Nov 2006; abstract 251

Targeting Vulnerable Plaque

medical whack-a-mole?

Thrombosis-prone plaques

1. **Origin**
   - **speed of development**
2. **How long does a VP persist?**
3. **Fate**
   - **healing without thrombosis**
   - **silent rupture/thrombosis**
   - **acute ischemic event (ACS, stroke)**

Targeting Vulnerable Plaque

medical whack-a-mole?

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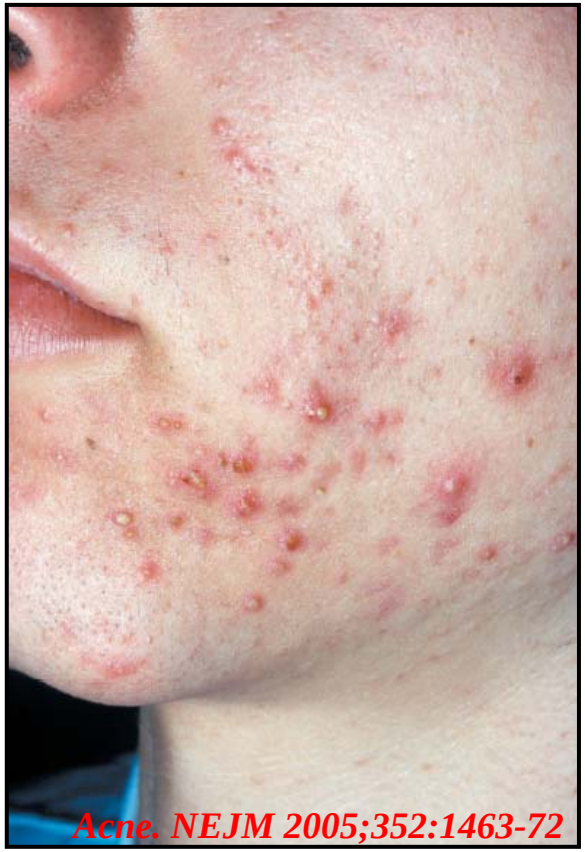
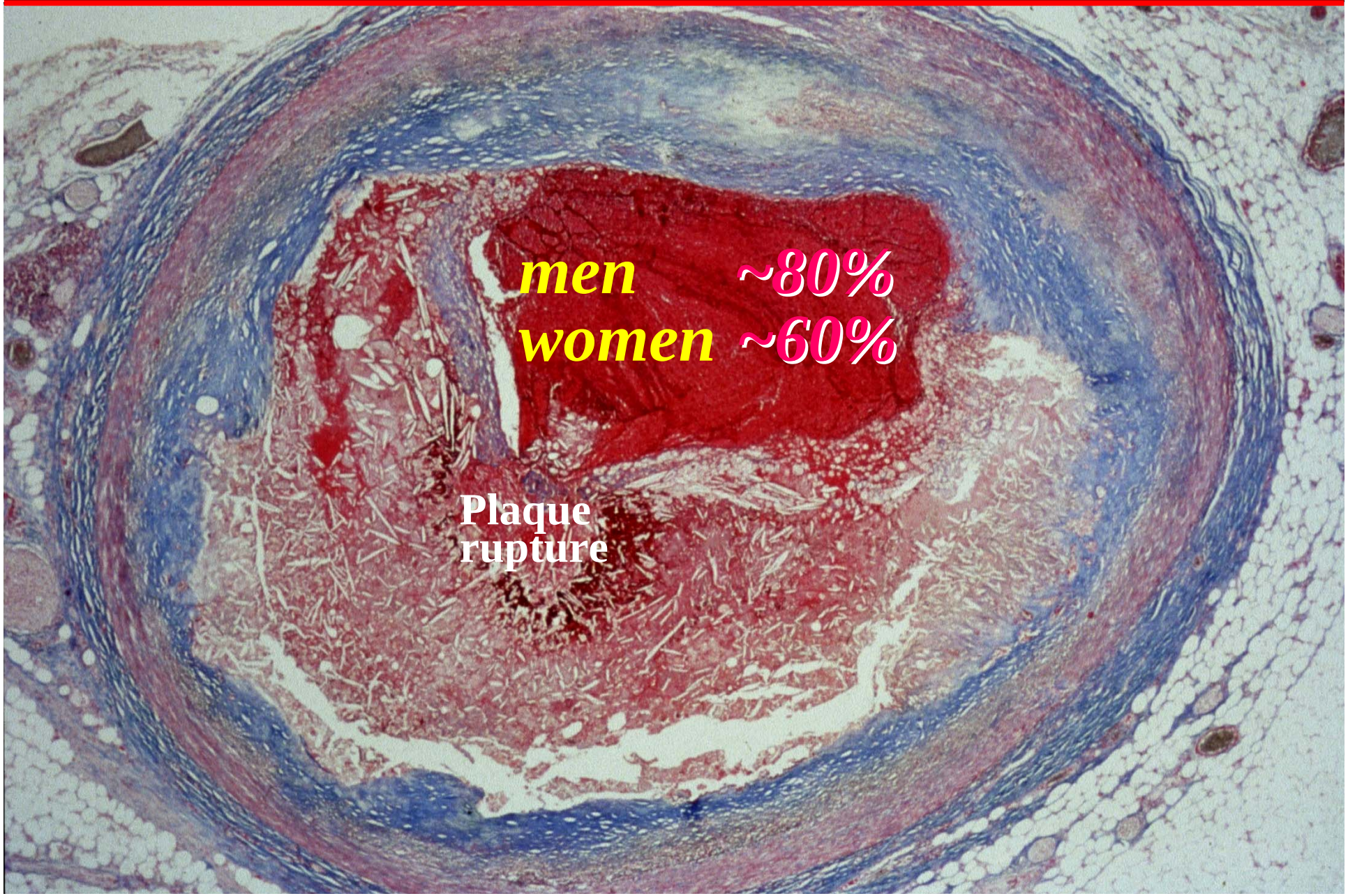
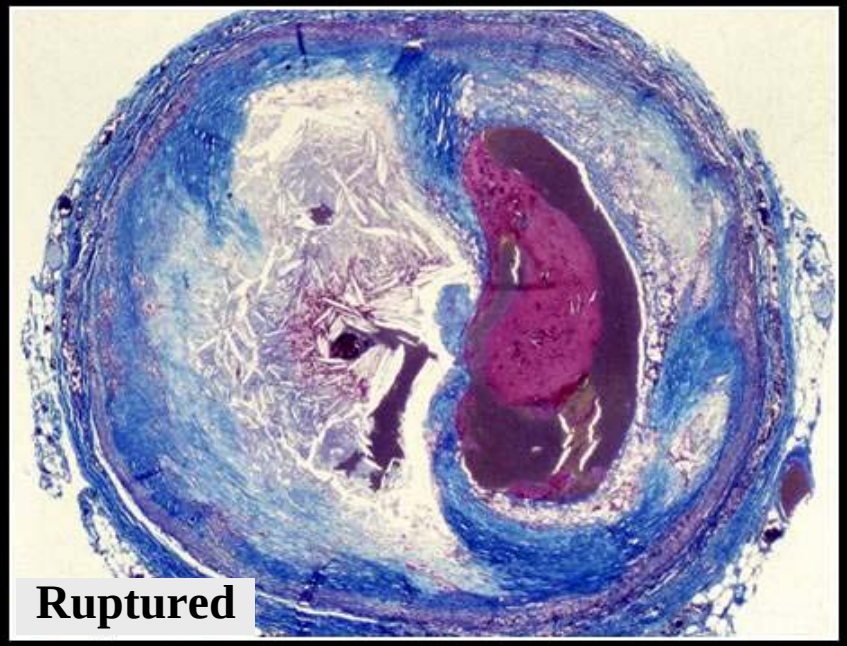


Acne. NEJM 2005;352:1463-72

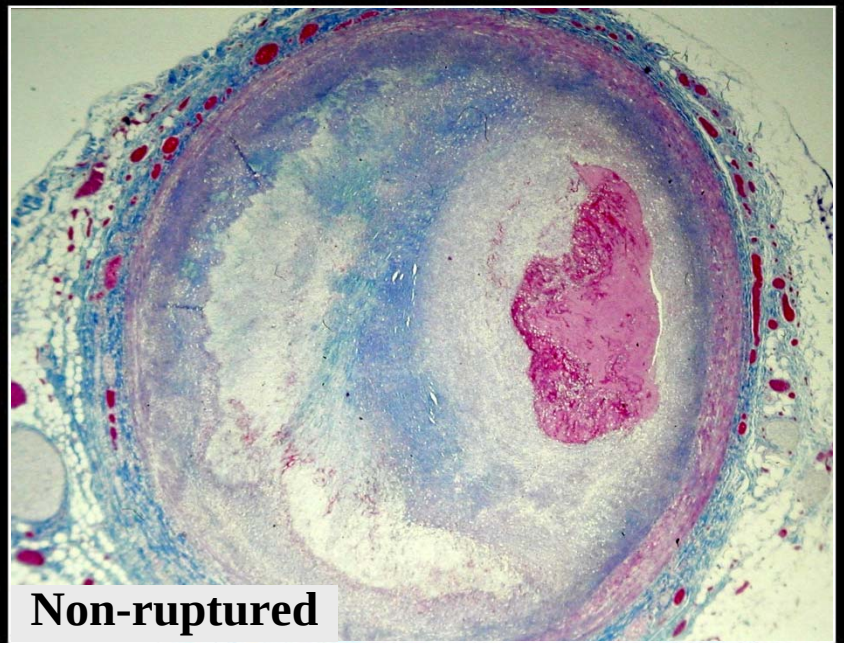
Plaque Rupture → Coronary Thrombosis



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



Ruptured



Non-ruptured

Coronary Thrombosis
plaque rupture

- men ~80%
- women ~60%

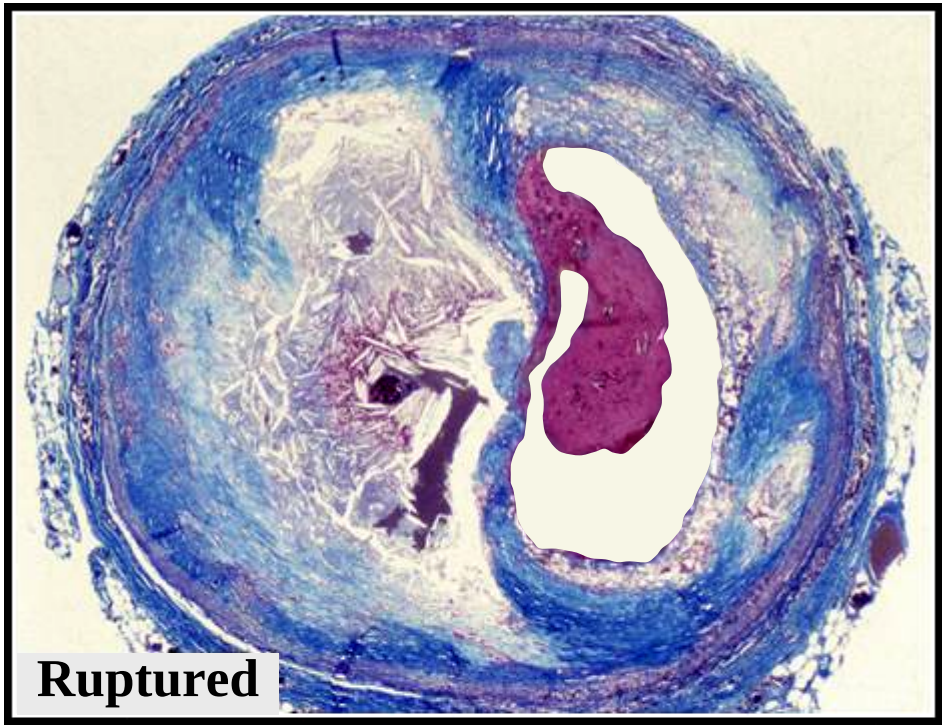
Fatal Coronary Thrombi Precipitated by Plaque Rupture

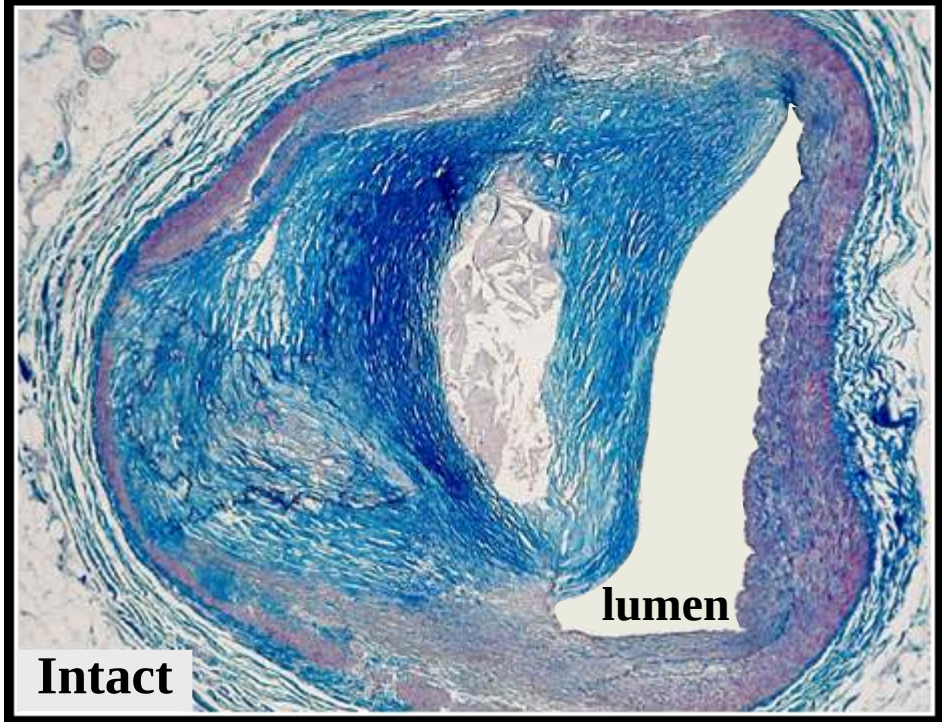
Patients	Age (yrs)*	n	Rupture	Study†
Hospital, —	—	19	19 = 100%	Chapman, 1965
Hospital, —	—	17	17 = 100%	Constantinides, 1966
Hospital, AMI + SCD	58	40	39 = 98%	Friedman et al., 1966
Hospital, AMI	62	88	71 = 81%	Bouch et al., 1970
Hospital, AMI	66	91	68 = 75%	Sinapius, 1972
Coroner, SCD	53	20	19 = 95%	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**

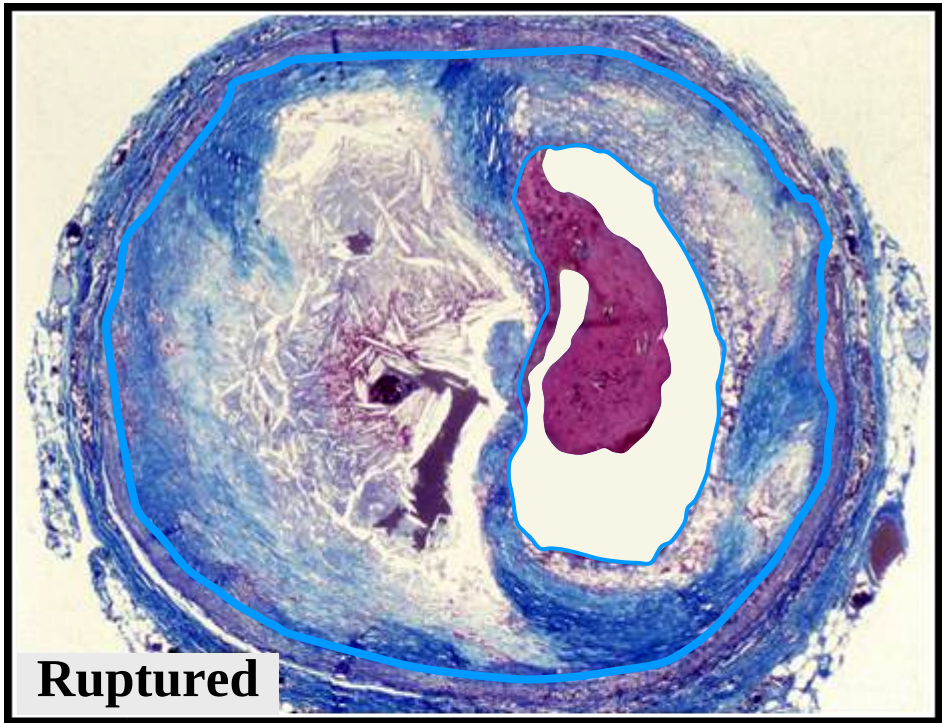
Falk. JACC 2006;47:C7-12

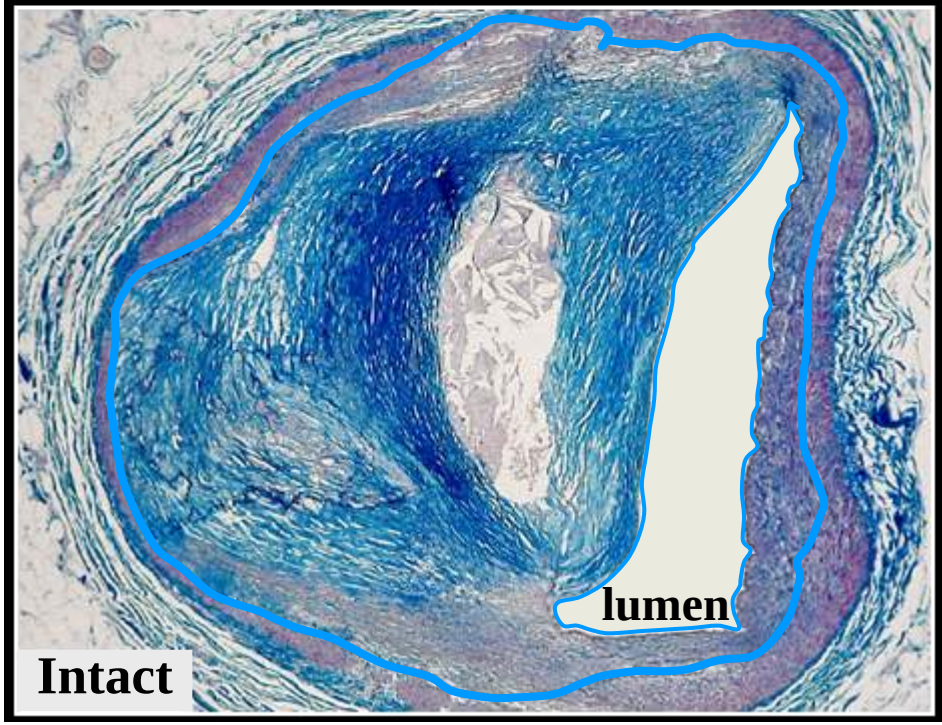
Coronary Atherosclerosis

ruptured vs intact plaque









Coronary Atherosclerosis

ruptured vs intact plaque

- **Plaque size↑**

How Big Are Coronary Atherosclerotic Plaques That Rupture?

