Coronary Artery Disease: Predictors of Recurrent Clinical Events Following Coronary Revascularization Procedures

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Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
October 16, 2003

This is to acknowledge that Dr. Cigarroa has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Cigarroa will not be discussing off-label uses in his presentation.

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Clinical and Research Interests:

1. Evaluation and Treatment of Coronary Artery Disease
2. Effects of Cocaine on Coronary Artery Disease
3. Valvular Heart Disease

Epidemiology:

Coronary heart disease (CHD) accounts for approximately 500,000 deaths annually in the United States alone[1]. For an individual, the lifetime risk of developing CHD after the age of 40 for men is 49% and for women is 32%[2]. Currently, 12.6 million Americans complain of angina pectoris or a prior myocardial infarction. Each year 650,000 Americans experience their first myocardial infarction, while 450,000 Americans experience a recurrent myocardial infarction. Given these statistics, considerable effort to reduce the incidence of myocardial infarction and or cardiovascular death is focused on risk stratification based on traditional risk factors including serum cholesterol, hypertension, smoking history, diabetes mellitus, and prior myocardial infarction. In addition, a considerable effort is made to identify patients with epicardial coronary artery disease in order to perform cardiac catheterization and percutaneous or surgical revascularization to reduce the frequency of angina and/or to decrease mortality in those with multivessel coronary artery disease and depressed left ventricular systolic function[3]. For patients undergoing revascularization, there is often a misperception, by physicians and patients, that these patients are now "cured" and are at a low risk for future myocardial infarction or death. This perception is incorrect. These patients are at the highest risk of coronary artery disease progression, recurrent angina, future myocardial infarction, and cardiovascular death.

Percutaneous coronary interventions and coronary artery bypass grafting are performed on vessels with significant angiographic stenoses and are effective in reducing the

frequency of angina. In the year 2000, there were 1 million percutaneous coronary revascularization procedures and 519,000 coronary artery bypass procedures performed in the United States[1]. Although performed with the intention of reducing the rate of future myocardial infarctions, the risk of subsequent myocardial infarctions remains high. The identification of these patients with symptomatic coronary artery disease treated with a revascularization procedure should highlight patients in the highest risk category of future adverse cardiovascular events.

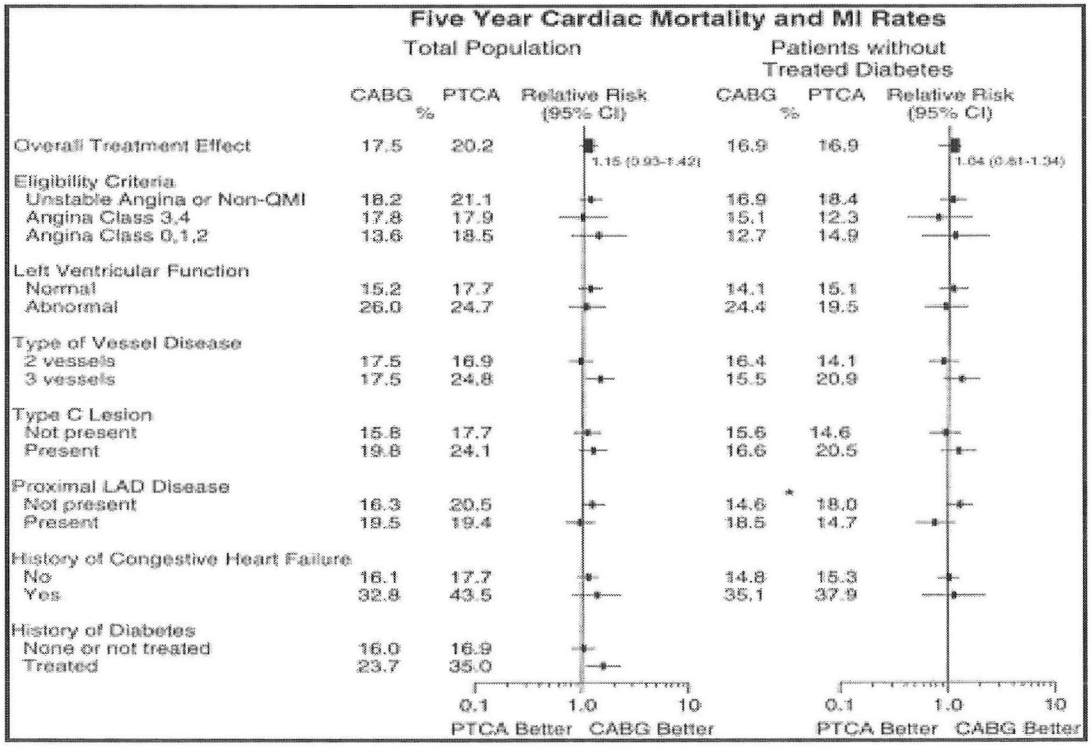
Probability of Adverse Events Following Coronary Revascularization:

