29. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.
30. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103:1813–8.
31. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347: 1557–65.
32. Kushner I, Sehgal AR. Is high-sensitivity C-reactive protein an effective screening test for cardiovascular risk? Arch Intern Med 2002;162:867–9.
33. Weintraub WS, Harrison DG. C-reactive protein, inflammation and atherosclerosis: do we really understand it yet? Eur Heart J 2000;21: 958–60.
34. Greenland P, Abrams J, Aurigemma GP, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. Circulation 2000;101:E16–22.
35. Grundy SM, Bazzarre T, Cleeman J, et al. Prevention Conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: medical office assessment: Writing Group I. Circulation 2000;101:E3–11.
36. McManus RJ, Mant J, Meulendijks CF, et al. Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice: cross sectional study. BMJ 2002;324:459–64.
37. Fedder DO, Koro CE L', Italien GJ. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population. Circulation 2002; 105:152–6.
38. The sixth report of the Joint National Committee on prevention detectionevaluation and treatment of high blood pressure. Arch Intern Med 1997;157:2413–46.
39. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000;160:459–67.
40. Fonarow GC, Ballantyne CM. In-hospital initiation of lipid-lowering therapy for patients with coronary heart disease: the time is now. Circulation 2001;103:2768–70.
41. Fonarow GC, Gawlinski A. Rationale and design of the cardiac hospitalization atherosclerosis management program at the University of California Los Angeles. Am J Cardiol 2000;85:10A–7A.
42. U.S. Preventive Services Task Force. Guide to clinical preventive services. 2nd edition. Washington, DC: U.S. Department of Health and Human Services, 1996.
43. Gheorghiade M, Bonow RO. Coronary artery disease. In: Kelley's Textbook of Internal Medicine. Philadelphia, PA: WB Lippincott Co., 1996:371–85.
44. Grover SA, Coupal L, Hu XP. Identifying adults at increased risk of coronary disease. How well do the current cholesterol guidelines work? JAMA 1995;274:801–6.

Task Force #2—What Is the Pathologic Basis for New Atherosclerosis Imaging Techniques?

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Atherosclerosis is composed of cellular and acellular elements that combine to form a variety of plaque types (Table 1, Fig. 1). With respect to atherosclerosis imaging, four plaque histologic characteristics are considered in this Task Force report: necrotic core, fibrous cap, calcium, and inflammatory activity. The relative prevalence of these components depends on the degree of stenosis, the clinical coronary heart disease syndrome, and nonlocal factors including the patient's gender and traditional and nontraditional risk factors.

COMPONENTS OF ATHEROSCLEROSIS THAT FORM TARGETS FOR ATHEROSCLEROSIS IMAGING

Several studies (1–4) have reported the relationship between the following types of plaque components and degree of stenosis.

Necrotic core. A necrotic core is present in approximately 25% of plaques with less than 50% cross-sectional stenosis, and this increases in prevalence with increasing stenosis severity. Above 70% cross-sectional luminal narrowing, about 75% of plaques will demonstrate a necrotic core.

Fibrous cap. Fibrous cap atheromas are defined as plaques with a well-defined lipid core covered by a fibrous cap, which may be relatively acellular (made of dense collagen) or may be rich in smooth cells. No data in autopsy studies are available regarding the prevalence of fibrous caps of various thickness. Stenosis severity is directly related to the proportion of dense fibrous tissue (type I collagen) in the fibrous cap, and inversely related to smooth-muscle-cell–rich areas (2–4).

Calcium. The presence of calcium is strongly correlated with stenosis severity (3–6) (Fig. 2) and is modulated by age. As age advances, the mean percent calcified area increases both for plaques with moderate (greater than or equal to 50% to less than 75% cross-sectional area) luminal narrowing and severe (75% to 90% cross-sectional luminal area) narrowing (5). Importantly, a thrombotic, recanalized total occlusion may be devoid of calcification. The incidence of calcification in total occlusions may be partly a function of lesion age (7).

Inflammatory activity. Inflammation, both of the intima and adventitia, increases in prevalence with increasing percent stenosis (1).

Table 1. Atherosclerotic Plaque Classifications

	Traditional Classification	Stary et al. (34,76)	Virmani et al. (32)	
			Initial	Progression
Early plaques		Type I: microscopic detection of lipid droplets in intima and small groups of macrophage foam cells	Intimal thickening	None
	Fatty streak	Type II: fatty streaks visible on gross inspection, layers of foam cells, occasional lymphocytes and mast cells	Intimal xanthoma	None
		Type III (intermediate): extracellular lipid pools present among layers of smooth muscle cells	Pathologic intimal thickening	Thrombus (Erosion)
Intermediate plaque	Atheroma	Type IV: well-defined lipid core; may develop surface disruption (fissure)	Fibrous-cap atheroma	Thrombus (Erosion)‡
Late lesions			Thin fibrous-cap atheroma	Thrombus (Rupture) Hemorrhage/fibrin§
		Type Va: new fibrous tissue overlying lipid core (multilayered fibroatheroma)*	Healed plaque rupture, erosion	Repeated rupture or erosion with or without total occlusion
		Type Vb: calcification†	Fibrocalcific plaque (with or without necrotic core)	
	Fibrous plaque	Type Vc: fibrotic lesion with minimal lipid (could be result of organized thrombi)		
Miscellaneous/ complicated features	Complicated/advanced plaques	Type VIa: surface disruption Type VIb: intraplaque hemorrhage Type VIc: thrombosis	Calcified nodule	Thrombus (usually nonocclusive)