Michael C. Fishbein, MD; Robert J. Siegel, MD

Circulation 1996;94:2662-6

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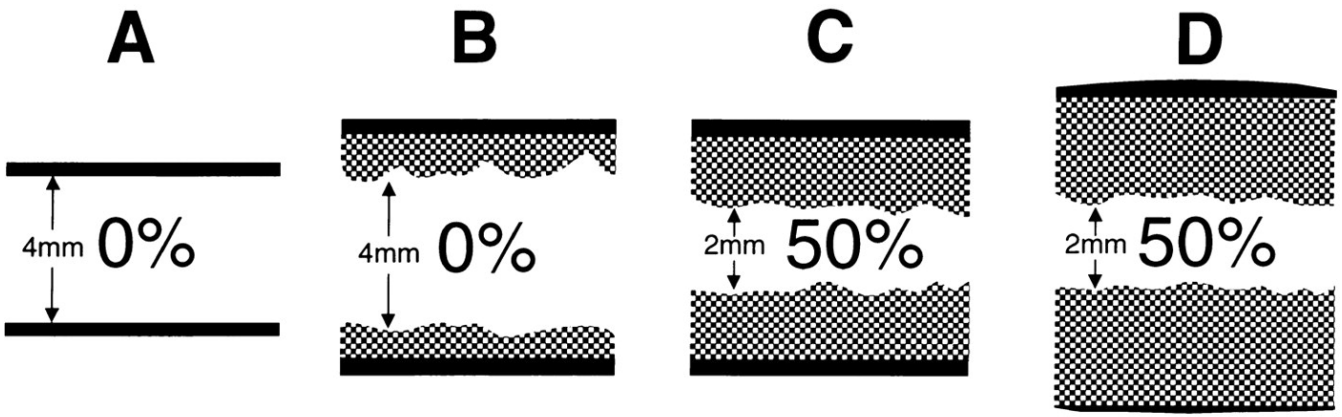
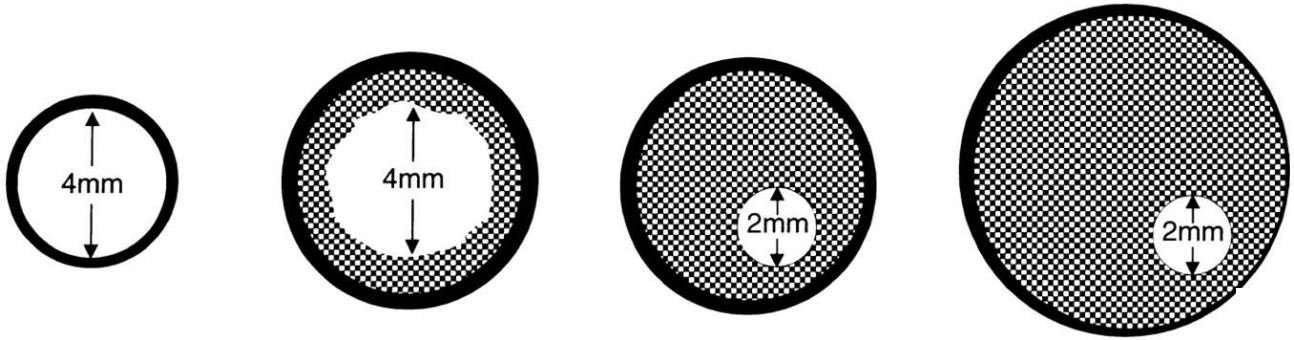


ANGIOGRAPHY
luminal narrowing
(diameter reduction)



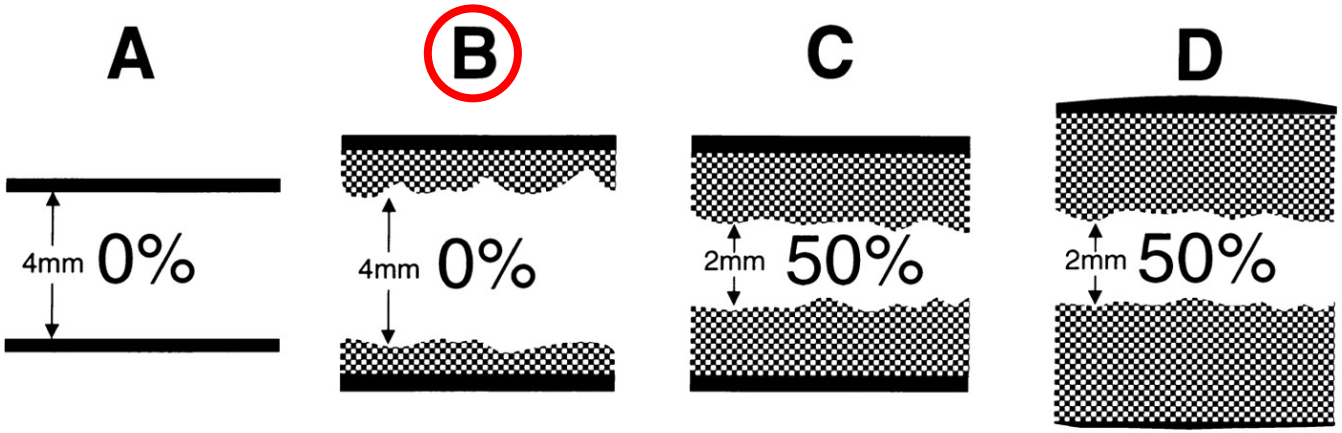
IVUS/HISTOLOGY
wall disease (plaque)

0%	50%	89%	95%
0%	0%	75%	75%

How Big Are Coronary Atherosclerotic Plaques That Rupture?

Michael C. Fishbein, MD; Robert J. Siegel, MD

Circulation 1996;94:2662-6



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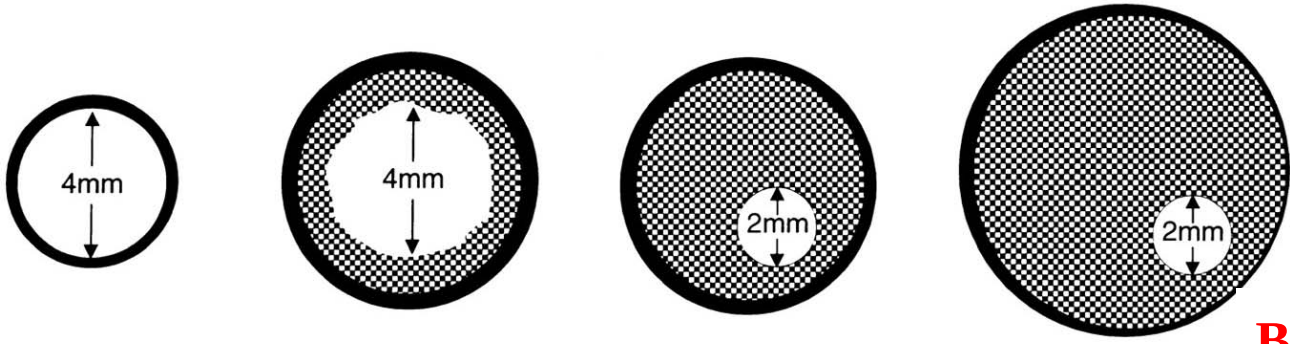


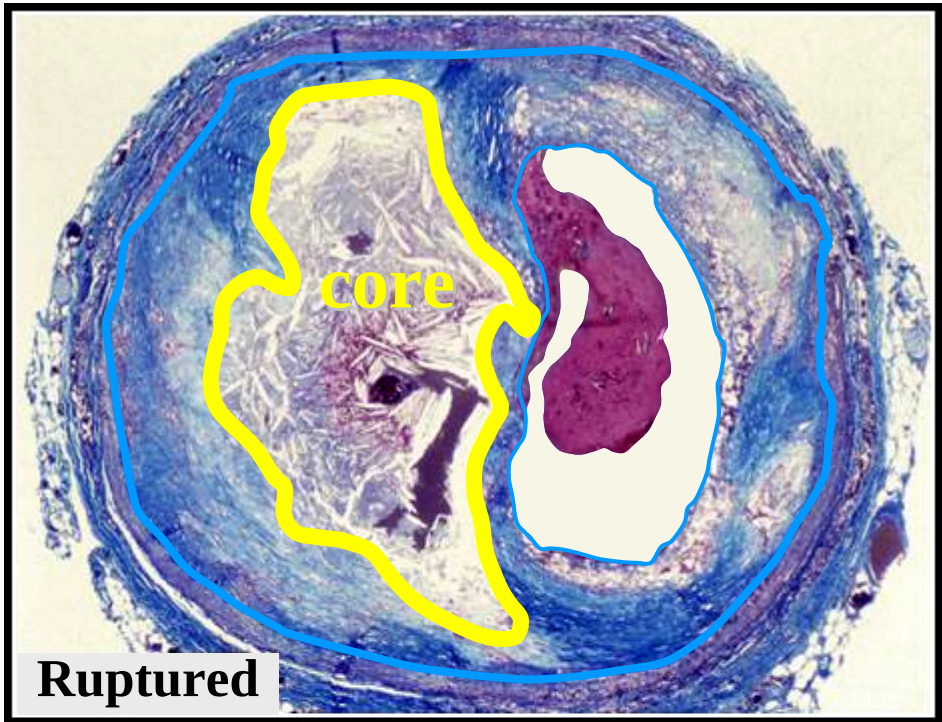
IVUS/HISTOLOGY
wall disease (plaque)

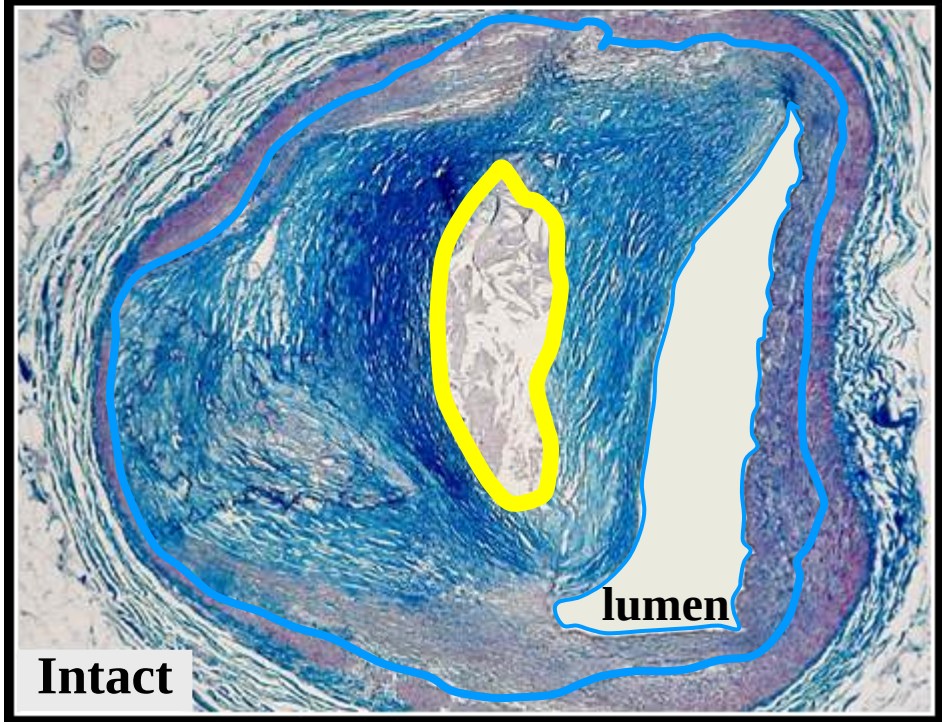
0%	50%	89%	95%
0%	0%	75%	75%

B:

Wall: 50% X-sectional↓

Lumen: normal





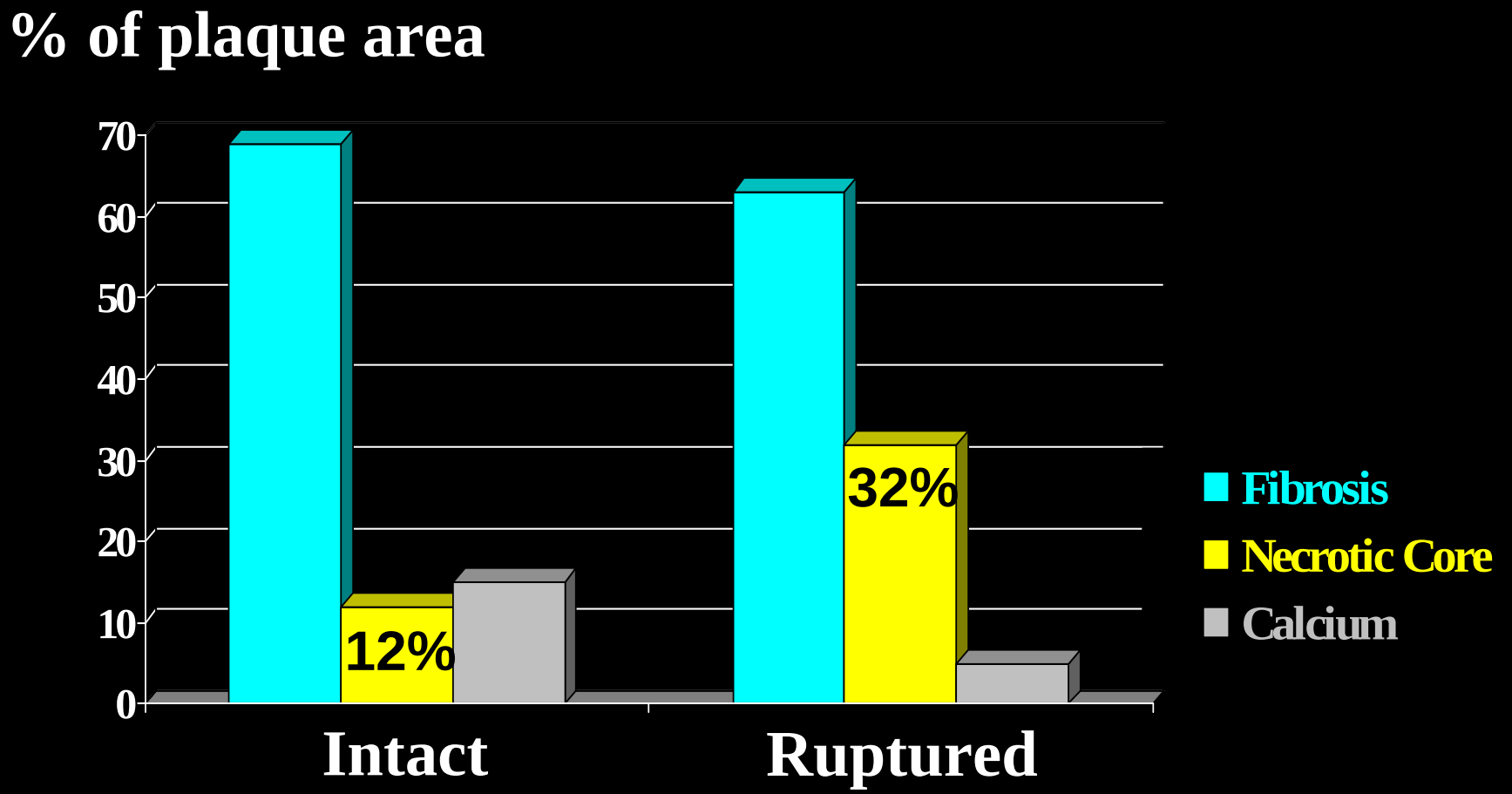
Coronary Atherosclerosis
ruptured vs intact plaque