Various randomized clinical trials comparing percutaneous coronary intervention versus surgical coronary revascularization have been performed during the last decade including EAST, ERACI II, GABI, CABRI, RITA, ARTS, and BARI trials[4-10]. These recent studies provide insight into the history of patients that have undergone coronary arterial revascularization. Today, I will focus on: (a) the probability of recurrent adverse major clinical events including myocardial infarction and death following coronary revascularization and (b) possible explanations for recurrent event rates.

The Bypass Angioplasty Revascularization Investigation (BARI) Randomized Trial was performed in 1,829 patients to investigate the efficacy of percutaneous versus surgical revascularization on long term outcomes in patients with multivessel coronary artery disease amenable to PTCA or bypass surgery. Five year combined cardiac mortality and myocardial infarction rates were similar for the percutaneous and surgical

revascularization rates patients (17% in both groups except those with treated diabetes mellitus (35% vs 24%)[9]. Several factors including diabetes mellitus, depressed left ventricular systolic function, and a history of congestive heart failure identified patients at increased risk of adverse cardiac events, irrespective of type of revascularization procedure (See Figure 1). In addition, the occurrence of a postprocedure myocardial infarction increased the probability of death by a relative risk of 10.

Figure 1. BARI: Five Year Cardiac Mortality and Myocardial Infarction Rates



These statistics have also been confirmed by the Arterial Revascularization Therapies Study Group (ARTS trial) which compared stenting versus coronary artery bypass grafting for patients with multivessel coronary artery disease. At one year, the probability of death or myocardial infarction for patients treated with stents was 9% and for patients treated with coronary artery bypass grafting was 8%[10]. Thus, despite successful

revascularization, these patients remain at high risk for myocardial infarction and death. Therefore, one must couple a strategy of coronary revascularization with aggressive medical therapies including antiplatelet therapy, lipid-lowering therapy, ace-inhibitors, and beta blockers (for select patients)[11-14].

The high rate of future myocardial infarctions and/or death following successful coronary revascularization has led us to challenge the notion that revascularization of severe, focal coronary lesions reduces the progression of CHD and the associated risk of future myocardial infarction and/or cardiovascular death. In fact, coronary revascularization does not reduce the risk of myocardial infarction (except in patients with acute coronary syndromes) and only reduces the risk of death in patients with multivessel coronary artery disease with depressed left ventricular function[3].

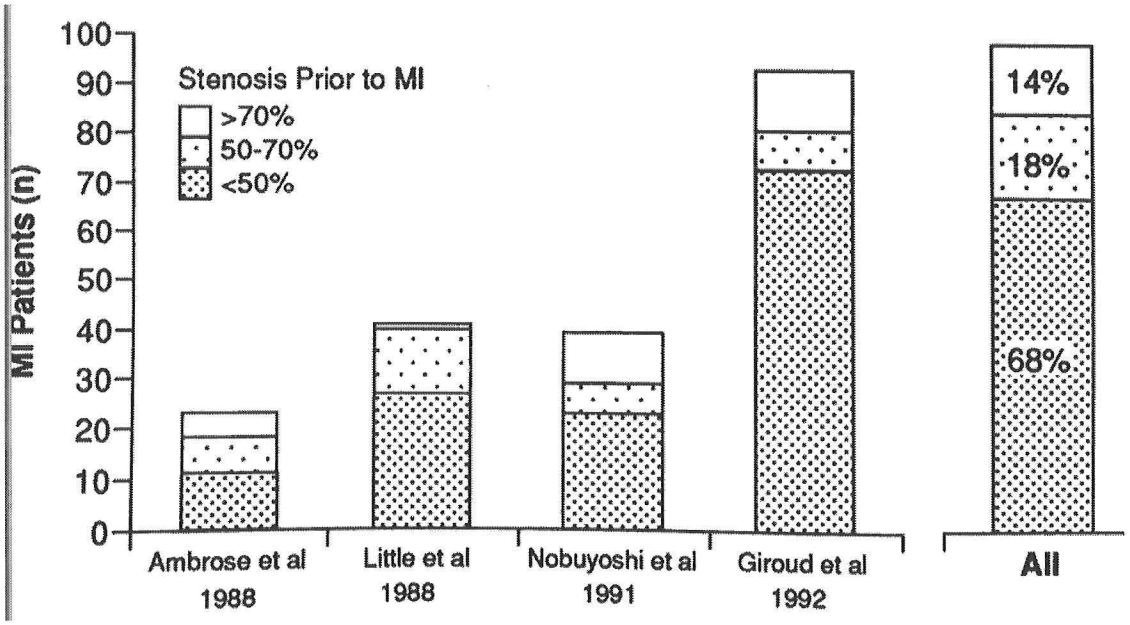
In order to understand why coronary revascularization does not reduce the progression of coronary artery disease, one must first understand how coronary arteries adapt to the onset of atherosclerosis and how coronary lesions progress and or cause myocardial infarctions.