*May overlap with healed plaque ruptures; †Occasionally referred to as type VII lesion; ‡May further progress with healing (healed erosion); §May further progress with healing (healed rupture).

GENERAL ISSUES RELATED TO DETECTION OF PLAQUE COMPONENTS BY ATHEROSCLEROSIS IMAGING

Should the anatomic targets we image vary by the type of future events under consideration? Detection of lipid-rich lesions is likely more important in screening individuals for their risk of myocardial infarction (MI) than it is for screening for sudden coronary death risk (Fig. 3) (1–4). The composition of plaques in patients dying with acute MI reflects a larger proportion of lipid, as compared to those plaques of patients dying suddenly. These findings are corroborated by quantitation of atheromas and thin-cap atheromas in various coronary syndromes (see below). The preponderance of data for calcium does not suggest significant differences in coronary syndromes when plaque burden is factored.

Autopsy and atherectomy studies have compared components of plaque across groups of patients dying with stable angina, unstable angina, acute MI, and sudden death. In stable angina, the culprit plaque consists of either a lipid-rich fibrous tissue (40%) or is a predominantly pure fibrous lesion (60%) in plaques causing greater than 75% cross-sectional luminal narrowing (8). Atherosclerotic plaques from unstable angina patients are more cellular than plaques from patients with stable angina, resembling plaques removed from patients with restenosis lesions (9). In unstable angina and MI, the plaque area occupied by macrophages and the number of T-lymphocytes within the plaque are significantly greater than in plaques from stable angina patients, and activation of these cells, as shown by HLA-DR expression, is increased (10–12).

The likelihood and size of a necrotic core is greatest in plaques with moderate or worse stenosis severity (Fig. 4) (3,4). Baroldi et al. (1) demonstrated that plaques causing moderate luminal narrowing (less than 70% cross-sectional area narrowing) are more likely to have necrotic cores in patients dying with acute MI (56%) than those dying suddenly with chronic ischemia, sudden death, or accidental causes (30% to 40%). The same invesigators showed that calcium and inflammation are most prevalent in moderately and severely narrowed vessels of patients dying with acute MI, moderately prevalent in chronic ischemic syndromes and sudden coronary death, and least prevalent in accidental deaths. In contrast, Kragel et al. (3) showed that the percent calcium area within the intima of severely narrowed arteries was actually greater in sudden death (approximately 16%) as compared to unstable angina and acute MI (8% to 10%). Autopsy data from the Armed Forces Institute of Pathology (unpublished data) showed similar coronary calcification in patients dying from coronary disease, as compared to those dying of noncoronary causes. In this study, after adjustment for overall plaque burden, gender, and age, there was a lesser