- **Plaque size↑**
- **Necrotic core↑**
  - **~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

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)$^{\tau}$
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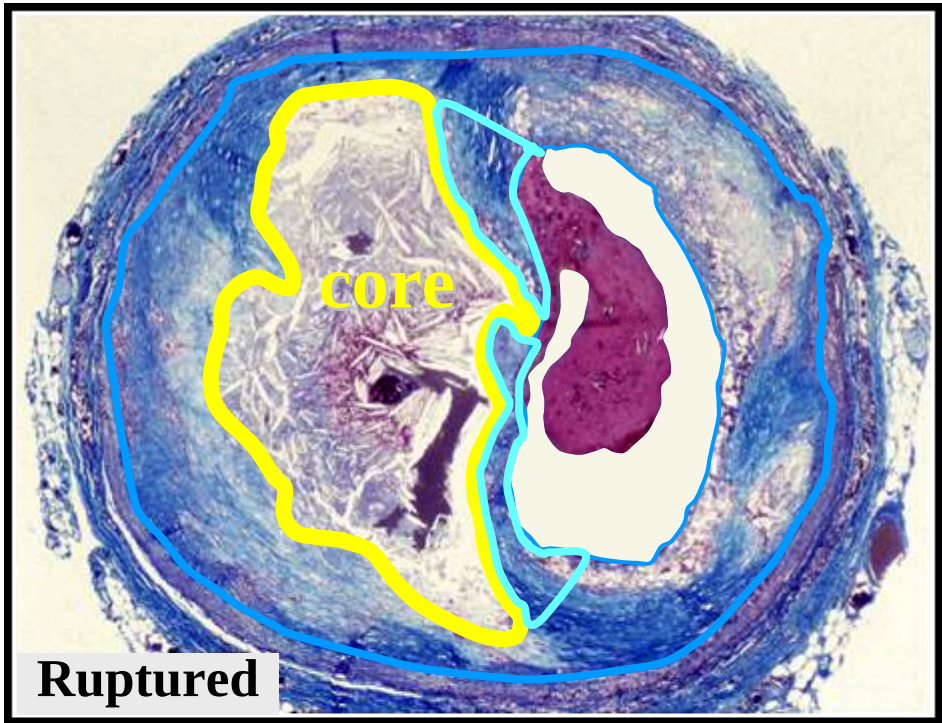
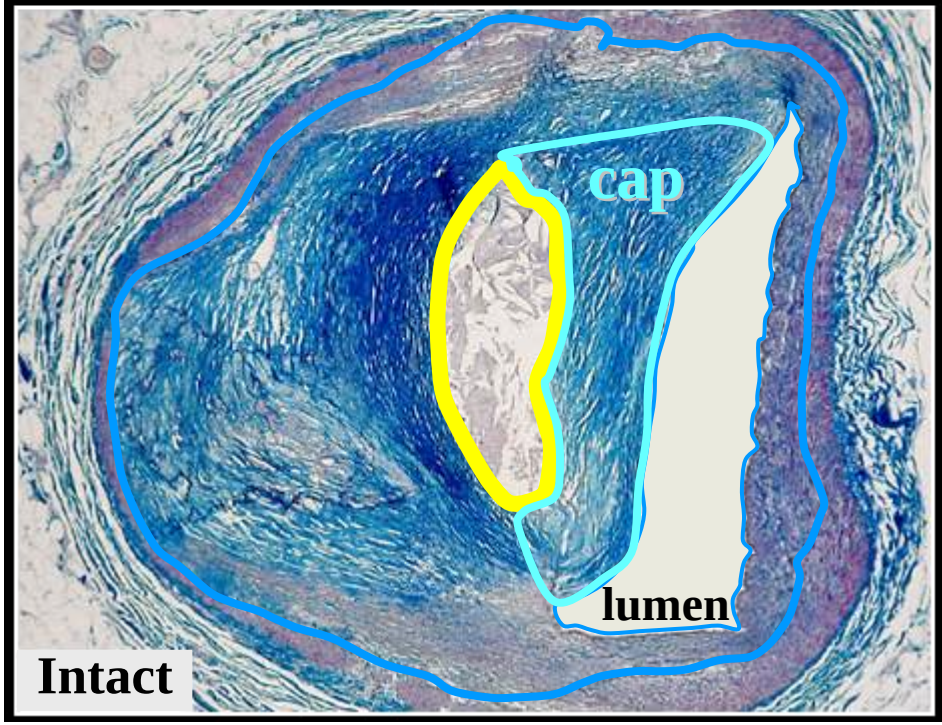
Overlap:

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





Coronary Atherosclerosis
ruptured vs intact plaque

- **Plaque size↑**
- **Necrotic core↑**
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  - **~3.8 mm^2 & ~9 mm long***
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  - **thinkness↓, ~23 μm (95% <65 μm)***

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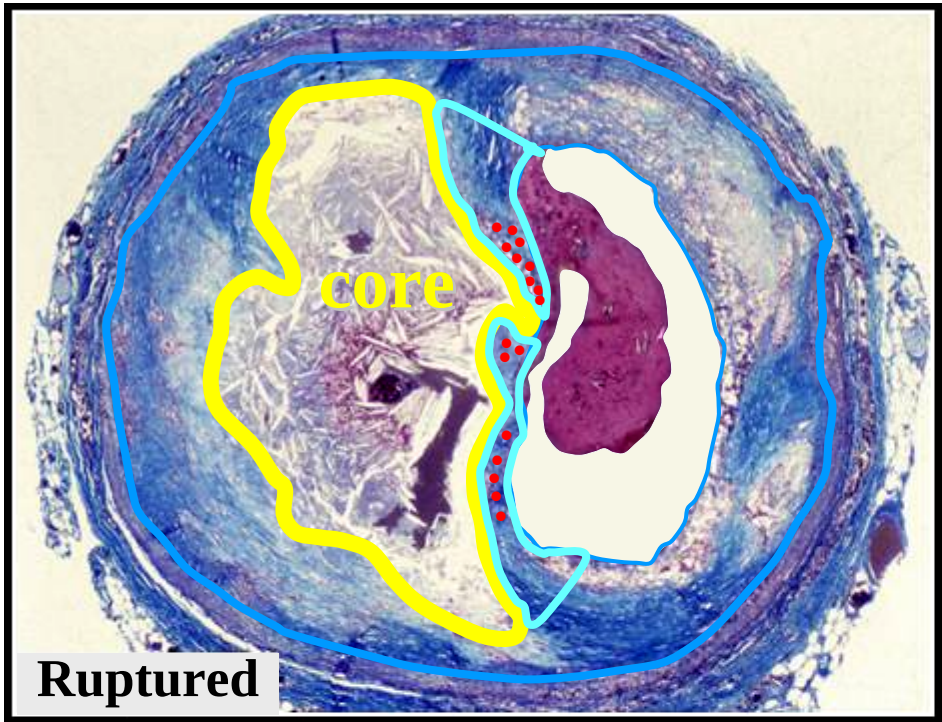

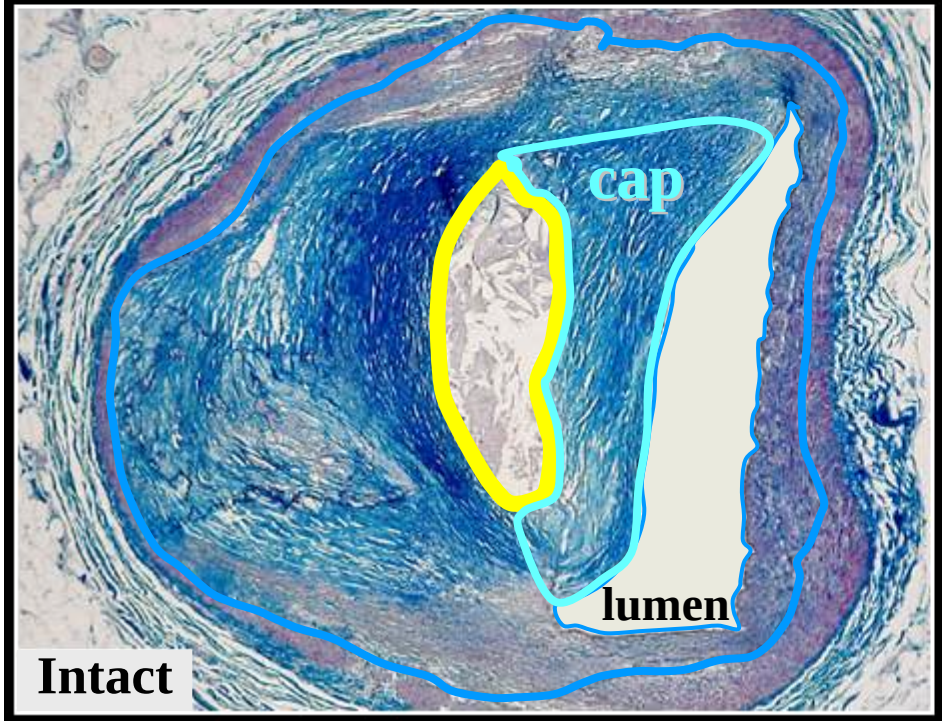

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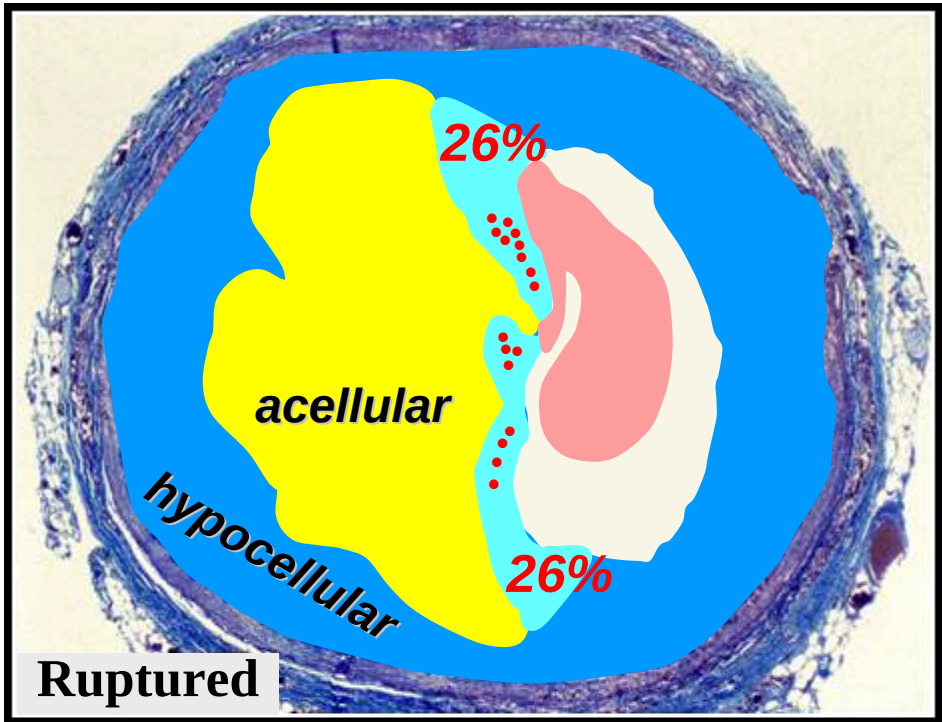

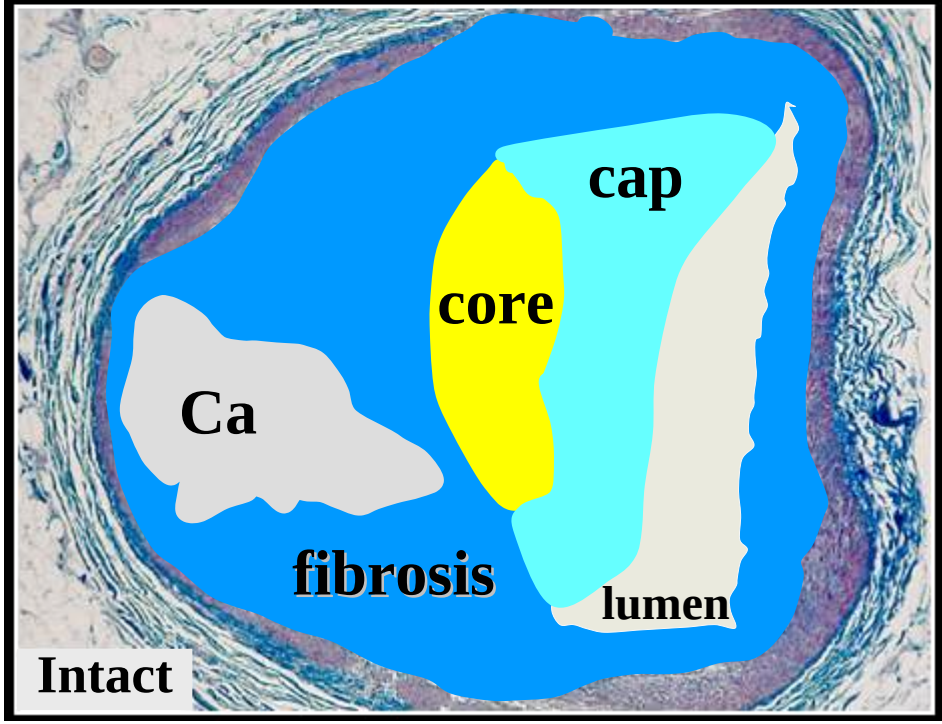

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TABLE 2. Morphometric Assessment of Vessel Area, Stenosis, Necrotic Core Size, and Macrophages Density in a Large Series of Paraffin-Embedded Human Coronary Sections (n=488) From Sudden Coronary Death Patients

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
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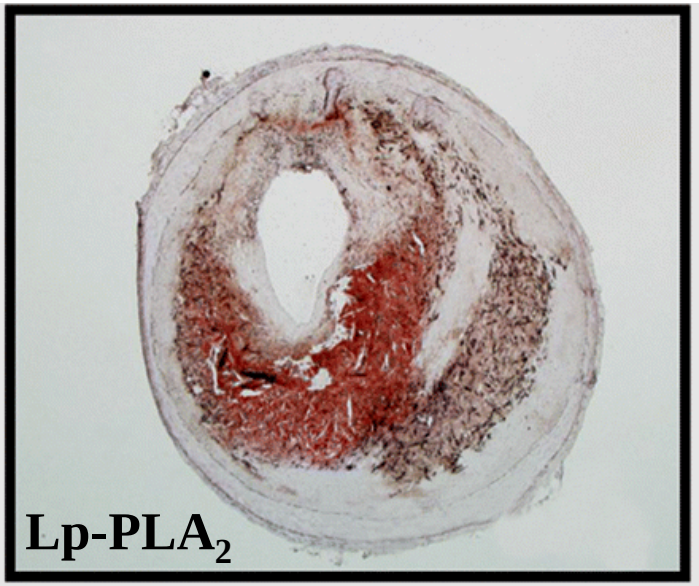

Mean ~ SD

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

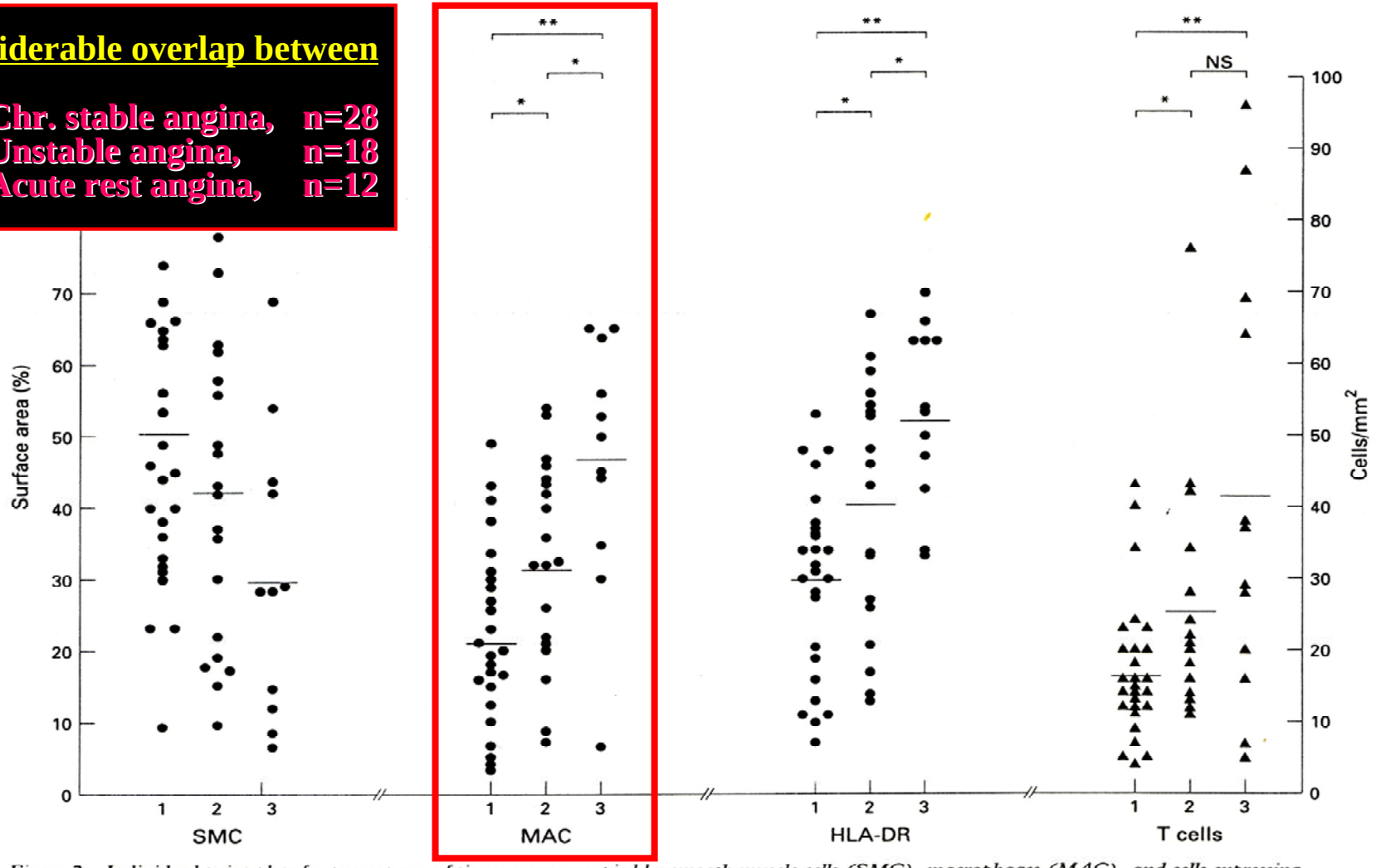

*Figure 2 Individual point plots for percentages of tissue areas occupied by smooth muscle cells (SMC), macrophages (MAC), and cells expressing HLA-DR (HLA-DR) and the number of T lymphocytes per mm² for each atherectomy specimen in the three patient groups. Note the considerable overlap between the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