Myocardial Infarction

The disruption of an atherosclerotic plaque with superimposed thrombus formation is the most common cause of ST segment elevation myocardial infarction[15, 16]. In 1980, DeWood and colleagues demonstrated the prevalence of coronary occlusion during the first 24 hours following an acute myocardial infarction[17]. Of patients presenting within the first 4 hours of symptom onset of their acute myocardial infarction, 89% had an occluded infarct related artery. Over the subsequent 20 hours, the prevalence

of an occluded infarct related artery decreased to 65% due to endogenous thrombolysis. Subsequent studies by Little et al provided additional insight regarding the ability of coronary angiography to predict the site of a subsequent myocardial infarction in patients with mild to moderate coronary artery disease[18]. The study group included 29 patients who had undergone coronary angiography at the time of their acute myocardial infarction and 1 to 24 months previously. In 2/3 of the patients, the site of the coronary arterial occlusion had a stenosis less than 50% on the initial angiogram.

Figure 2 Prevalence of Infarct Related Artery Occlusion



This study coupled with studies by Ambrose and others (Figure 2)[19, 20] led to two conclusions. First, coronary angiography is ineffective at predicting the coronary lesion responsible for subsequent myocardial infarctions. Second, most ST segment elevation myocardial infarctions occur at sites of angiographically insignificant lesions. These findings may, in part, explain why coronary revascularization procedures are ineffective in reducing the occurrence of myocardial infarctions; coronary arteries with stenoses < 50% are not routinely revascularized. Although Little and Ambrose concluded that

acute myocardial infarction occurs most frequently at a previously non-severe lesion, subsequent studies incorporating either post-mortem studies or intravascular ultrasound have challenged this notion.

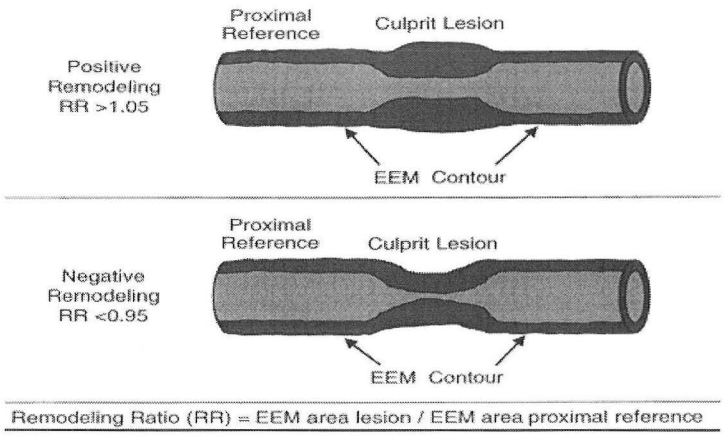
Coronary Arterial Remodeling:

Prior to 1987, little was known about human coronary arterial remodeling. Subsequently, Glagov and colleagues examined histologic sections of the left main coronary artery in 136 hearts obtained at autopsy and found coronary arterial enlargement occurred at the site of atherosclerosis with preservation of the cross sectional area of the lumen, so called "positive remodeling". They determined the magnitude of arterial enlargement was proportional to the plaque area, with the lumen remaining constant until the plaque occupied 40% of the area delineated by the internal elastic lamina . Thus, coronary angiography, which only delineates the luminal diameter of the vessel, underestimates the coronary atherosclerotic burden (i.e. may appear normal despite the presence of extensive coronary artery disease). While Glagov's observation shows that positive remodeling reduces the probability of developing flow limiting lesions, it did not provide insight into whether positive remodeling reduces the risk of acute myocardial infarctions.