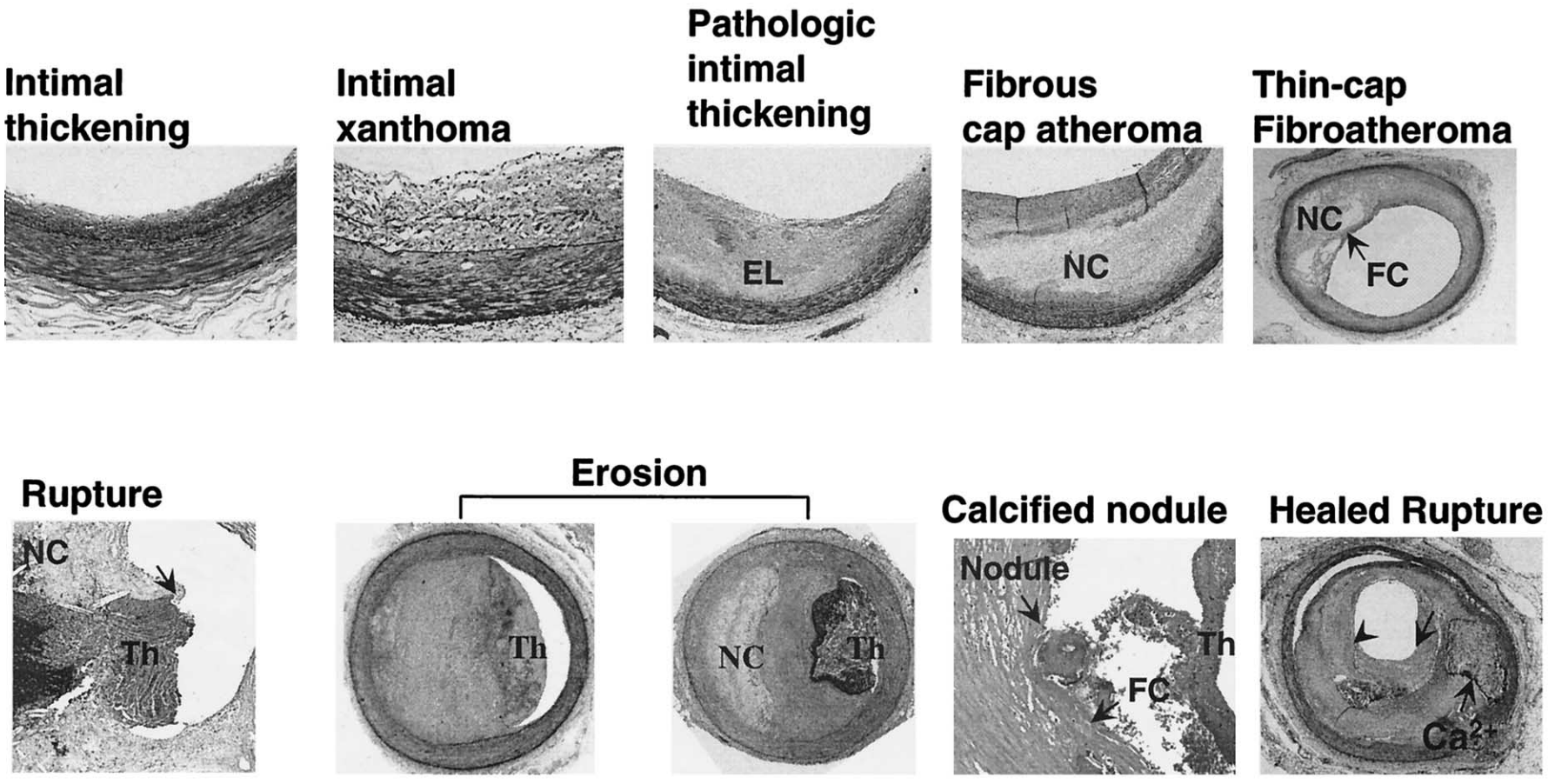

Figure 1. Histopathology of plaque progression. Descriptions begin at top, from left to right. Intimal thickening is normal in all age groups and is characterized by smooth muscle cell accumulation within the intima. Intimal xanthoma corresponds to the fatty streak and denotes the accumulation of macrophages and lymphocytes within the intimal thickening lesion. Pathologic intimal thickening denotes the accumulation of extracellular lipid. Fibrous cap atheroma indicates the presence of a necrotic core under a fibrous cap, which may become thinned (thin-cap atheroma). This lesion may rupture, with exposure of thrombus to the lumen. The thrombus of a plaque erosion may overlie pathologic intimal thickening **(left)** or fibrous cap atheroma **(right)**. Calcified nodule is a rare form of coronary thrombus. Acute rupture may progress to healing (healed plaque rupture) without luminal occlusion. EL = extracellular lipid; NC = necrotic core; FC = fibrous cap; Th = thrombus.

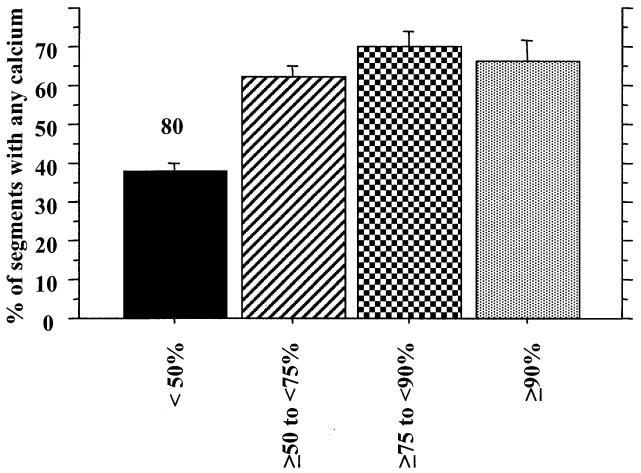

Figure 2. Histomorphometric study demonstrating the percent cross-sectional luminal narrowing is positively correlated with the presence of any calcification. Burke AP, et al. Pathophysiology of Calcium Deposition in Coronary Arteries. HERZ 2001;26:239–44. (Copyright Urban & Vogel. Reproduced with permission.)

degree of calcification in patients dying with sudden coronary death, as compared to those dying of other causes.