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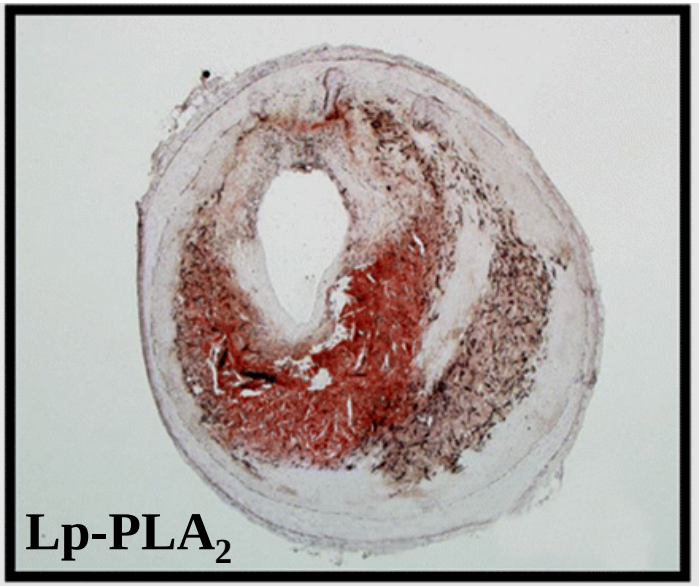

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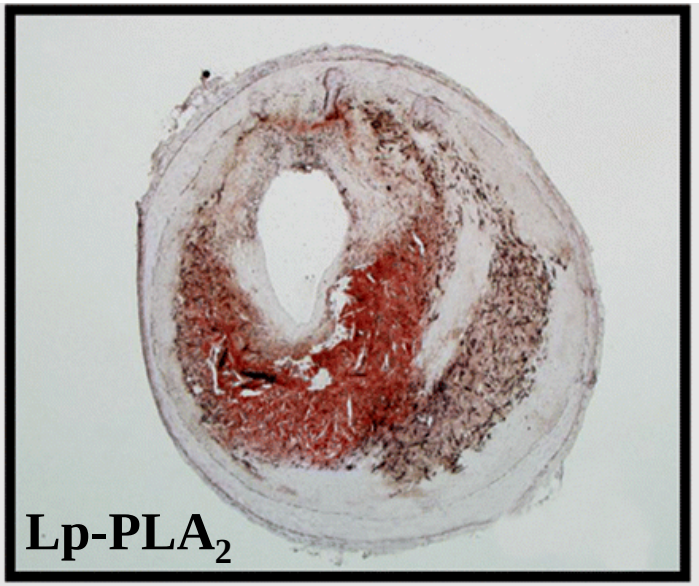

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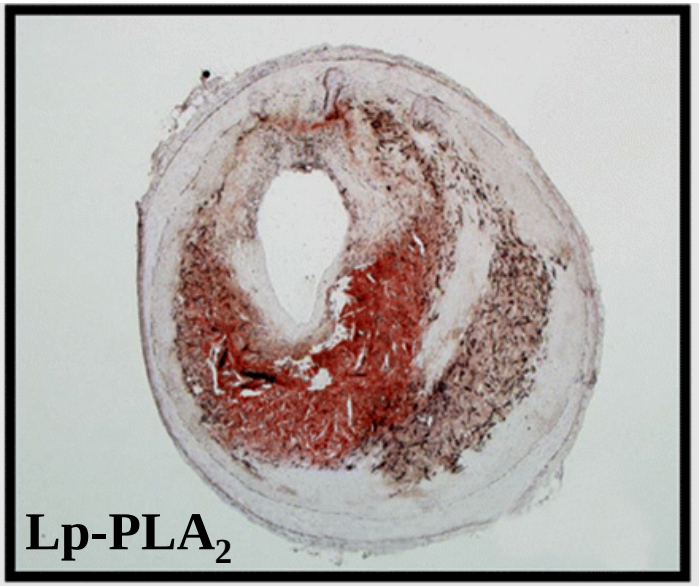

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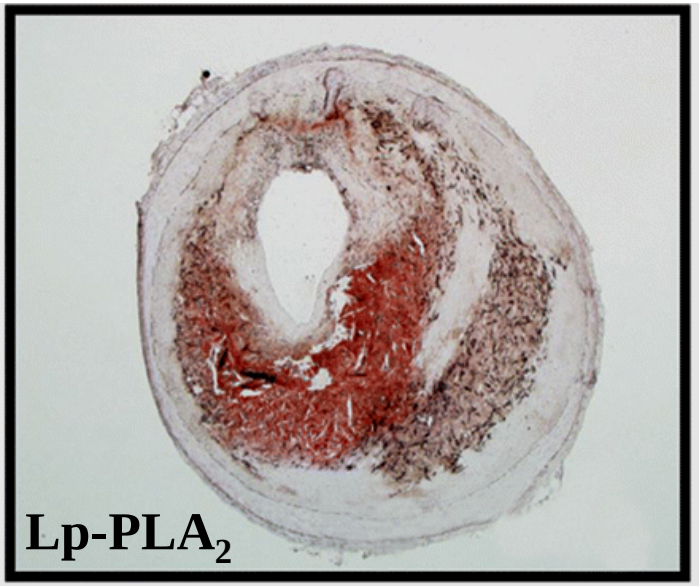

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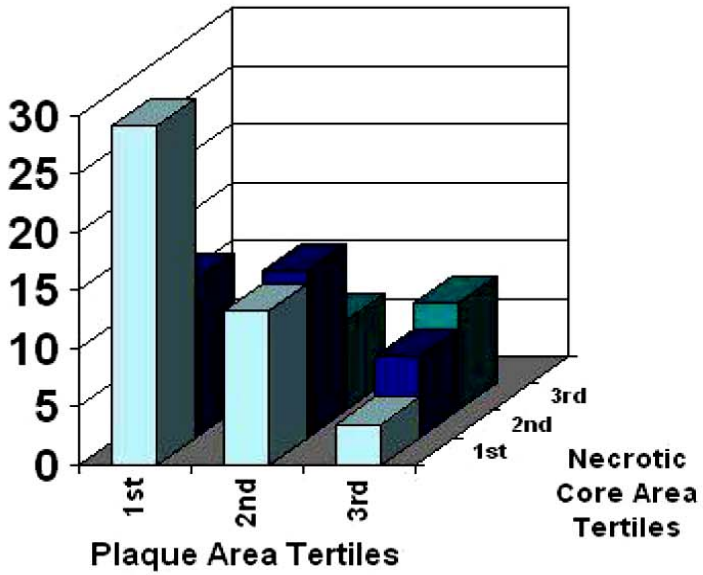
AHA Nov 2006

[1914] Vulnerable Plaque Pathology for Imagers

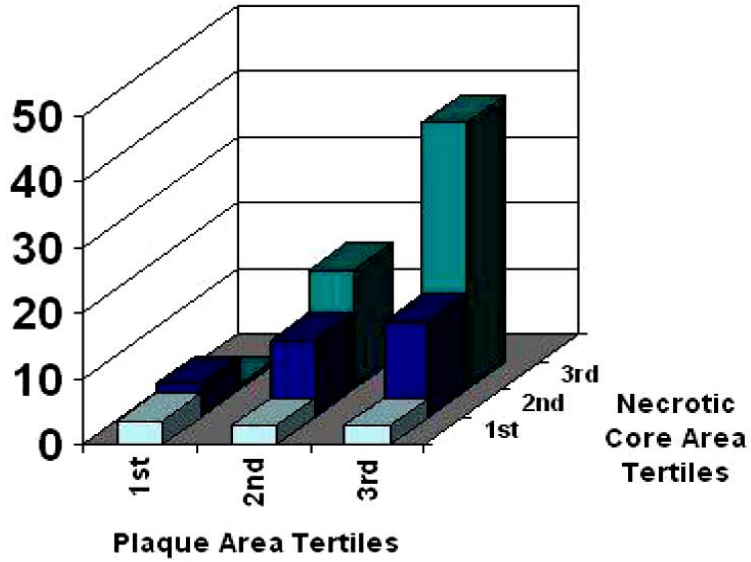
Renu Virmani, CV Pathology, Gaithersburg, MD; Shaista Malik, Univ of California, Irvine, CA; Allen Burke, Kristi Skorija, CV Pathology, Gaithersburg, MD; Nathan Wong, Univ of California, Irvine, CA; Frank Kolodgie, CV Pathology, Gaithersburg, MD; Aloke Finn, Massachusettes General Hosp, Boston, MA; Jagat Narula, Univ of California, Irvine, CA

Background: Knowledge of precise characteristics of vulnerable plaques (VP) is needed to develop noninvasive imaging technology for their detection. Ruptured atherosclerotic plaques associated with acute coronary events are pathologically described as positively remodeled vessels containing atheromatous cores, with thin and inflamed disrupted caps. It is expected that the VP demonstrate similar pathologic features. Methods: 375 atherosclerotic plaques were histopathologically analyzed from the victims of sudden coronary death and classified as early or late core fibroatheromas (FA; n=254), thin-cap fibroatheroma (or VP; n=52) and ruptured plaques (RP; n= 69). Descriptive analyses of various plaque characterisitics were performed with ANOVA and chi square tests. A multivariate logistic regression adjusting for age, gender, race, and plaque characteristics predicted unstable (VP+RP) versus stable (FA) plaques. Results: Independent predictors of the likelihood of unstable plaque were 1) necrotic core area: odds ratio [OR] and 95% confidence intervals of 2.8 (1.3-6.2) for 2nd and 6.0 (2.5-14) for 3rd, vs. 1st tertile, 2) plaque area: 4.9 (2.1-11.3) for 3rd vs. 1st tertile, and 3) macrophage area: 4.0 (2.0-8.1) for 3rd vs. 1st tertile (all $p<0.05$ to $p<0.001$). Bivariate relationship was significant only for plaque area and necrotic core area relationship, relationship was not affected by macrophage area. Conclusions: Larger extent of the plaque area and the largest magnitude of necrotic core determine the likelihood of plaque rupture. Any noninvasive diagnostic strategy will need to target these two morphological features for the detection of unstable lesions.

Stable Plaque
$\chi 2=55.6$ $p < .0001$



Ruptured and Vulnerable Plaque
$\chi 2=24.2$ $p < .0001$



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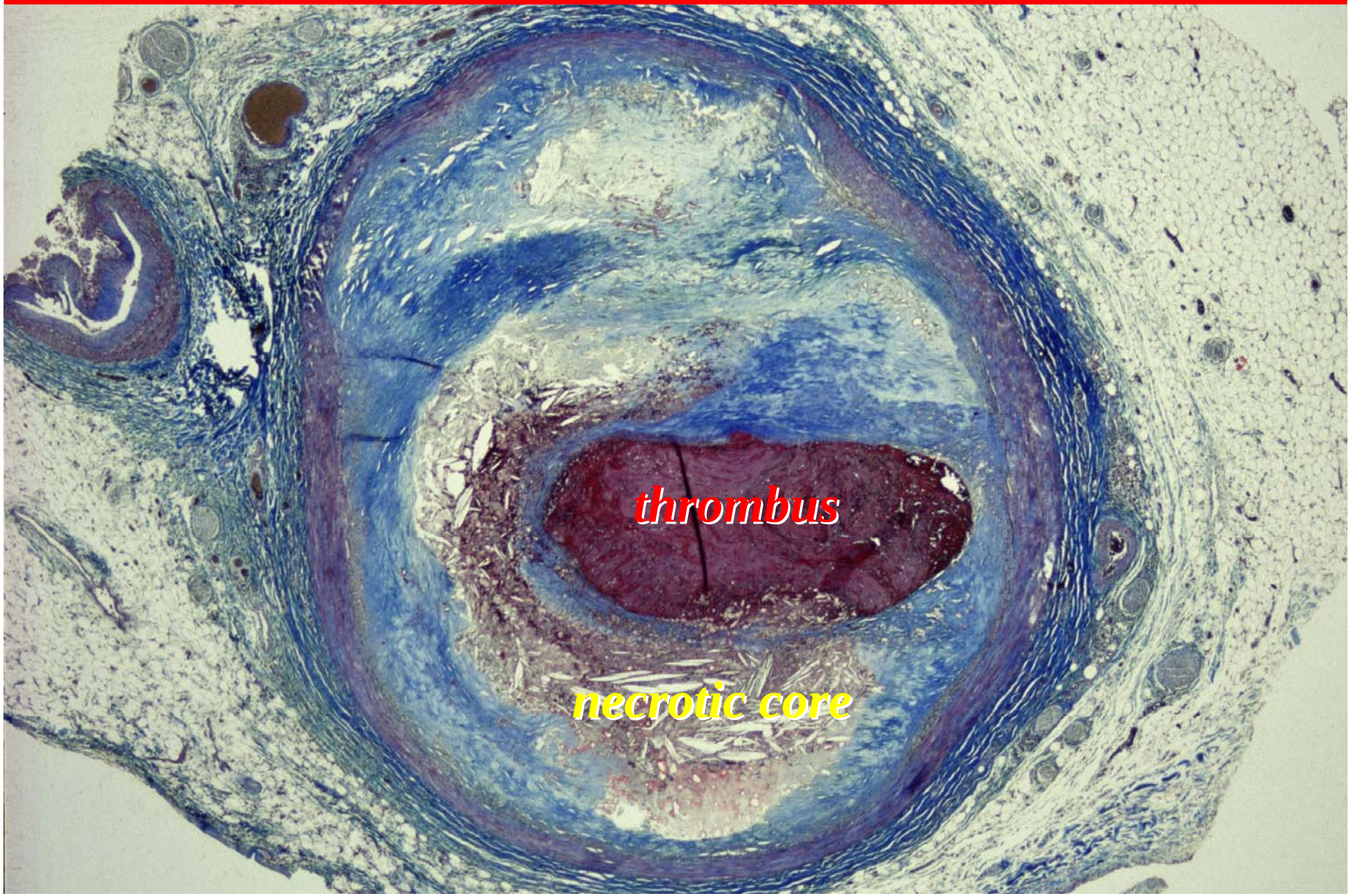
Plaque component	TCFA+RP relationship	
	predictor	bivariate
• plaque size	+	+
• necrotic core size	+	+
• inflammation (macr)	+	-

Conclusion: ***Plaque area and necrotic core determine the likelihood of plaque rupture***