The introduction of intravascular ultrasound coupled with coronary angiography has provided additional insights into the role of remodeling in patients with chronic stable angina and those with unstable coronary syndromes including unstable angina or acute myocardial infarction. Using intravascular ultrasound, Shoenhagen and colleagues studied the morphological characteristics of coronary plaques in patients with stable versus unstable coronary syndromes[21]. Arterial remodeling (a comparison of external

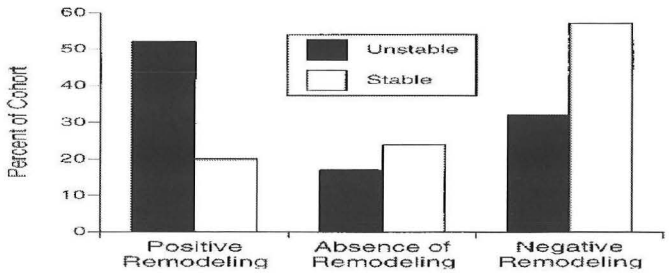
elastic membrane area at the lesion compared to the external elastic membrane area at a normal proximal reference segment) was defined as positive remodeling ratio (RR of >1.05) or negative remodeling (RR of <0.95). (See Fig. 3). Patients with unstable angina more often had positive remodeling than those with stable angina (52% vs 20% respectively) whereas patients with chronic stable

Figure 3 Example of Positive vs Negative Remodeling



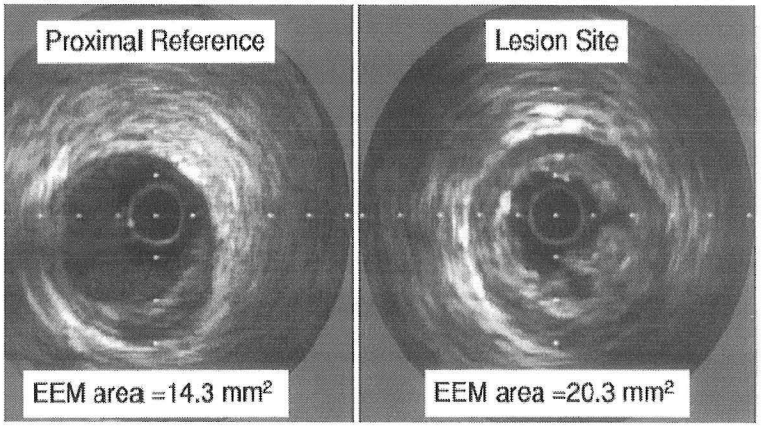
angina more often had negative remodeling than those with unstable angina (57% vs 32% respectively, see Figure 4). Furthermore, lesions with positive remodeling were more often echolucent than those with negative remodeling (20% vs 3%), a finding consistent with it being a lipid rich lesion.

Figure 4 Frequency of Positive and Negative Remodeling in Stable vs Unstable Angina



Although positive remodeling preserves the cross sectional luminal area, it is associated with lesions that are more prone to rupture and, in turn, more likely to precipitate an acute coronary syndrome (Figure 5).

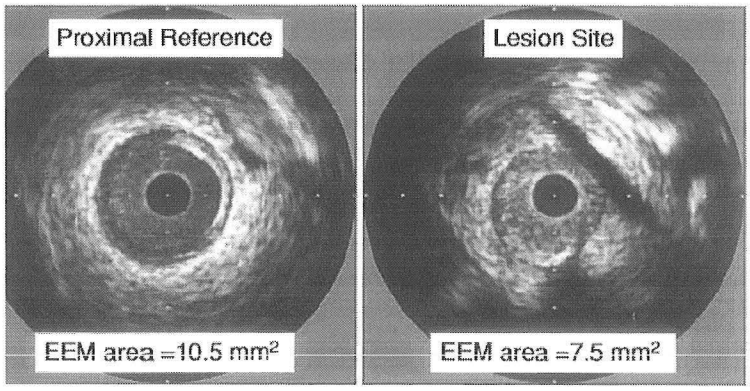
Figure 5: Positive Remodeling in Patient with Unstable Angina



EEM: External elastic membrane

In contrast, negative remodeling is associated with a reduced cross sectional luminal area and stable lesions which result in a stable anginal pattern (Figure 6).