Could regional variability in atherosclerosis (e.g., coronary vs. peripheral) influence the accuracy of certain modalities/pathologic targets for CHD prediction? Few anatomic studies have compared, in individual patients, the composition of plaques from different arterial beds. A recent autopsy study by Vink et al. (13) demonstrated that, in elderly patients (age 82 ± 10 years), the coronary circulation had the greatest luminal narrowing, followed by the internal iliac arteries, femoral arteries, abdominal aorta, common iliac arteries, common carotid arteries, radial arteries, renal arteries, brachial arteries, superior mesenteric arteries, external iliac arteries, ascending aorta, middle cerebral arteries,

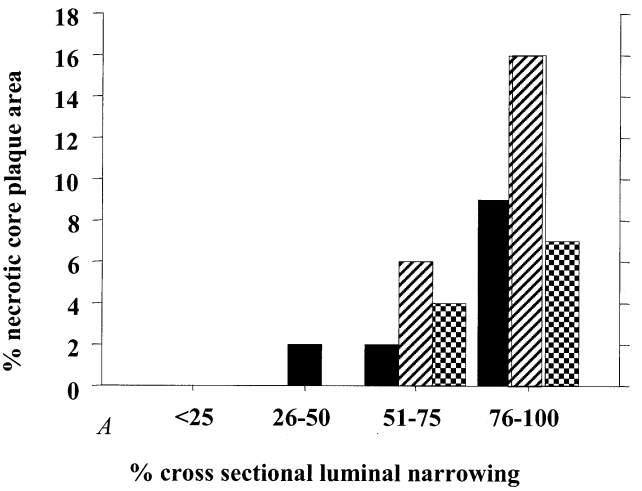

Figure 3. Histomorphometric data demonstrate that, with increasing stenosis, necrotic core increases, especially in patients with acute myocardial infarction (3,4).

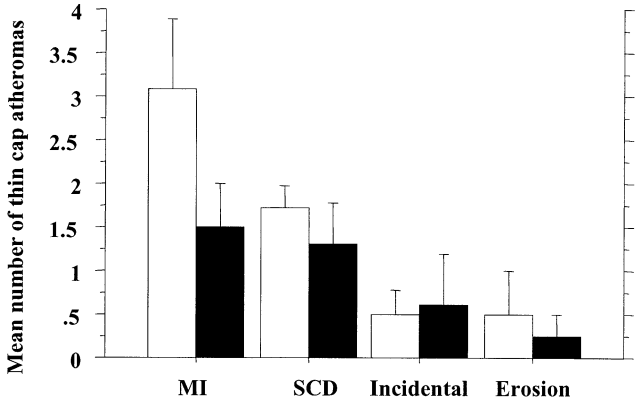

Figure 4. Thin-cap atheromas are most frequent in patients dying with acute myocardial infarction (MI), followed by sudden coronary death (SCD) victims and incidental disease. Fibroatheromas and thin cap atheromas are not common in patients dying with plaque erosion (32).

basilar arteries, internal carotid arteries, anterior cerebral arteries, and posterior cerebral arteries. The extent of lipid-rich regions (determined by absence of collagen staining with picrosirius red) was greatest in the carotid arteries, followed by the coronary, brachial, and iliac arteries. No data are available that evaluate lipid rich necrotic core in individual patients across arterial beds.

In comparison to coronary artery plaques, corrected for degree of cross sectional area luminal narrowing, carotid plaques are more likely to have intraplaque hemorrhage, acute plaque ruptures, and thin caps (14,15). After rupture, carotid plaques are more likely to ulcerate as compared to coronary plaques. When the infiltrate of macrophages is analyzed, carotid plaques have fewer cap macrophages at the site of rupture than do coronary plaques. In general, calcification of carotid plaques is similar to that of coronary plaques, although calcification is more likely in the carotid to begin at the luminal surface, resulting in eruption of calcific nodules.

Targeting lesions: culprits versus generalized atherosclerosis interrogations: do we need to target the culprit plaque? "Vulnerable plaque," a term coined by Little in 1990 (16) and further defined by Muller in 1992 (17), refers to a lesion prone to thrombosis. If atherosclerosis were a gradually, linearly progressive diffuse disease, the most important task of imaging would be to determine overall plaque burden. However, it has been shown that sudden thrombotic occlusion often occurs in areas of only moderate pre-existing atherosclerosis, and that plaque progression occurs largely as a result of episodic thrombosis and organization. Serial angiographic and necropsy studies have shown that the risk of plaque rupture correlates only weakly with the degree of stenosis (18). However, coronary artery disease is generally widespread in patients with acute coronary syndromes. Estimates of overall plaque burden (for example, composite calcium scores using computed tomography) are predictive of future acute events (19), and autopsy studies of sudden coronary death have shown diffuse disease in a majority of cases. Guthrie et al. (20) demonstrated that