Plaque rupture: role of inflammation



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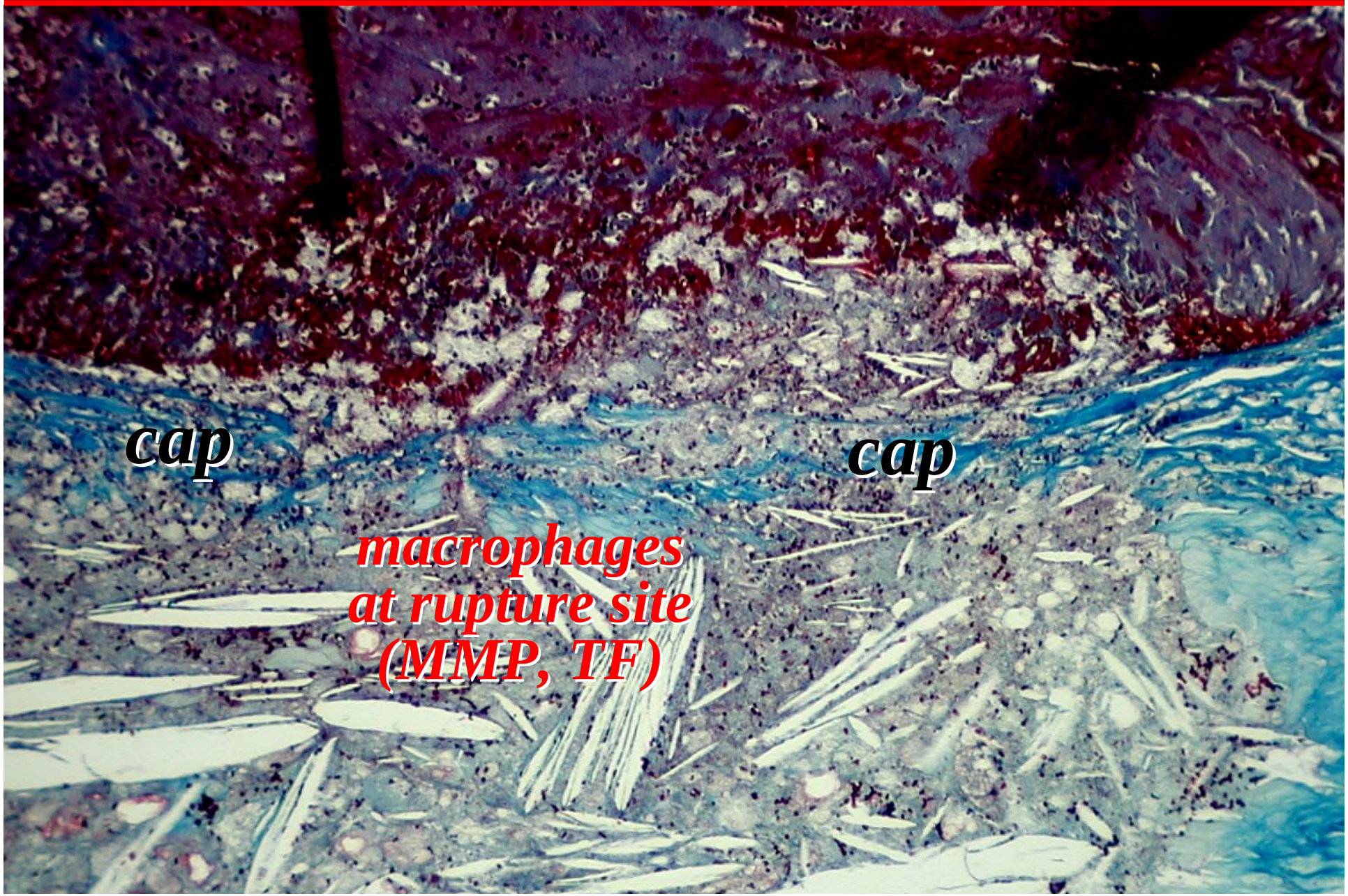

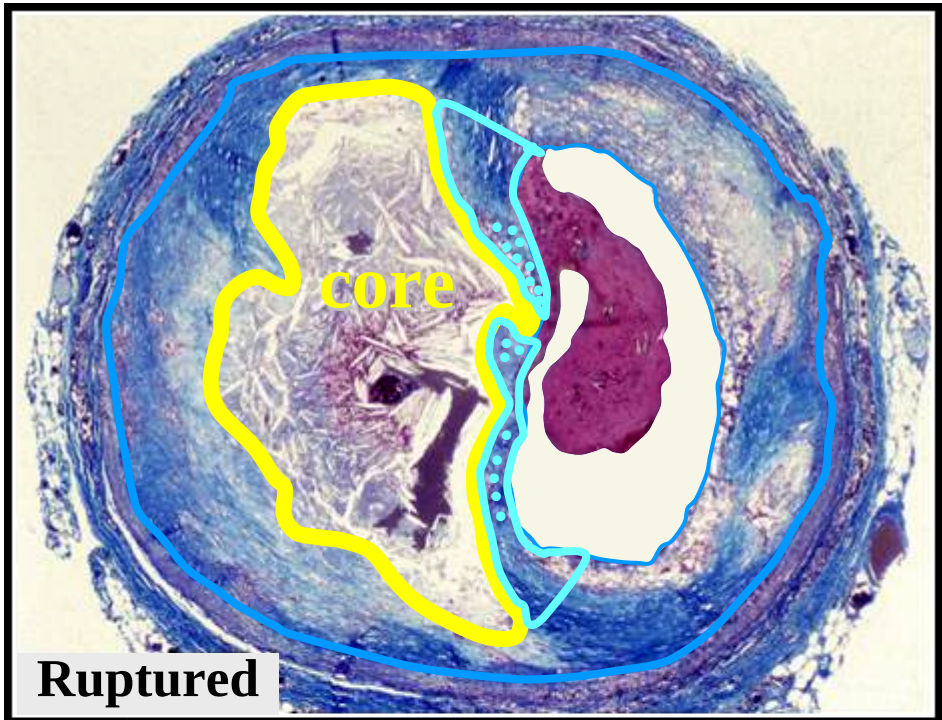

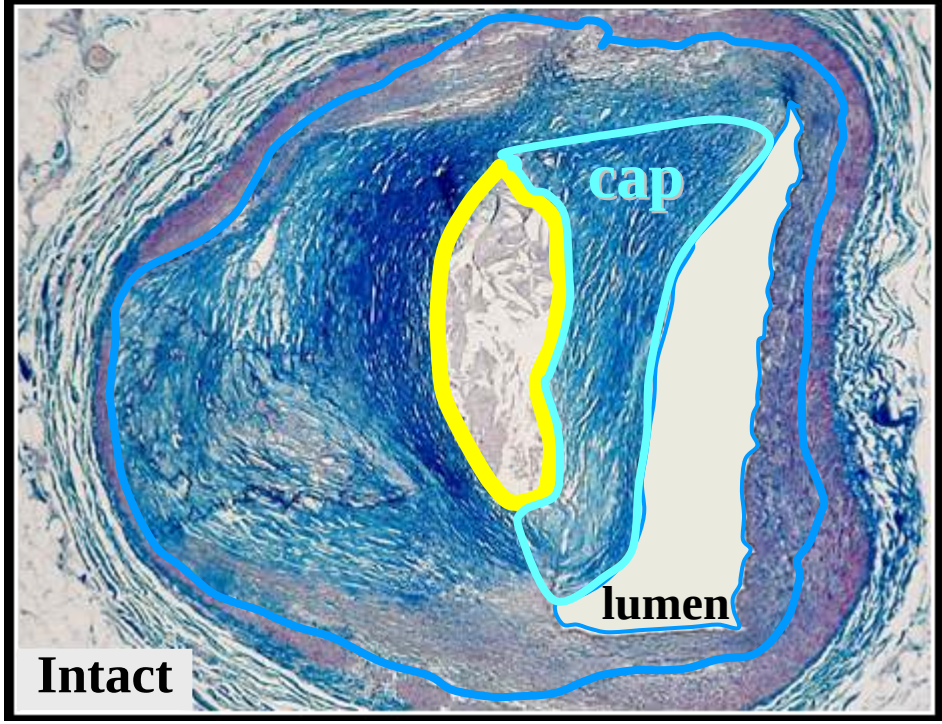

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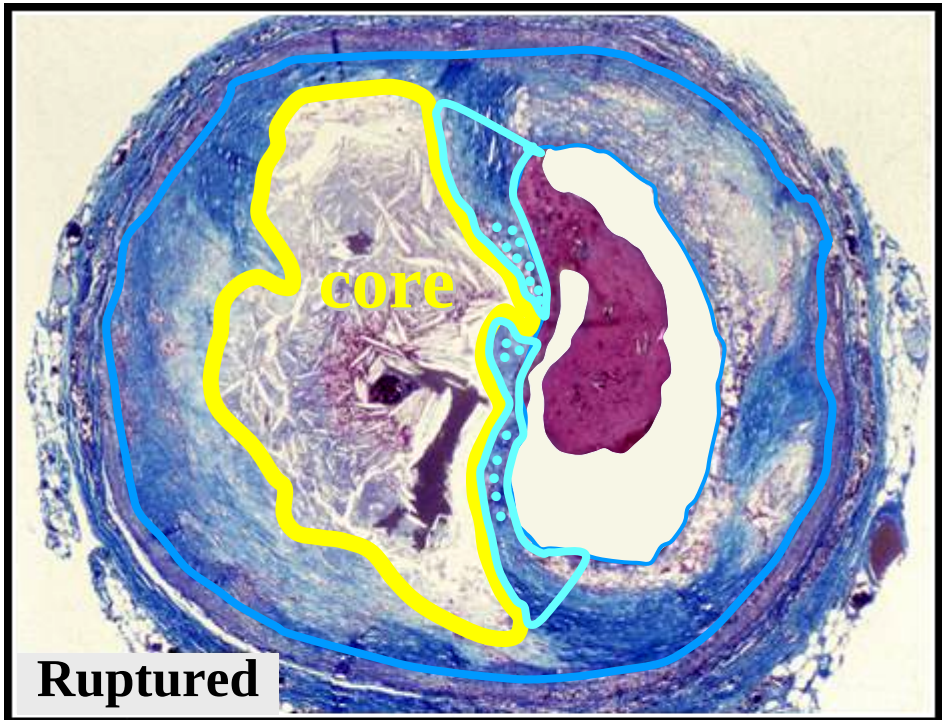

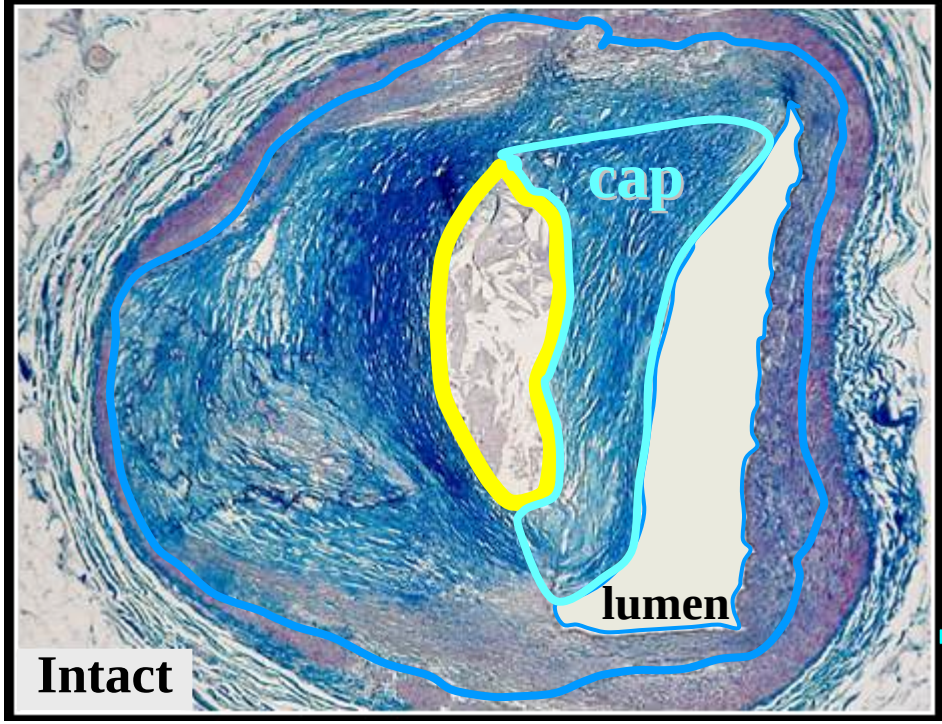

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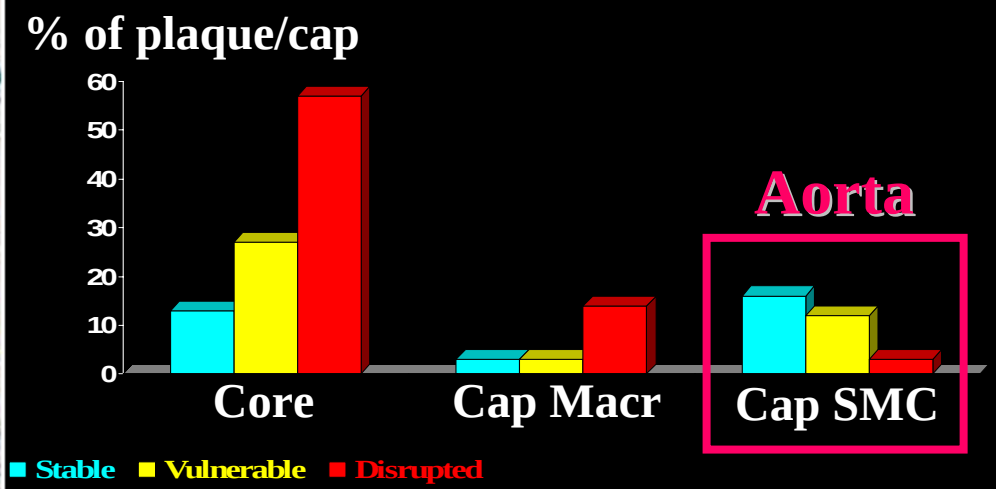

Davies et al. Br Heart J 1993;69:377-81

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MINI-SYMPOSIUM

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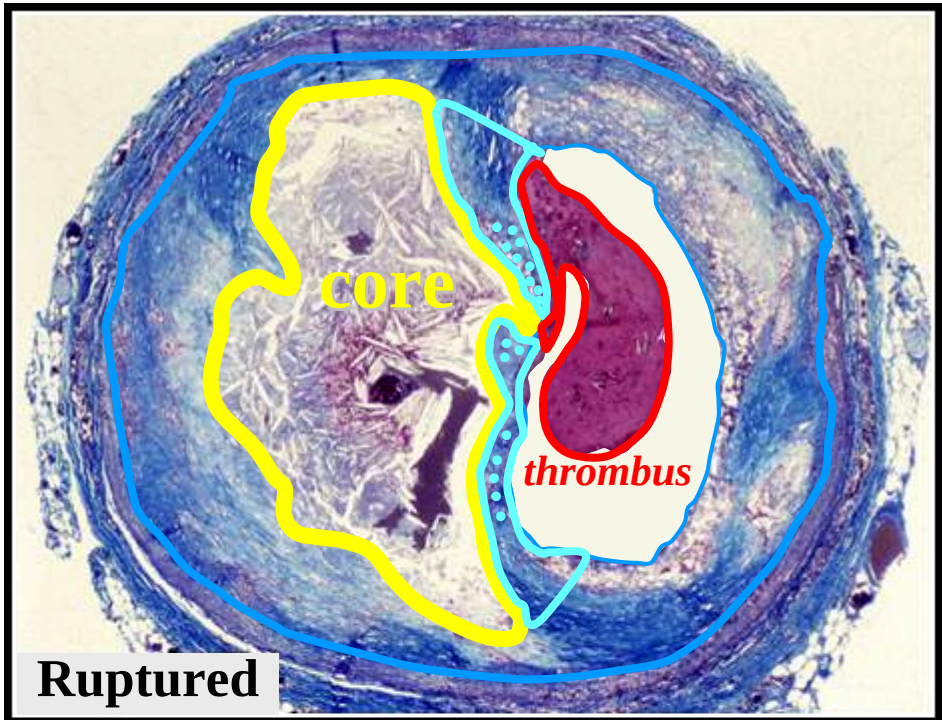