Figure 6: Negative Remodeling in Patient with Chronic Stable Angina



EEM: External elastic membrane

In patients with multivessel coronary artery disease and an acute myocardial infarction, Kotani and colleagues used coronary angiography and intravascular ultrasound to characterize the "culprit" lesion (i.e. the lesion responsible for the MI) including the type of remodeling and compare it to the "nonculprit" lesions[22]. Thirty eight patients with an acute ST segment elevation myocardial infarction were studied within one week of their infarction. Compared to the non-culprit lesion, culprit lesions more often had positive remodeling (50% vs 79%, respectively), possessed a greater percentage of plaque (65% vs 79%), and were more often lipid rich (63% vs 38%). Compared to a group of patients with chronic stable angina, patients with acute ST segment elevation myocardial infarction more often had lesions with thrombus, positive remodeling, and a larger plaque burden. These studies have improved our understanding of Little's and Ambrose's contribution to the understanding of acute ST segment elevation myocardial infarction. Although it appears that angiographically demonstrated minimal stenoses are more prone to cause acute myocardial infarctions, such infarctions are not secondary to "minimal lesions." Rather, these sites have often undergone positive remodeling and appear minimally diseased by angiography which only reveals the luminal diameter whereas intravascular ultrasound, which allows one to study the lumen and vessel wall, actually demonstrates a larger plaque burden and vessel size at the site of infarction. Although positive remodeling is helpful in reducing the probability of developing chronic stable angina, it is associated with an excess risk of lesions that[23] cause acute vessel occlusion and myocardial infarctions.

Predictors of Arterial Remodeling in the Presence of Coronary Atherosclerosis:

Amongst patients with atherosclerosis, individual segments of a coronary artery display variable degrees of positive and negative remodeling. An autopsy study by Burke and colleagues of 36 hearts from patients who died from coronary artery disease investigated the relation of plaque morphology to coronary arterial remodeling. Coronary arteries were fixed at physiologic pressures and sectioned into 1,318 segments. Each segment was classified as fibrous plaque, fibroatheroma, plaque rupture, plaque erosion, thin-cap atheroma, calcified nodule, healed plaque rupture or total occlusion. For each segment, remodeling was determined by a comparison of the internal elastic lamina (IEL) at the lesion site, to the IEL at a proximal reference segment. The largest degree of positive remodeling was noted in lesions classified as acute rupture, hemorrhage, thin-cap atheroma and healed rupture whereas negative remodeling was noted in fibrous lesions and plaque erosion (Figures 7 and 8).

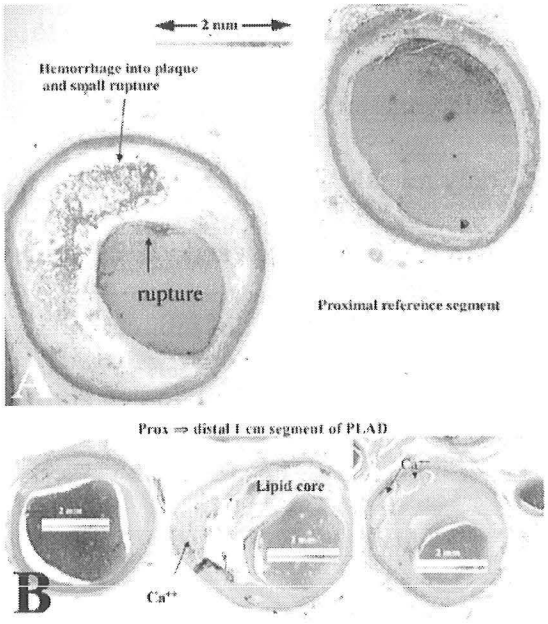
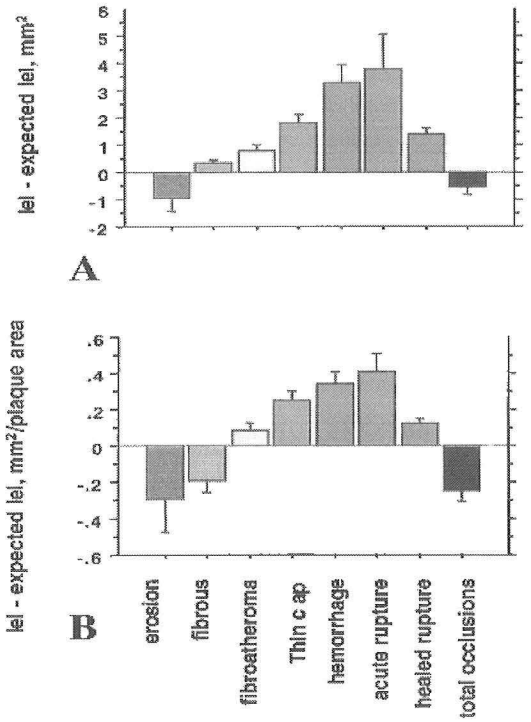


Figure 4: A: Positive remodeling at rupture site. B: Negative remodeling at fibrous site

Figure 8: Remodeling according to Lesion Type



Abbreviations: iel = internal elastic lamina
A: Absolute increase in area B: Increase in area adjusted for plaque area

These findings are consistent with studies utilizing intravascular ultrasound which reveal positive remodeling at culprit lesions and negative remodeling in patients with chronic stable angina.