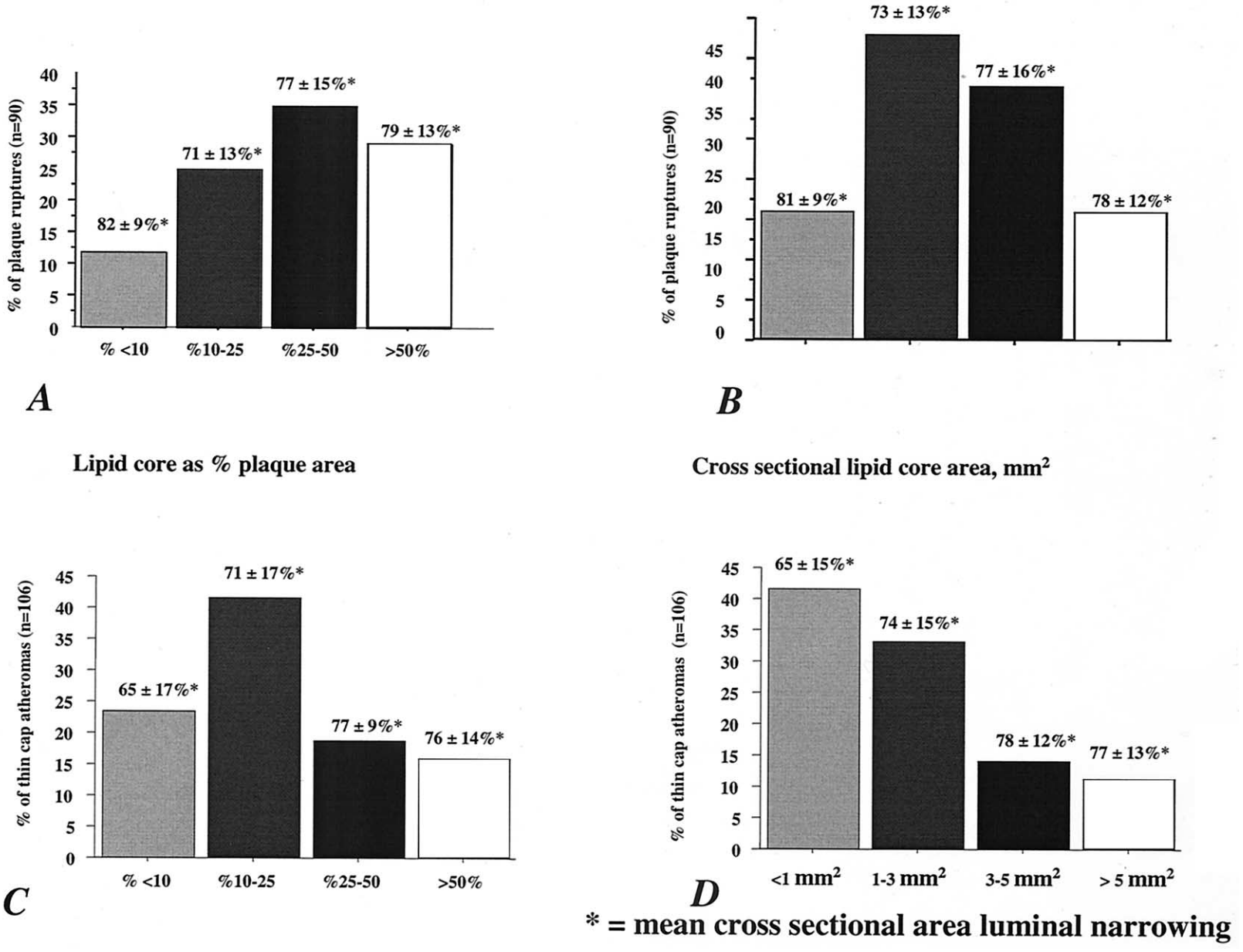

Figure 5. The distribution frequency of plaque ruptures **(A,B)** and thin-cap atheromas **(C,D)** by size of lipid core or lipid core as a percent of plaque area (*x*). The majority of plaque ruptures occur when lipid core area forms 25% to 50% of plaque area, or 1 to 3 mm^2 lipid core area. In the case of thin-cap atheromas, the degree of cross-sectional area luminal narrowing and area of necrotic core is shifted to the left (lesser or smaller) as compared to plaque ruptures. Data derived from sudden death registry, Armed Forces Institute of Pathology (32).

Table 2. Approximate Sizes of Necrotic Core, in Fibroatheroma, Thin-Cap Atheroma, and Acute Rupture (32)

Dimension	Plaque Type		
	Fibrous-Cap Atheroma	Thin-Cap Atheroma	Acute Plaque Rupture
Length, mm, mean/range	6 mm (range 1–18 mm)	8 mm (range 2–17 mm)	9 mm (range 2.5–22)
Necrotic core area, mm^2	1.2 ± 2.2	1.7 ± 1.1	3.8 ± 5.5
% Necrotic core area	15% ± 20%	23% ± 17%	34% ± 17%

nearly 75% of patients dying with angina or MI demonstrate vessel disease of three or more vessels. Data from autopsies indicate that the number of affected vessels in patients dying with severe coronary artery disease is lowest in patients dying with plaque erosion, intermediate in patients dying with plaque rupture, and highest in patients dying with stable plaque and healed MI (21). However, the degree of overall plaque burden varies tremendously in sudden coronary death. The overall plaque burden increases in patients dying with severe coronary disease as age advances. Therefore, the identification of "vulnerable plaques" is of special importance in younger individuals.