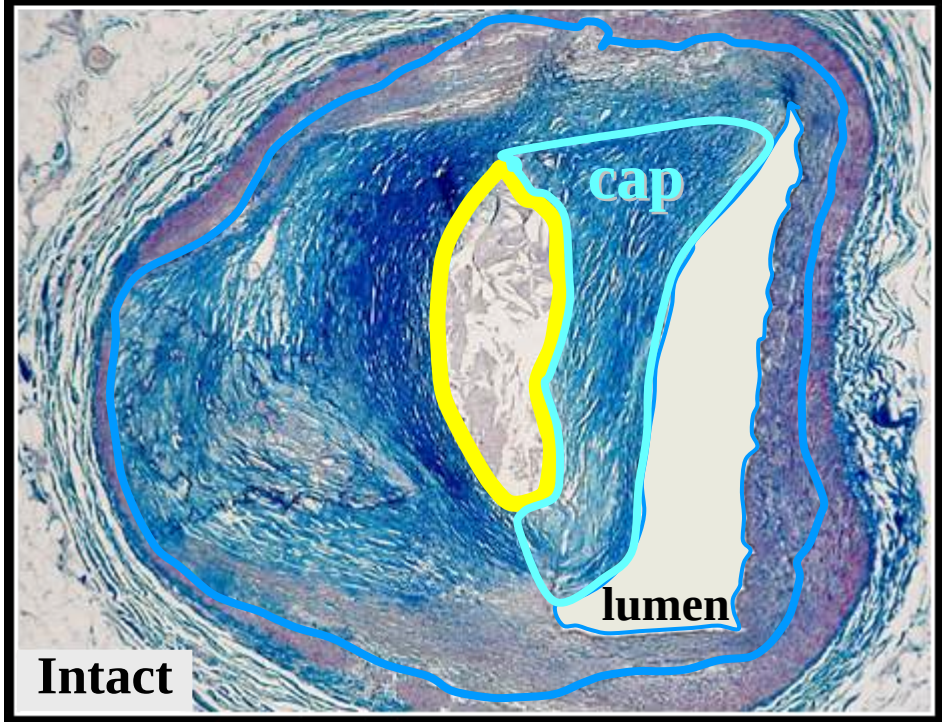

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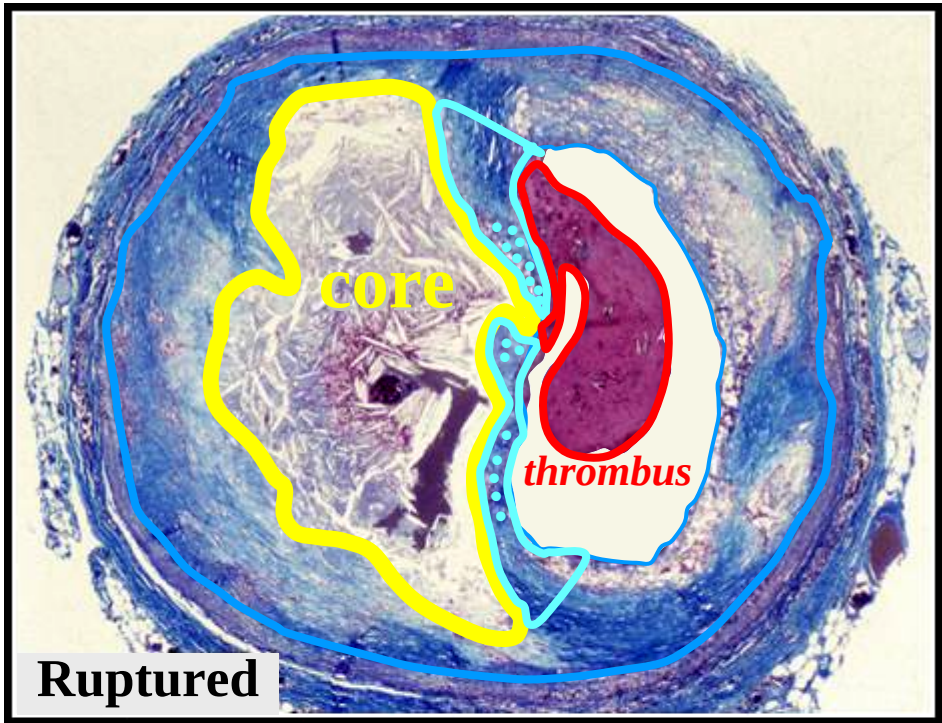
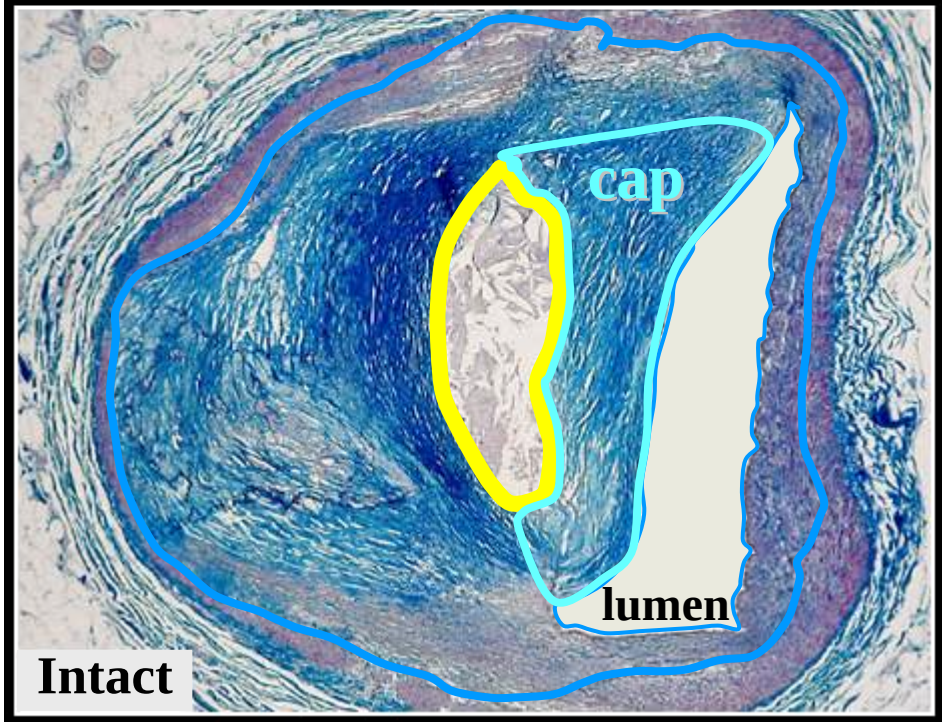
  - ***thrombus*↑**

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
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- **Expansive remodeling↑**

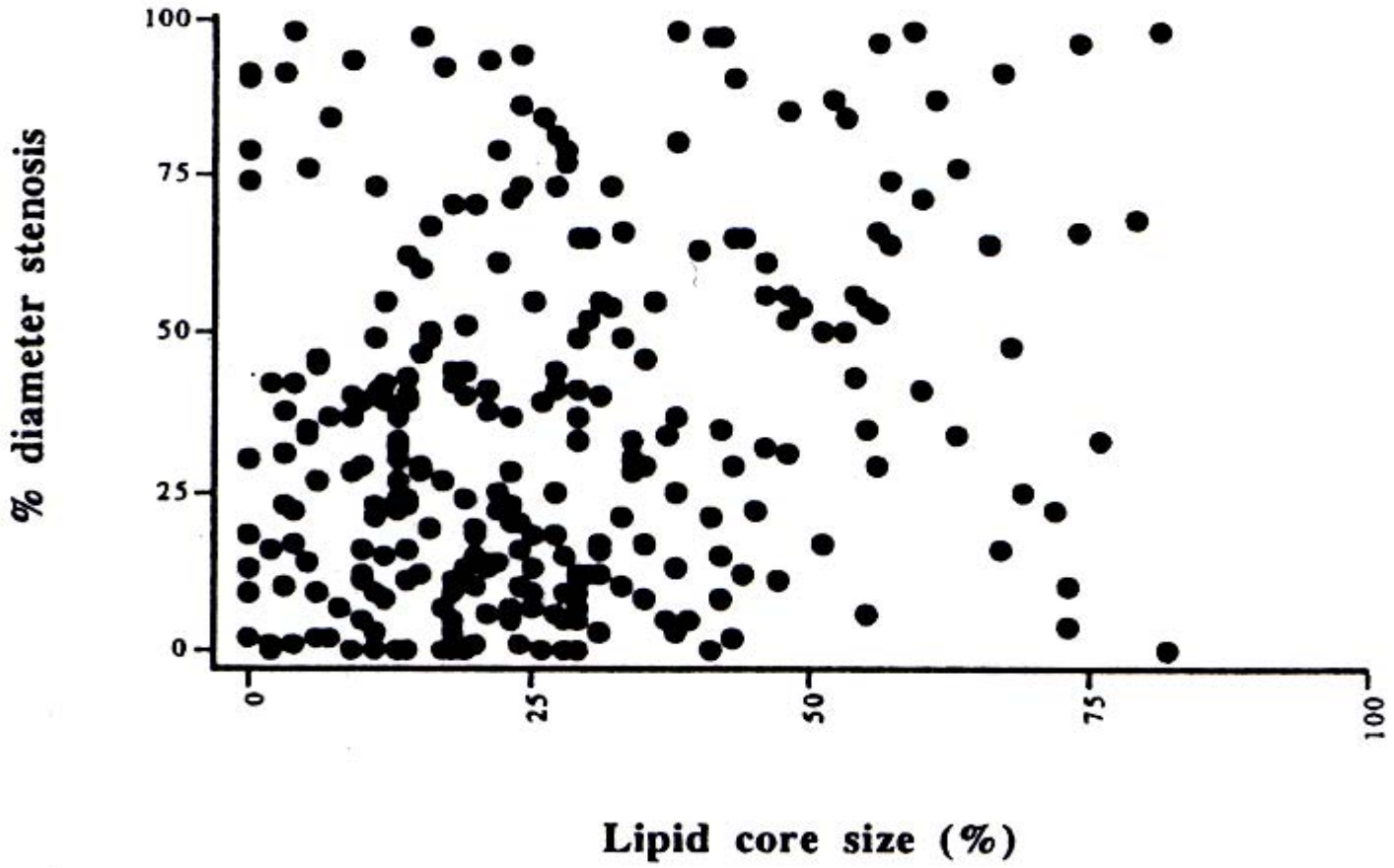
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

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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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.

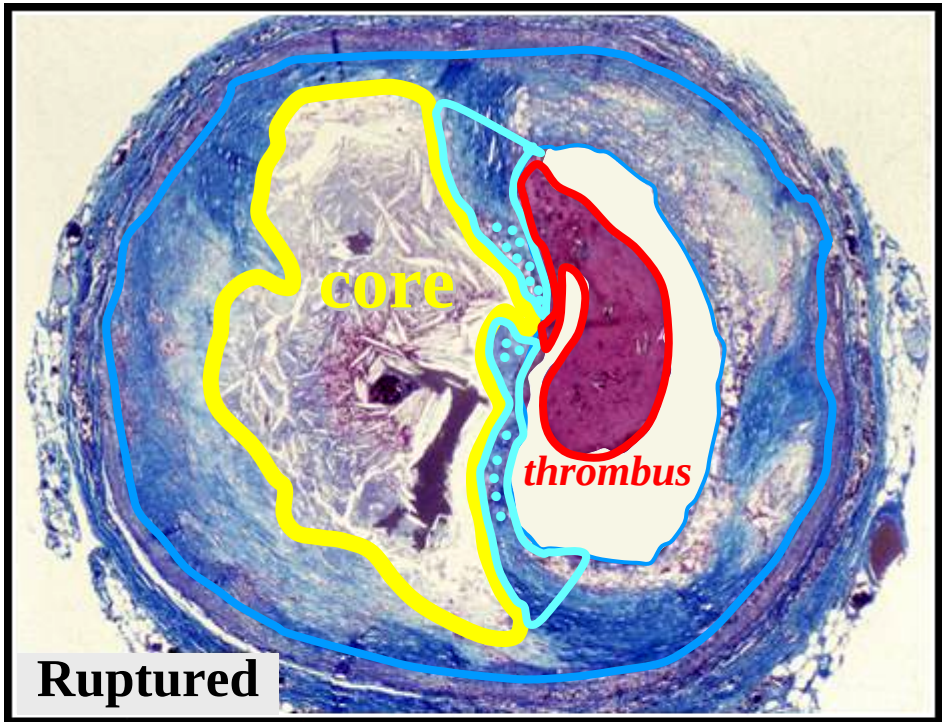
Background. Plaque rupture often occurs at sites with minor luminal stenosis and has retrospectively been characterized by colocalization of inflammatory cells. Recent studies have demonstrated that luminal narrowing is related with the mode of atherosclerotic arterial remodeling.

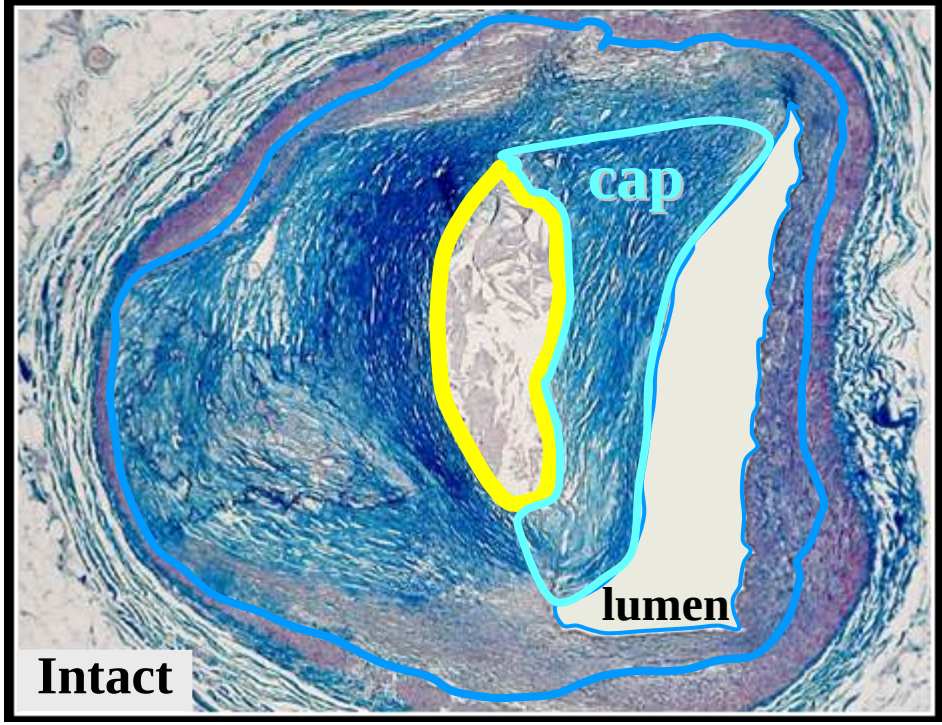
Methods. We obtained 1,521 cross section slices at regular intervals from 50 atherosclerotic femoral arteries. Per artery, the slices with the largest and smallest lumen area, vessel area and plaque area were selected for staining on the presence of macrophages (CD68), T-lymphocytes (CD45RO), smooth 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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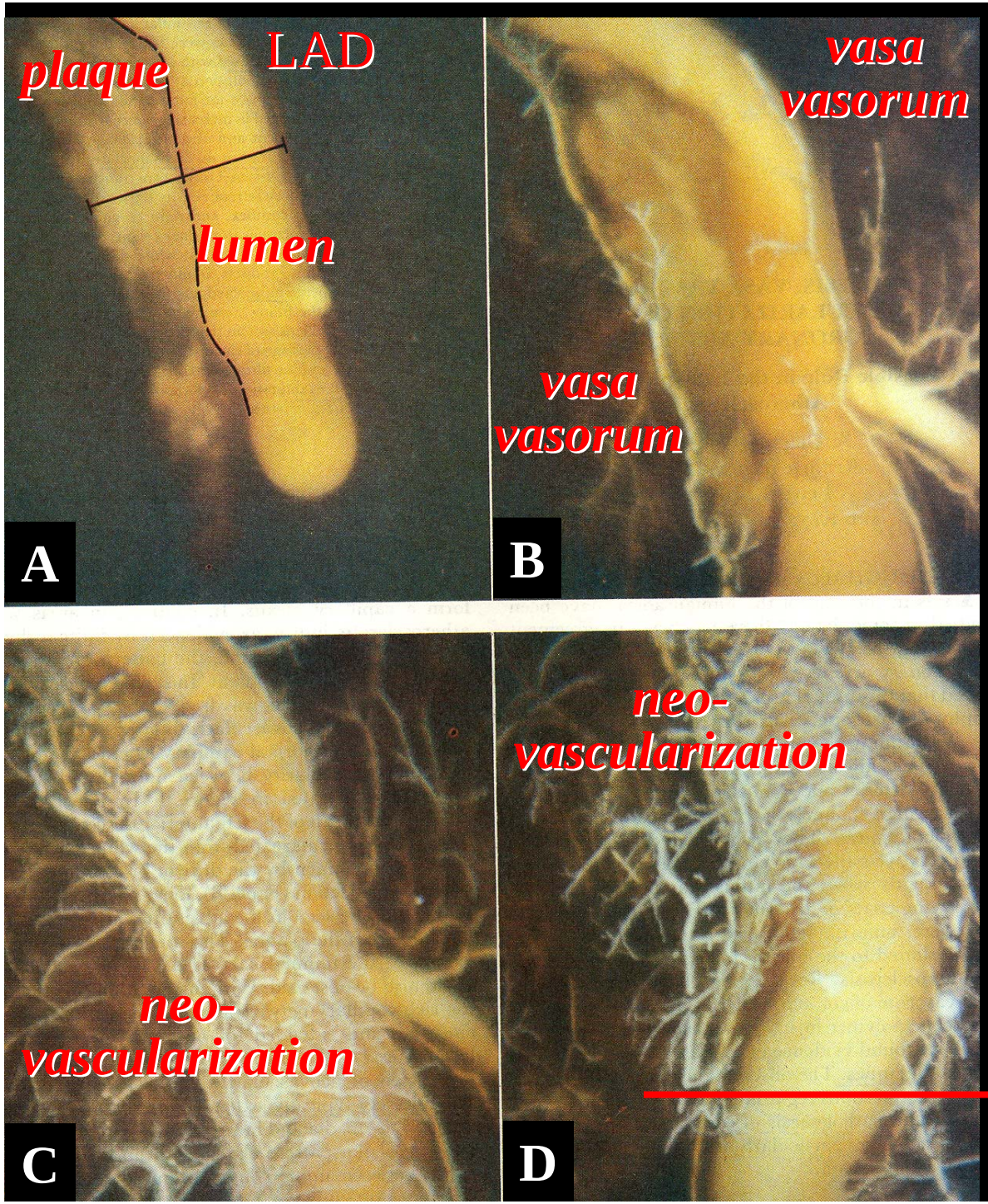
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*