In addition, studies of plaque constituents revealed that plaques with hemorrhage, inflammation, large lipid cores, macrophages and calcified deposits result in internal elastic lamina expansion resulting in positive remodeling whereas fibrous plaques were associated with internal elastic lamina contraction and negative remodeling (See Table 1).

Table 1. Plaque Components Associated with Positive vs Negative Remodeling

Plaque Parameter	T	*P*
% Macrophages	5.3	<0.0001
Fibrous calcium	4.5	<0.0001
% Lipid core (total)	4.3	<0.0001
% Fibrous tissue	-3.8	<0.0001
% Calcified lipid core	3.0	0.002
Medial atrophy	2.0	0.05
Adventitial thickness	-1.6	0.11

*IEL area-expected IEL area/plaque area. IEL = Internal Elastic Lamina

This study supports the hypothesis that inflammatory plaque constituents are associated with positive remodeling and increase the probability of an acute coronary syndrome.

Pasterkamp and colleagues studied the role of inflammation in patients with positive remodeling[24]. They demonstrated the increased macrophage infiltration in the intimal medial interface and increased levels of macrophage derived metalloproteinases 2 and 9. These constituents are known markers of vulnerable plaques and predispose patients to acute coronary syndromes. Moreno et al obtained 140 atherectomy specimens from patients with chronic stable angina, unstable angina and non ST segment myocardial infarctions[25]. Compared to atherectomy specimens obtained from patients with stable angina, specimens from patients with unstable angina had an increase in macrophage-rich area and macrophage rich sclerotic tissue, and those with non-ST segment myocardial infarctions had an increase in macrophage rich gruel. These findings support the role of inflammation in the destabilization of vulnerable plaques and the development of unstable angina and/or myocardial infarction.

The role of endothelial dysfunction and intimal disease in patients with atherosclerosis is well known. Only recently have abnormalities of the media and adventitia been described. Histologic sections of 598 lesions obtained from human

abdominal aortas were classified as early or advanced lesions[26]. The advanced lesions were further classified by their composition as being an atheroma, fibroatheroma, calcified plaque, fibrotic plaque or disrupted plaques (i.e. from less to more complex lesions). The more complex the lesion, the larger the plaque area and the lipid area (Table 2) and the more likely to have medial inflammation, fibrosis and atrophy, which was associated with thin fibrous caps, internal elastic lamina rupture and adventitial inflammation (Table 3).

Table 2. Characteristics of Plaques According to AHA Classification

AHA Classification	No. (%)	RIEL, %	Plaque Area, mm^2	Lipid Area, mm^2	Lipid Percent, %	FCT, μm
Early lesions						
Intimal thickening (I)	55 (9)	0	...	...	...	...
Fatty streak (II)	26 (4)	4	...	...	...	...
Preatheroma (III)	92 (15)	8	...	...	...	...
Advanced lesions						
Atheroma (IV)	68 (12)	18	6.7±3.5	2.6±1.9	38±15	198±153
Fibroatheroma (Va)	164 (27)	26	10.1±5.6	4.2±3.2	40±15	237±210
Calcific plaque (Vb)	59 (10)	20	11.3±6.5	3.6±3.2	31±26	183±183
Fibrotic plaque (Vc)	15 (3)	27	11.7±4.7	1.6±1.4	15±14	452±384
Disrupted plaque (VI)	119 (20)	85	14.1±6.6	7.4±3.8	53±15	34±16
Total and *P* value	598 (100)	0.0001	0.0001	0.0001	0.0001	0.0001

RIEL indicates rupture of the IEL; FCT, fibrous cap thickness.