Plaque erosions versus plaque rupture. The nature of plaque disruption underlying coronary thrombosis is heterogeneous. It has recently been reported that thrombi in sudden coronary death may occur from two distinctly different plaque morphologies. One is plaque rupture, accounting for 60% of thrombi, and the other is plaque erosion, accounting for the remaining 40% in young victims of sudden coronary death (22). However, plaque ruptures are several times more common in the elderly than plaque erosion. For example, in the fifth decade, the estimated rate of fatal rupture was for men 17 per 100,000 per year, compared to 6 per 100,000 per year for erosions (23). The relative incidence of plaque rupture and plaque erosion is similar in different clinical coronary heart disease syndromes—for example MI and sudden death (24,25). Histologically, plaque erosions are much less frequently calcified (23% vs. 69% of plaque ruptures) and more often occur with nonocclusive thrombi and eccentric plaques (82% vs. 57%, $p=0.08$; 82% vs. 54%, $p = 0.07$, respectively) (22).

Smoking is associated with atherothrombosis and is related either to erosion or rupture (21). In autopsy studies, 75% of normotensives dying with severe coronary atherosclerosis demonstrate acute thrombi. In comparison, only 36% of hypertensives dying suddenly with severe coronary disease demonstrate acute thrombi, with the remainder demonstrating stable plaque, with either healed infarct or cardiomegaly (48%) or stable plaque with severe narrowing in the absence of infarction, thrombus, or cardiomegaly (16%) (26). These results demonstrate that identifying a plaque prone to thrombosis will predict the majority of acute infarcts and sudden deaths in normotensives, and only about one-third of sudden deaths in hypertensives.

The relationship between risk factors and culprit plaque morphology is similar in women and men (27). The proportion of women dying suddenly with plaque erosion is higher than in men, especially in those dying under age 50 years. In general, the coronary plaques of women have been shown to be more cellular than those of men (28,29). Plaques of premenopausal women demonstrate relatively little necrotic core and calcification in comparison to both men and to postmenopausal women, probably because of the relatively high rate of plaque erosion in young women, and because of the protective effect of estrogen on the formation of large necrotic cores (30).

CONSIDERATIONS OF INDIVIDUAL PLAQUE COMPONENTS

Necrotic core. DOES SIZE OF THE NECROTIC CORE MATTER AND SHOULD IT BE EVALUATED WITH ATHEROSCLEROSIS IMAGING? Data from the laboratory of W.C. Roberts showed that the infarct-related artery at the site of rupture had much larger atheromatous cores as compared to plaques with intact plaque (3,4,31), supporting the concept that a large lipid core is associated with plaque vulnerability and MI. Virmani et al. (32) have corroborated these data in coronary arteries (Table 2) showing that mean necrotic core size, independent of cross-sectional luminal narrowing, was greatest in plaque ruptures, followed by thin-cap atheromas and fibrous cap atheromas. Eighty percent of ruptured plaques contained necrotic cores larger than 1.0 mm^2 and, in nearly 90%, lipid core comprised greater than 10% of the plaque area (Fig. 5). The length of necrotic cores underlying fatal and nonfatal plaque ruptures was found to average 9 mm, with a range of 3.5 mm to 22 mm (33).

Because of the a wide variation of necrotic core size in relation to rupture, it is difficult to assign specific parameters as cut-points for coronary heart disease (CHD) risk prediction. For example, it is unknown if plaque rupture, either fatal or nonfatal, occlusive or nonocclusive, occurs over the largest necrotic core in a patient, or if local inflammatory, hemodynamic, or other factors are more important. Based on data such as that shown in Table 2, a plaque with a core shorter than 3 mm, with an area of less than 1.0 mm^2 (34), and with a percent core of less than 10% appears to be unlikely to rupture.

CHEMICAL COMPOSITION OF NECROTIC CORE. Although the chemical composition of necrotic core may not be currently relevant to imaging techniques, newer techniques are being developed to take advantage of pH and temperature changes. Also, magnetic resonance imaging and in-

frared scanning utilize biochemical properties of plaques. Early lipid pools (type II lesions) are composed primarily of cholesterol esters (77%), with minor components of free cholesterol and phospholipid. The increase and confluence of separate extracellular lipid pools along with macrophage breakdown result in late necrotic cores, with a lowering of the melting point, and an increase in free cholesterol, fatty acid, sphingomyelin, lysolecithin, and triglyceride (35,36). Because only later cores are prone to rupture, the biochemical differences between early and late necrotic core may be relevant to plaque vulnerability. Felton et al. (37), using aortic samples, have shown that disrupted plaques have high-free cholesterol content in the center, with a low-free to esterified cholesterol ratio at the edges, relative to intact plaques, possibly because of macrophage breakdown and active inflammation.