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☆

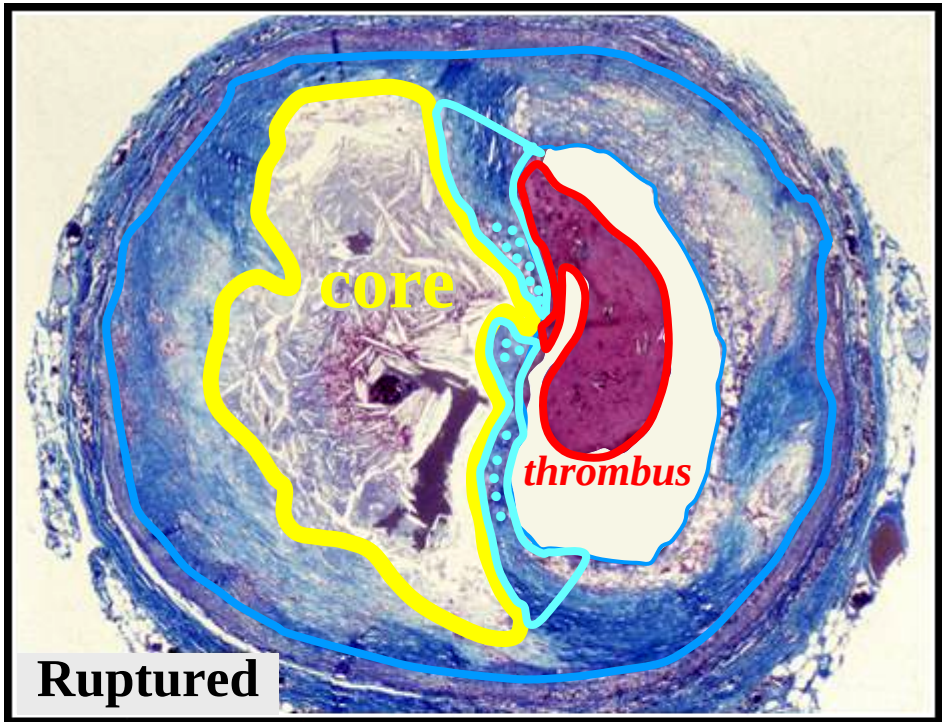
Toshiaki Nakano MD[a,b], Yutaka Nakashima MD, PhD[a], Yoshikazu Yonemitsu MD, PhD, FAHA[a,*], Shinji Sumiyoshi MD[a], Young-Xiang Chen PhD[a], Yuri Akishima MD[c], Toshiharu Ishii MD, PhD[c], Mitsuo Iida MD, PhD[b], Katsuo Sueishi MD, PhD[a]

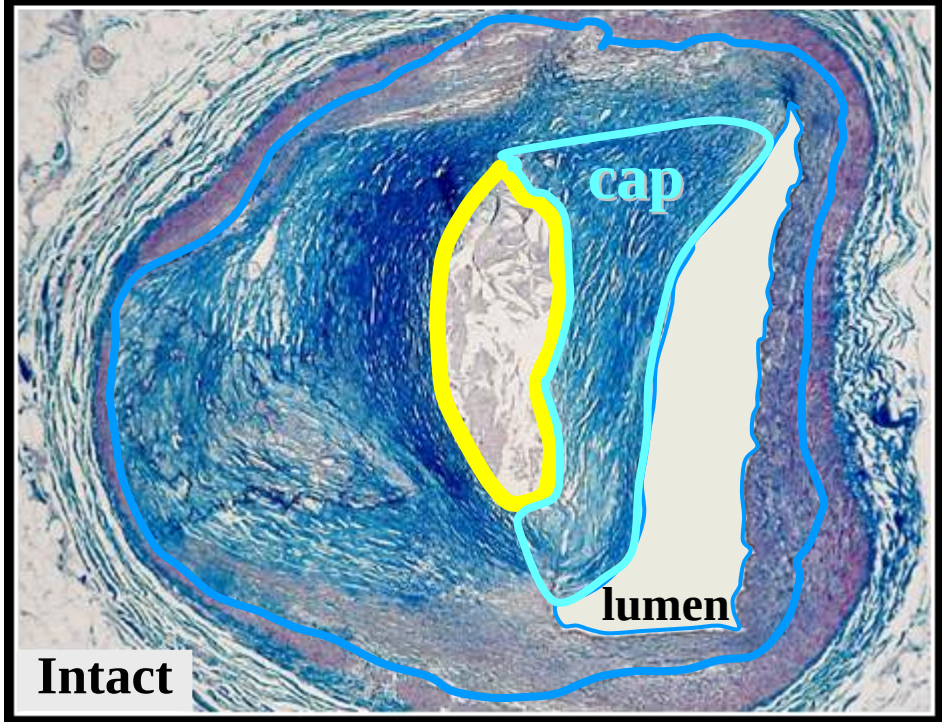
[a]*Division of Pathophysiological and Experimental Pathology, Department of Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[b]*Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan*
[c]*Department 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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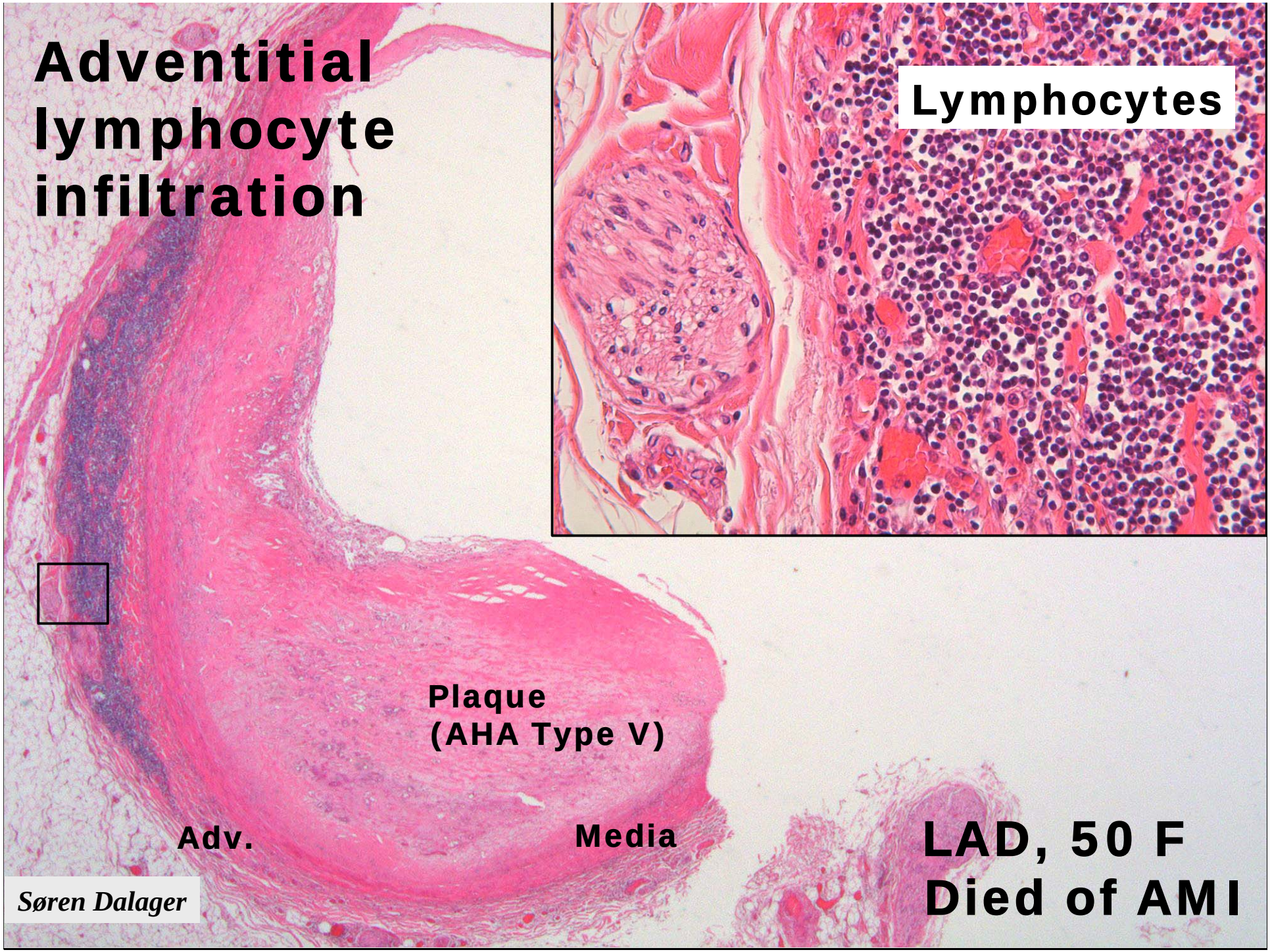
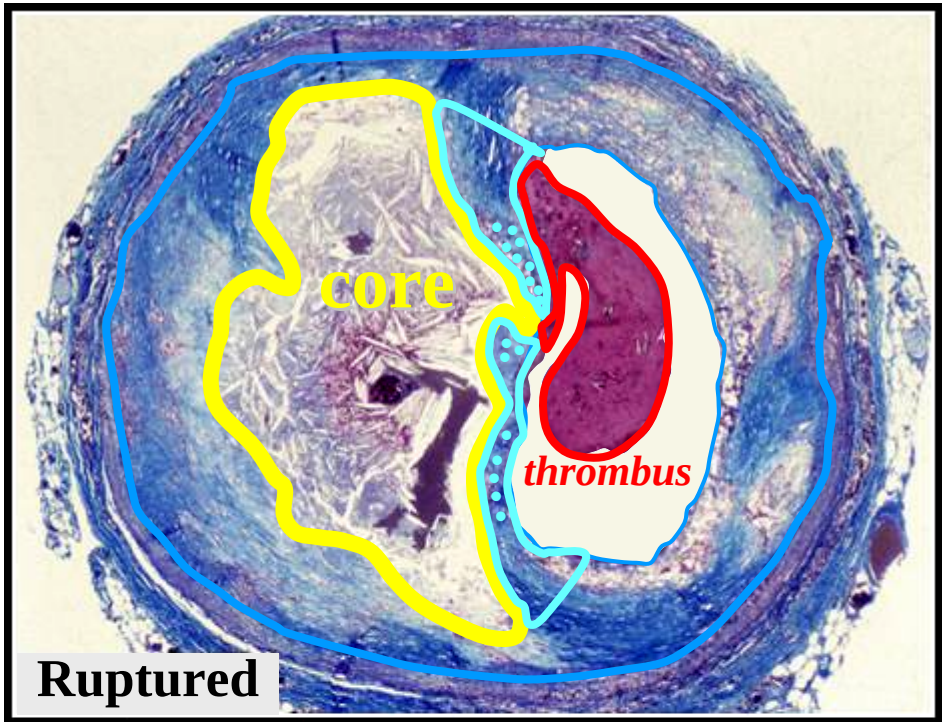
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

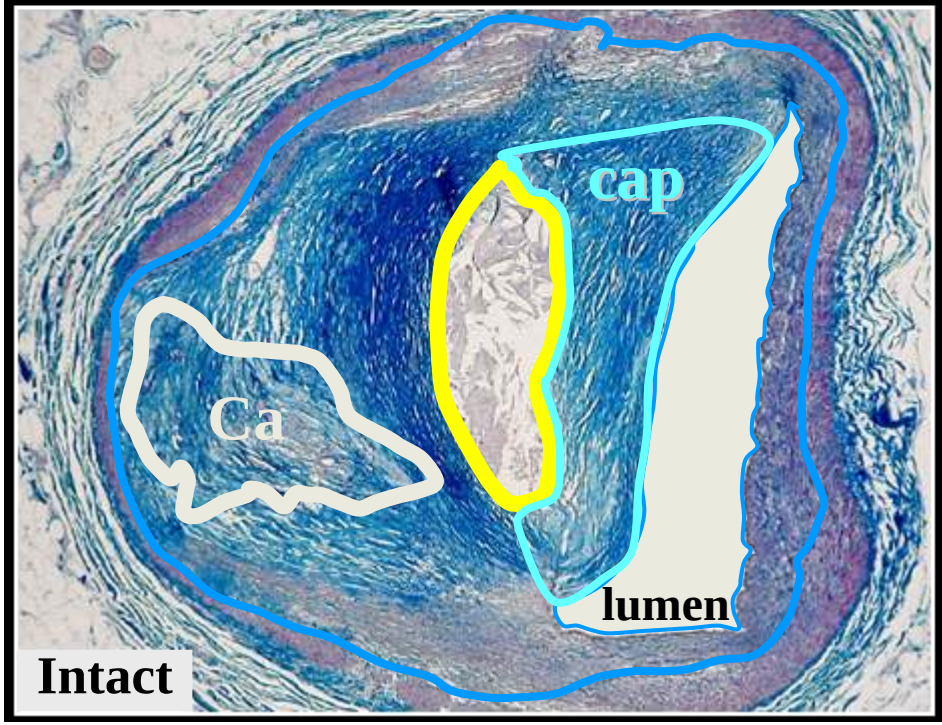

Adventitial lymphocyte infiltration
Lymphocytes
Plaque (AHA Type V)
Adv.
Media
LAD, 50 F
Died of AMI
Søren Dalager

[294] Adventitial Inflammation Reflects Intimal Coronary Atherosclerotic Plaque Morphology

Allen P Burke, Bob Kutys, Frank Kolodgie, Renu Virmani, CVPath, Gaithersburg, MD

The role of adventitial inflammation in coronary atherosclerosis is not clear. The relationship between adventitial inflammation, plaque type and culprit plaque morphology has not been studied in depth. We studied semiserial sections of coronary arteries at autopsy from patients dying with severe coronary disease, 81 men (age 50 Â± 12 years) and 14 women (age 52 Â± 13 years). Lesions were classified at 3-5 mm segments according to modified AHA criteria. Culprit plaque morphology was assessed as acute plaque rupture (n=44), acute plaque erosion (n=12), and stable plaque (n=39). Inflammation was assessed at every 5 mm interval and graded semiquantiatively: 0 (no inflammation), 1+ (scattered lymphocytes without aggregates), 2+ aggregates of lymphocytes > 25 cells in 1 quadrant of the adventitia; 3+ aggregates in 2 quadrants; and 4+ aggregates in 3-4 quadrants. By culprit plaque morphology, mean adventitial inflammation score was 0.53 Â± .05 in plaque erosion, .50 Â± .22 in plaque rupture, and .28 Â± .01 stable plaque (p<. 0001 vs. rupture and erosion). By univariate analysis of individual plaques, inflammation was correlated with percent stenosis (p0.2). Mean adventitial inflammation score was 1.1 Â± 0.1 for acute ruptures, 1.1 Â± 0.2 for erosions, 0.9 Â± 0.3 for plaque fissures, 0.9 Â± 0.3 for thin cap atheroma, and 0.7 Â± .07 for fibroatheromas with hemorrhage, 0.6 Â ± .04 for fibroatheromas with late cores, and < 0.5 for fibrous plaques, pathologic intimal thickening, fatty streaks, and fibrocalcific plaques. Hemorrhage into late core, rupture, erosion, and thin caps all had greater adventitial inflammation independent of percent stenosis compared to plaques without these characteristics (p<.0001). Features associated with plaque instability are associated with significantly greater degrees of adventitial inflammation. Further study is required to determine the nature of the association between intimal and adventitial inflammation.