Table 3. Medial Changes by AHA Classification

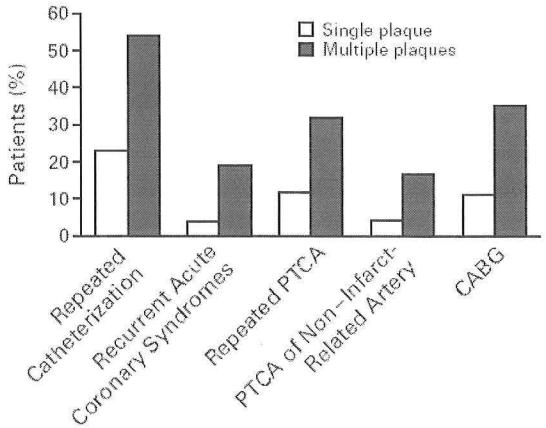
AHA Classification	Inflammation, n (%)	Fibrosis, n (%)	Atrophy, n (%)
Intimal thickening (I)	0 (0)	0 (0)	0 (0)
Fatty streak (II)	0 (0)	0 (0)	0 (0)
Preatheroma (III)	0 (0)	18 (20)	0 (0)
Atheroma (IV)	17 (25)	11 (16)	13 (19)
Fibroatheroma (Va)	30 (18)	37 (23)	36 (22)
Calcific plaque (Vb)	10 (17)	18 (30)	17 (29)
Fibrotic plaque (Vc)	2 (13)	3 (20)	1 (7)
Disrupted plaque (VI)	42 (35)	65 (55)	81 (68)
P	0.008	0.0001	0.0001

Values of central and peripheral medial thickness in micrometers.

Thus, it appears that a more diffuse inflammatory process affects the entire vessel wall and is associated with the development of vulnerable plaques and acute coronary syndromes.

For many years, we have approached patients with acute coronary syndromes and acute ST segment elevation myocardial infarctions as having a single culprit lesion. The findings of inflammation and remodeling at the site of plaque rupture including macrophages and metalloproteinases coupled with systemic markers of inflammation including C reactive protein challenge the idea of a single active plaque and suggest a more diffuse process involving the entire coronary artery bed. Goldstein and colleagues evaluated coronary angiograms from 253 patients with acute ST segment elevation myocardial infarctions[27] and found evidence of multiple complex lesions were noted in 40% of patients. The presence of multiple complex plaques was associated with an increase in the incidence of subsequent adverse events (Figure 9).

Figure 9 One Year Outcomes by Single vs Multiple Complex Plaques



Rioufal further tested the concept of multiple complex coronary plaques by using IVUS to study all three major coronary arteries in patients presenting with unstable angina[28]. He found multiple ruptured plaques with positive remodeling in 80% of patients and multivessel involvement in 71%. The presence of multiple ruptured lesions of which not all are severe, is important since non-severe lesions are typically not revascularized and may be a source for recurrent myocardial infarctions. The finding of multiple ruptured vulnerable plaques is consistent with a generalized inflammatory state[29]. The hypothesis that inflammation triggers plaque rupture in patients with acute coronary syndromes is further supported by a study done by Buffon and colleagues[30]. They studied various groups of patients including patients with acute coronary syndrome, chronic stable angina, and controls. In patients with acute coronary syndromes, they found a marked decrease in neutrophil myeloperoxidase content (a marker of neutophil activation) in all coronary beds, irrespective of the site of the most severe stenosis. These findings of a generalized inflammatory state across the coronary vascular bed suggests that widespread inflammation is involved with plaque destabilization and the development of multiple ruptured plaques.

The presence of remodeling and multiple ruptured plaques involving various coronary arteries has altered our understanding of the pathophysiology of acute coronary syndromes. Whereas we use to think of a single culprit lesion, we now know that patients with acute coronary syndromes have multiple ruptured plaques with evidence of both local and systemic inflammation. Revascularization strategies address significant epicardial stenoses but do not (a) attenuate or alter the type of coronary arterial

remodeling or (b) decrease the probability of vulnerable plaque rupture and consequent recurrent clinical events. Vulnerable lesions with positive remodeling that often appear as minimal lesions on angiography are not revascularized, yet they may serve as a site of plaque rupture and future acute infarction. The diffuse nature of coronary artery disease underscores the need for using medications including antiplatelet agents, ACE-inhibitors, and HMG co-reductase inhibitors which favorably affect the entire coronary tree and are effective in primary and secondary prevention of myocardial infarctions.

Current research initiatives are attempting to couple novel risk factors such as C reactive protein[31, 32], CD40 ligand[33], Interleukin-6. fibrinogen, and homocysteine[34] with new imaging techniques including coronary thermography, optical coherence tomography, and coronary MRI in order to identify "at risk" lesions[35]. The combination of biomarkers coupled with new imaging may allow us to "tailor" our medical therapes and time our revascularization strategies in patients with impending vulnerable plaques rupture.

REFERENCES:

1. *Heart and Stroke Statistical Update.* 2003, American Heart Association.
2. Lloyd-Jones, D.M., et al., *Lifetime risk of coronary heart disease by cholesterol levels at selected ages.* Arch Intern Med, 2003. **163**(16): p. 1966-72.
3. Killip, T., E. Passamani, and K. Davis, *Coronary artery surgery study (CASS): a randomized trial of coronary bypass surgery. Eight years follow-up and survival in patients with reduced ejection fraction.* Circulation, 1985. **72**(6 Pt 2): p. V102-9.
4. *First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants.* Lancet, 1995. **346**(8984): p. 1179-84.