Fibrous cap. **FREQUENCY AND DISTRIBUTION IN SUDDEN CORONARY DEATH.** Both the frequency and the distribution of fibrous-cap atheromas in the various coronary syndromes vary with risk factor profile, age, and gender. The proportional distribution of different plaque types is inherently variable within individual patients because of the continuous, evolutionary nature of atheroma formation. This progression is modified by changes in cardiovascular risk factors such as statin-mediated cholesterol lowering. Fibrous cap atheromas are most frequent in patients dying with acute MI or acute plaque rupture, followed by those dying with stable plaque, other incidental causes of death, and lastly plaque erosion (38). In the same study, the coronary distribution of fibrous-cap atheromas was similar to those of thin cap atheromas (39) and plaque ruptures, with 60% occurring in proximal segments, 30% in mid-arterial segments, and 10% in distal segments.

PATHOPHYSIOLOGY OF THE FIBROUS CAP. Because of the small size of fibrous caps, it has been difficult to develop tensometers to measure physical characteristics of lesions (40). Pressures required to rupture balloon-induced plaques in rabbit aortas are lower in lipid-rich plaques of cholesterol-fed animals than in standard chow-fed animals (41), supporting the connection between increased lipid content and plaque instability (42). Large-strain, finite-element analysis has shown that fibrous tissue and calcification decreases plaque stress, whereas lipid pools increase stress (43). Because the mechanical strength of arterial tissue depends mostly on the integrity of its collagen scaffold, potential changes that affect plaque collagen have been investigated in relation to vulnerability. Interestingly, collagen is, by mass, the most abundant component of advanced atheroma (1,3,4). However, cap stability may be predicted by the local variations in the distribution of collagen, as development of transverse gradients was found in disrupted caps and may be a critical aspect of vulnerability. Computerized reconstructions of simulated and histologic sections of real plaques suggest that stress may be concentrated at critical points in the cap, and that computed high-stress points in the shoulder region of the cap correlate with sites of rupture found at autopsy (44,45).

RELEVANCE OF THE FIBROUS CAP FOR ATHEROSCLEROSIS IMAGING. A common mechanism of disruption of the fibrous cap atheroma occurs via the thinning and weakening of the fibrous cap, resulting in breaks exposing tissue factor and with subsequent thrombosis and vasospasm. A fibrous cap has been defined as thin when it is less than 65 microns in its minimum thickness. This is based upon a study showing that the thickness of the fibrous cap in most (95%) acute plaque ruptures was less than this (21). Kolodgie et al. (39) demonstrated that the mean numbers of thin cap atheromas, as so defined, was greater than or equal to 1.5 in patients dying with acute MI and/or acute plaque rupture, between 1 and 1.4 (mean 1.1 $\pm$ 1.3) in patients dying with stable plaque, and least common in patients without acute rupture (0.9 $\pm$ 1.2), healed rupture (0.5 $\pm$ 0.8), or plaque erosion (0.2 $\pm$ 0.5). Thin-cap atheromas are more frequent in men dying with acute MI and sudden death. Their distribution in the coronary tree mirrors that of acute plaque rupture. The mean necrotic core size and core length of thin-cap atheromas are, however, smaller than in plaques that rupture, and not significantly greater than fibrous cap atheromas with a thicker cap (32) (Table 2).

THICKNESS OF THE FIBROUS CAP: RESOLUTION REQUIRED FOR IMAGING OF CHD RISK. Because the range of fibrous cap thickness in plaque rupture ranges from several microns to approximately 150 microns, with the majority being under 65 microns, at least in the coronary arteries, the resolution of imaging techniques should be at the level of 50 microns or better, in order to identify 50 microns caps (prone to rupture), 100 microns plaques (low risk), and over 150 microns (minimal risk). If fibrous cap is to be the only mechanism for identifying thin cap atheromas, then characterization of a plaque to the nearest 50 microns in thickness would be necessary to construct a clinical classification of plaques prone to rupture.

COMPENSATORY REMODELING: IS THIS A MARKER OF FIBROUS CAP INSTABILITY? Several studies, including autopsy and ultrasound investigations, have demonstrated that outward or positive coronary artery remodeling is more frequent in areas of unstable plaques (25,46–49). After adjusting for plaque area and measuring against proximal reference segments, acute plaque ruptures, plaques with large necrotic cores, especially those with intraplaque hemorrhage, and plaques rich in macrophages show expansion of the internal elastic lamina (46). These data indicate that one measure of plaque instability may be in identifying areas of positive remodeling. Unfortunately, as is the case with other indicators, remodeling should be a poor predictor of plaque erosion, as, if anything, eroded plaques are found in segments with little or no remodeling, or even contraction of the internal elastic lamina.