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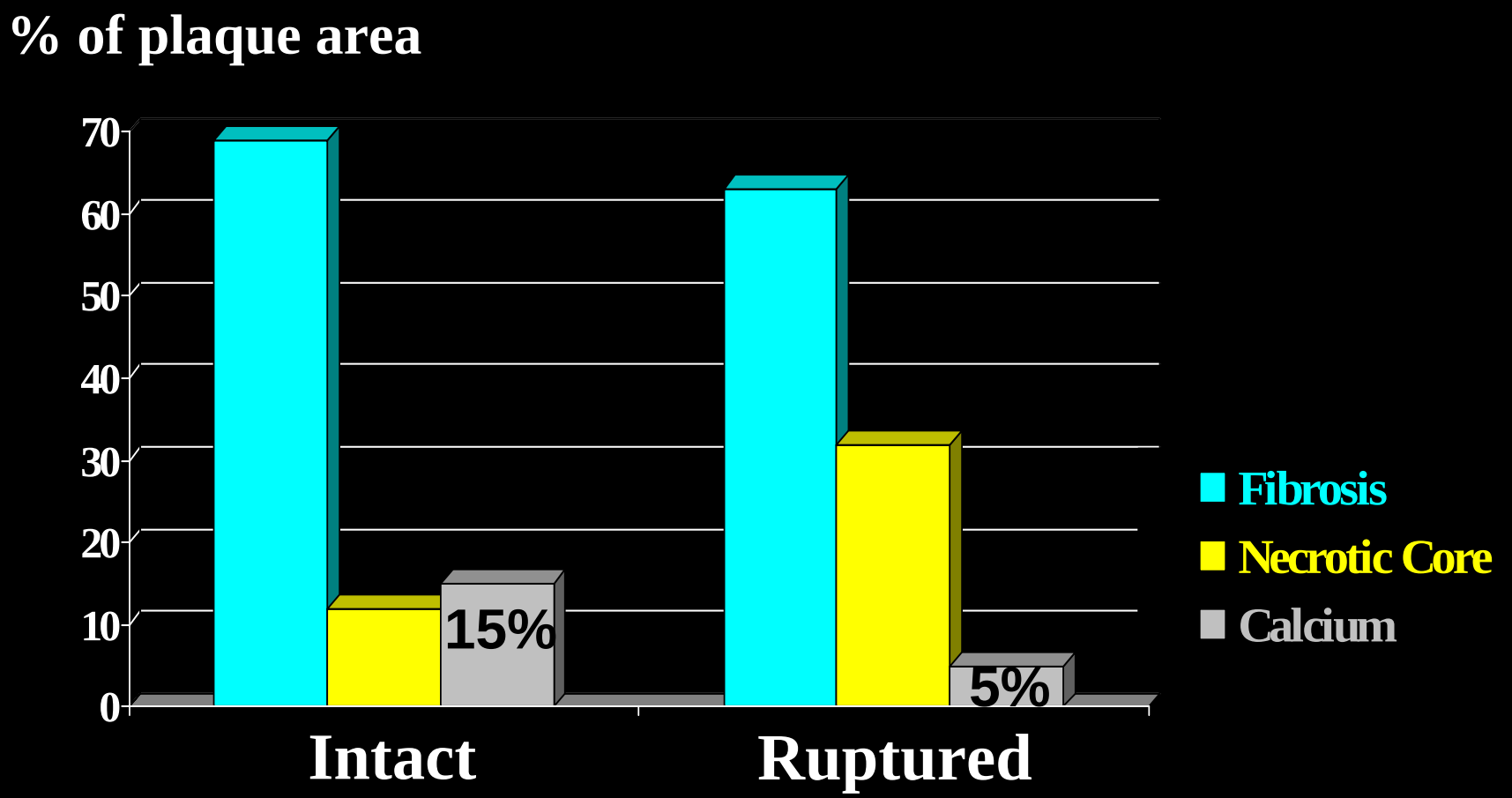
- **Calcification↓ & *spotty***

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

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

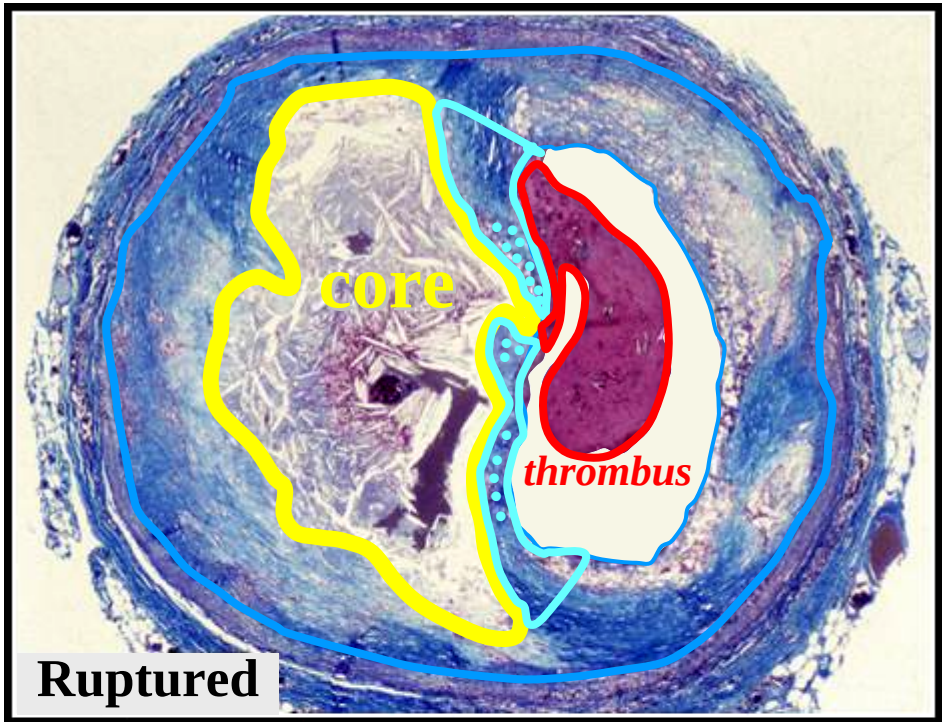
An Intravascular Ultrasound Study

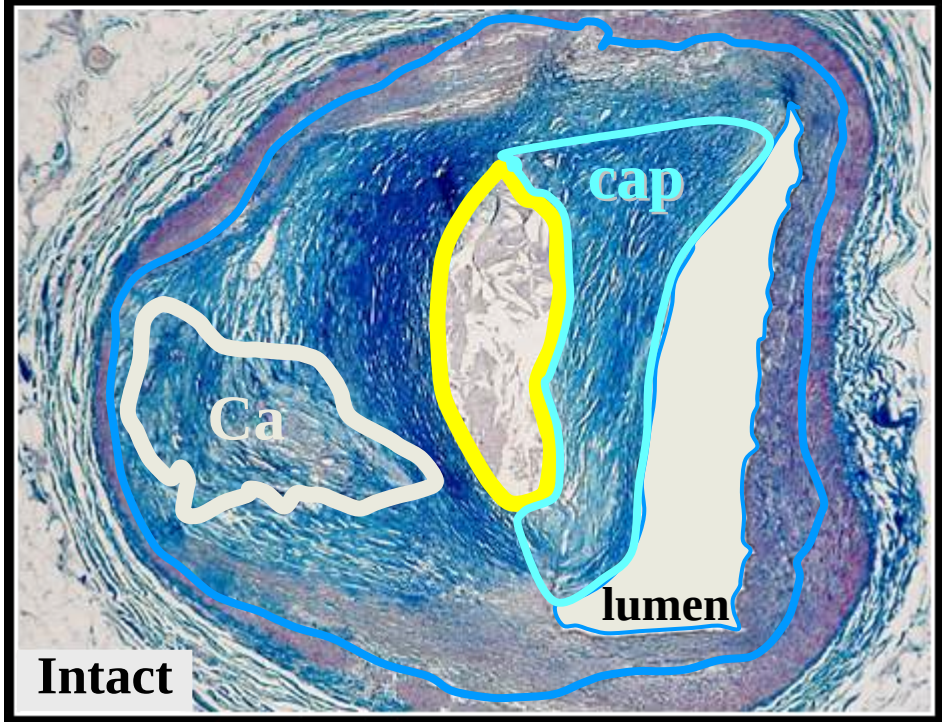
Shoichi Ehara, MD; Yoshiki Kobayashi, MD; Minoru Yoshiyama, MD; Kenei Shimada, MD; Yoshihisa Shimada, MD; Daiju Fukuda, MD; Yasuhiro Nakamura, MD; Hajime Yamashita, MD; Hiroyuki Yamagishi, MD; Kazuhide Takeuchi, MD; Takahiko Naruko, MD; Kazuo Haze, MD; Anton E. Becker, MD; Junichi Yoshikawa, MD; Makiko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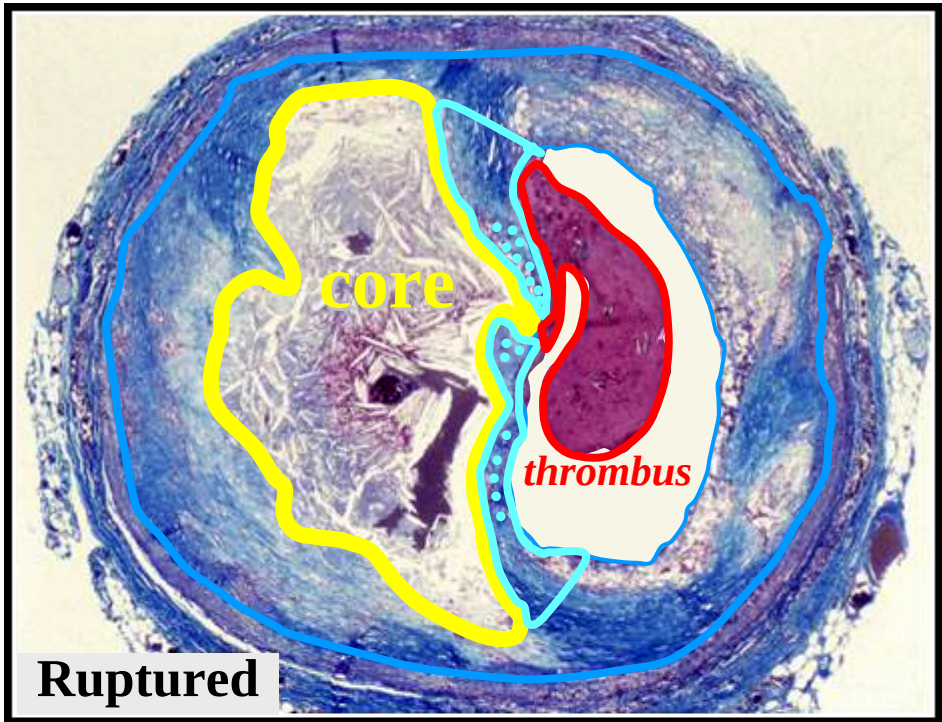

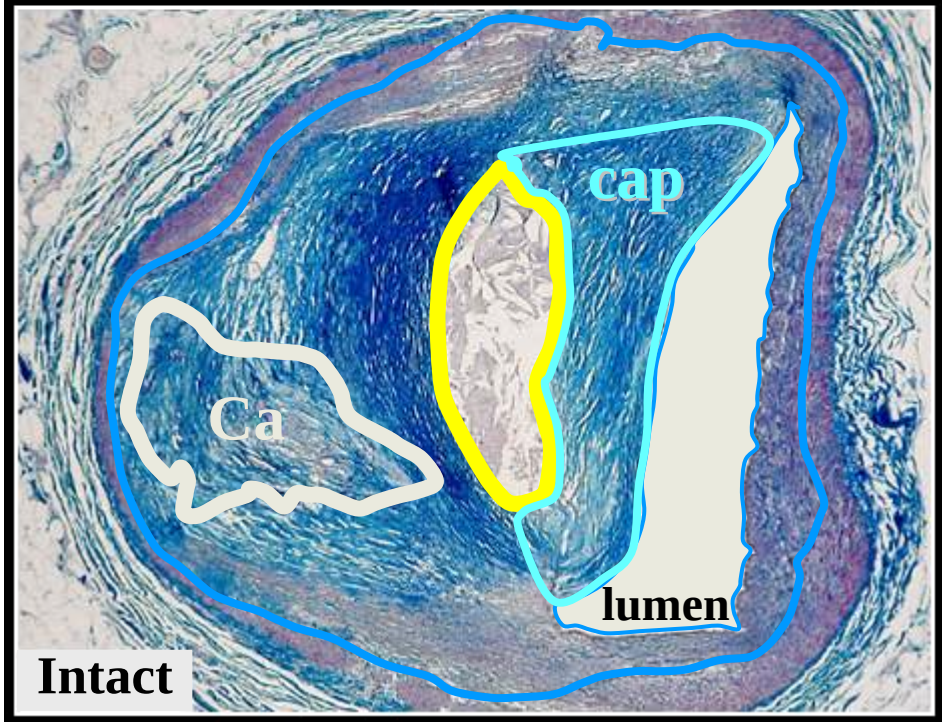

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targets for imaging

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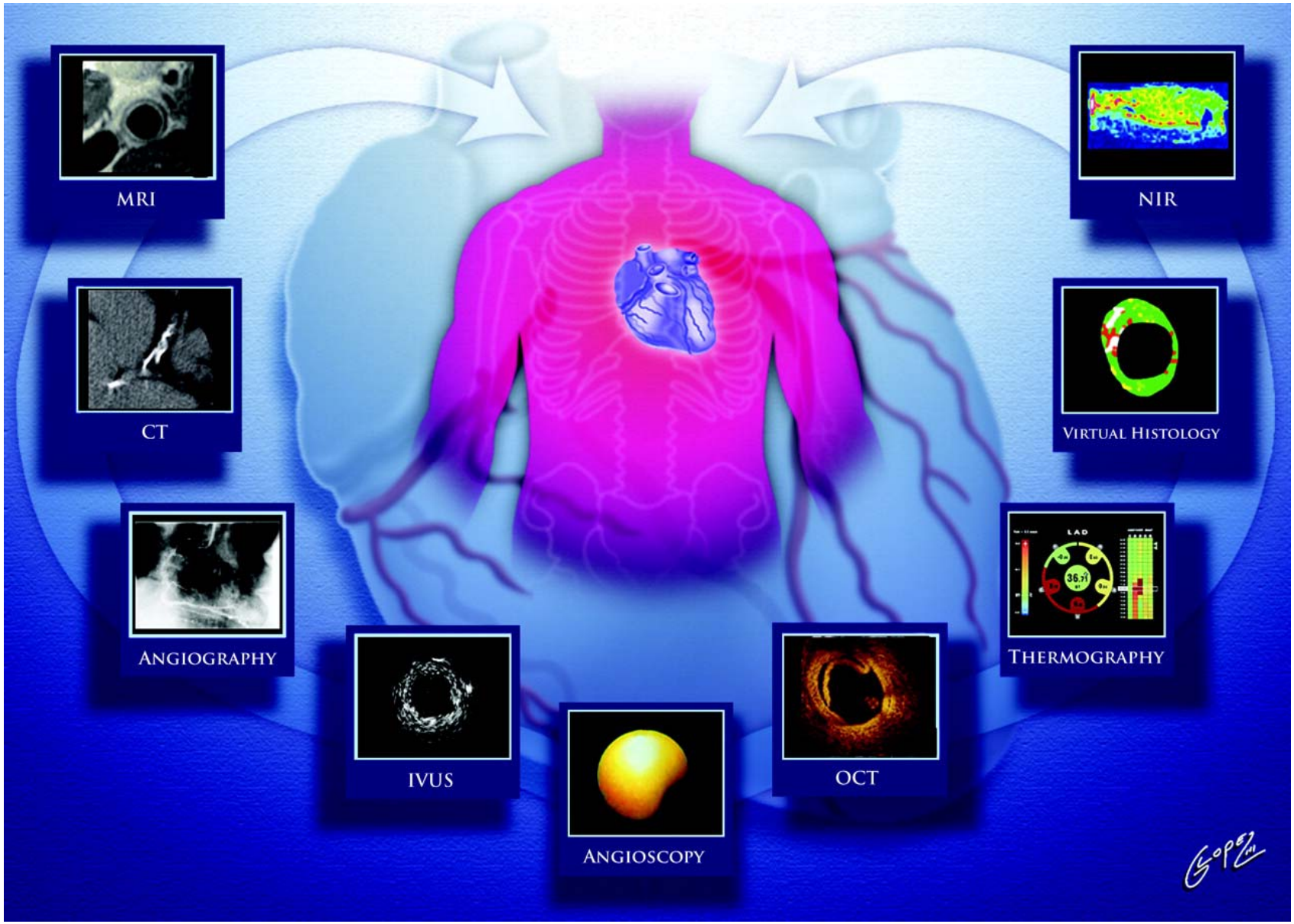
**Kolodgie, Virmani et al. Heart 2004;90:1385-91*

Finding Vulnerable Atherosclerotic Plaques

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



Detection and Treatment of Vulnerable Plaques and Vulnerable Patients

Novel Approaches to Prevention of Coronary Events

Sergio Waxman, MD; Fumiyuki Ishibashi, MD; James E. Muller, MD

There is growing interest in the possibility that identification and treatment of vulnerable plaques and vulnerable patients can enhance the progress made against coronary artery disease. Innovations in medical therapy—statins and other agents—and novel interventional cardiology techniques—eg, drug-eluting stents—have significantly decreased the morbidity and mortality caused by coronary atherosclerosis. However, coronary events continue to be the leading cause of death in the United States, accounting for >479 000 deaths (1 in 5) in 2003.[1]

Improved preventive measures are needed because, for many individuals, sudden coronary death is the first sign of the disorder. And even those who survive an acute coronary syndrome remain at high risk. After successful treatment of the initial culprit lesion by a percutaneous coronary intervention (PCI), the risk of a coronary event from a new lesion is ≈10% in the following year and 5% in each of the subsequent 4 years[2,3] (Figure 1).

These substantial levels of ongoing morbidity and mortality have led to heightened interest in new methods to prevent coronary events. For primary prevention, the effort has focused on plasma markers and noninvasive testing to identify vulnerable individuals. For secondary prevention, interest has focused on vulnerable patients and the vulnerable plaques they may possess that might be identified and treated during the catheterization for their initial event.

additional 30% to 40% of events, particularly in younger women, occur at proteoglycan-rich erosion sites.[11]

Most vulnerable plaque detection devices in development are designed to detect TCFAs. Because these devices will not detect erosion sites in advance, their sensitivity for predicting cardiac events will be limited. Specificity of a TCFA detector for predicting plaque rupture will also be limited because not all TCFAs will rupture, nor will all ruptures lead to a cardiac event.

Hence, the term "vulnerable patient" has been introduced to indicate an individual with a high likelihood of experiencing a cardiac event. Such a patient is likely to have vulnerable blood (prone to thrombosis), vulnerable myocardium (prone to arrhythmia), and ≥1 vulnerable plaque. To enhance primary prevention, a search is underway for novel methods to identify vulnerable patients.[7] Because a vulnerable plaque is likely to be the root cause of vulnerability of the patient and may be amenable to systemic or local therapy, the search for the vulnerable patient of necessity is closely linked to efforts to identify vulnerable plaques.

Systemic and Focal Manifestations of Atherosclerosis

Circulation 2006;114:2390-2411

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TCFA = thin-cap fibroatheroma (the most frequent VP)

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Novel Approaches to Prevention of Coronary Events

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