5. Hamm, C.W., et al., *A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI).* N Engl J Med, 1994. **331**(16): p. 1037-43.
6. King, S.B., 3rd, et al., *A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST).* N Engl J Med, 1994. **331**(16): p. 1044-50.
7. Rodriguez, A., et al., *Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators.* J Am Coll Cardiol, 2001. **37**(1): p. 51-8.
8. Weintraub, W.S., et al., *Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease.* J Am Coll Cardiol, 1998. **31**(1): p. 10-9.
9. Chaitman, B.R., et al., *Myocardial infarction and cardiac mortality in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial.* Circulation, 1997. **96**(7): p. 2162-70.
10. Serruys, P.W., et al., *Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease.* N Engl J Med, 2001. **344**(15): p. 1117-24.
11. *Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration.* Bmj, 1994. **308**(6921): p. 81-106.
12. *Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.* N Engl J Med, 1998. **339**(19): p. 1349-57.
13. Yusuf, S., et al., *Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators.* N Engl J Med, 2000. **342**(3): p. 145-53.
14. Freemantle, N., et al., *beta Blockade after myocardial infarction: systematic review and meta regression analysis.* Bmj, 1999. **318**(7200): p. 1730-7.
15. Davies, M.J. and A.C. Thomas, *Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina.* Br Heart J, 1985. **53**(4): p. 363-73.
16. Falk, E., *Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi.* Br Heart J, 1983. **50**(2): p. 127-34.
17. DeWood, M.A., et al., *Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction.* N Engl J Med, 1980. **303**(16): p. 897-902.
18. Little, W.C., *Angiographic assessment of the culprit coronary artery lesion before acute myocardial infarction.* Am J Cardiol, 1990. **66**(16): p. 44G-47G.
19. Nobuyoshi, M., et al., *Progression of coronary atherosclerosis: is coronary spasm related to progression?* J Am Coll Cardiol, 1991. **18**(4): p. 904-10.

20. Giroud, D., et al., *Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography.* Am J Cardiol, 1992. **69**(8): p. 729-32.
21. Schoenhagen, P., et al., *Extent and direction of arterial remodeling in stable versus unstable coronary syndromes : an intravascular ultrasound study.* Circulation, 2000. **101**(6): p. 598-603.
22. Kotani, J., et al., *Intravascular ultrasound analysis of infarct-related and non-infarct-related arteries in patients who presented with an acute myocardial infarction.* Circulation, 2003. **107**(23): p. 2889-93.
23. Burke, A.P., et al., *Morphological predictors of arterial remodeling in coronary atherosclerosis.* Circulation, 2002. **105**(3): p. 297-303.
24. Pasterkamp, G., et al., *Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox.* J Am Coll Cardiol, 1998. **32**(3): p. 655-62.
25. Moreno, P.R., et al., *Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture.* Circulation, 1994. **90**(2): p. 775-8.
26. Moreno, P.R., et al., *Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability.* Circulation, 2002. **105**(21): p. 2504-11.
27. Goldstein, J.A., et al., *Multiple complex coronary plaques in patients with acute myocardial infarction.* N Engl J Med, 2000. **343**(13): p. 915-22.
28. Rioufol, G., et al., *Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study.* Circulation, 2002. **106**(7): p. 804-8.
29. Liuzzo, G., et al., *The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina.* N Engl J Med, 1994. **331**(7): p. 417-24.
30. Buffon, A., et al., *Widespread coronary inflammation in unstable angina.* N Engl J Med, 2002. **347**(1): p. 5-12.
31. Biasucci, L.M., et al., *Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability.* Circulation, 1999. **99**(7): p. 855-60.
32. Tommasi, S., et al., *C-reactive protein as a marker for cardiac ischemic events in the year after a first, uncomplicated myocardial infarction.* Am J Cardiol, 1999. **83**(12): p. 1595-9.
33. Schonbeck, U., et al., *Soluble CD40L and cardiovascular risk in women.* Circulation, 2001. **104**(19): p. 2266-8.
34. Ridker, P.M., M.J. Stampfer, and N. Rifai, *Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease.* Jama, 2001. **285**(19): p. 2481-5.
35. MacNeill, B.D., et al., *Intravascular modalities for detection of vulnerable plaque: current status.* Arterioscler Thromb Vasc Biol, 2003. **23**(8): p. 1333-42.