PLAQUE CALCIFICATION

Calcification is prevalent in atherosclerotic plaques, and it forms the basis for radiographic methods of plaque burden screening. The earliest calcified elements are derived from apoptotic smooth muscle cells, which form membrane-bound matrix vesicles that actively calcify (50). These microcalcifications are not detected by standard imaging techniques, are readily identified in histologic sections only by stains for calcium such as von Kossa's stain, and are present in the majority of early cores and areas of extracellular lipid. With coalescence of microscopic calcium deposits, larger granules and plates of calcium form that may be visualized by standard imaging techniques. Such radiographically detectable calcification is present in the majority of plaques with severe stenosis (6), and is influenced by a variety of systemic and local factors. In an autopsy study of men dying with severe coronary disease, radiographic coronary calcification was present in 46% of men and women under age 40 years, 79% of men and women age 40 to 49 years, 90% of men and women age 50 to 60, and 100% of men and women older than 60. For women, the degree of calcification showed a 10-year lag compared to that of men, with equalization by the eighth decade.

RELATIONSHIP OF CALCIUM TO PLAQUE BURDEN: VALIDITY AS AN ATHEROSCLEROSIS SURROGATE. There is an excellent correlation between the extent of coronary calcification and overall plaque burden. Simons et al. (51) in a series of autopsy hearts, concluded that the detection of coronary calcification by ultrafast computed tomographic scanning is highly predictive of the presence of coronary atherosclerosis, and, as had been shown by Mautner et al. (6) is almost always present in a large segment or artery with obstructive disease. However, the correlation in an individual segment was somewhat limited, and total occlusions may be devoid of calcium. Other autopsy studies have shown a good correlation between calcified area and plaque burden (plaque size), a significant but weak correlation between calcified area and percent stenosis, and no correlation with lumen size in a given segment (5,52). These studies suggest that calcium imaging will provide a general indication of plaque burden, but will not be helpful in detecting areas of maximal stenosis in a given heart.

Patients with diffuse vascular calcification due to end stage renal disease or other metabolic disturbances may have marked, diffuse coronary calcification without significant luminal narrowing. Further radiographic and histologic characterization of such calcifications are needed accurately distinguish them from potential destabilizing nodular calcifications as described by Virmani et al. (32).

IS THERE INFORMATION TO BE GLEANED FROM THE PATTERN OF CALCIFICATION, OR IS TOTAL CALCIUM BURDEN THE ONLY RELEVANT VARIABLE? Postmortem radiographs of coronary artery segments with morphologically determined plaques have indicated a wide range of plaque types present at segments, showing a specific pattern of calcification (5) (Fig. 6). Plaque erosions were exclusively present in areas with stippled or no calcification. Plaque ruptures were most frequently seen in areas of speckled calcification, but were also present in fragmented or diffuse calcification. Curiously, no ruptures were seen in segments devoid of any calcification. Thin-capped atheromas were most frequently present in areas of speckled calcification, but were also seen in heavily calcified or uncalcified areas, suggesting that calcification pattern is not helpful in diagnosing these lesions. Healed ruptures are almost always seen in areas of calcification, and most frequently in diffusely calcified areas (5). Thus, in conjunction with other imaging modalities that recognize lipid core size, it is possible that the presence of irregular, mild to moderate calcification may aid in the detection of plaques particularly prone to rupture. In a plaque without a significant necrotic core, smooth muscle cells may calcify as a plate or solid mass, with little inflammatory activity in the form of macrophage infiltration or successive ruptures. However, multiple healed ruptures are typically accompanied by areas of irregular calcium deposits, possibly initiated by a series of intraplaque hemorrhages and organization.

IS CALCIUM A DESIRABLE OR UNDESIRABLE COMPONENT OF PLAQUES? There is an ongoing debate as to the effect of calcification on "stability" of plaques: Does calcification render a plaque more prone to rupture or is it a marker of plaque quiescence? Biomechanical studies based on computer models have suggested, as stated above, that calcium may impart stability to the atherosclerotic plaque (43). Several limitations must be considered within these issues. Pathology studies have shown that nearly 25% of acute plaque ruptures occur in areas of dense calcification. In addition, the debate about calcification overlooks thrombi arising in the absence of plaque disruption (i.e., plaque erosions, which have typically little or no calcium). Finally, plaque calcification has been associated with positive remodeling (46), probably as a function of inflammation, which is desirable in the sense of maintaining plaque lumen, but potentially undesirable in that remodeling is a marker of plaque activity.

Genetic variability in tissue calcification. Tomographically or radiographically detectable calcification is not present in all patients with severe coronary artery disease and coronary heart disease risk factors, but it is a function of age, renal function, vitamin D levels, and other aspects of bone metabolism (53), the insertion/deletion (I/D) polymorphism for angiotensin-converting enzyme (54), and diabetes in women (5). Genetic variations in matrix inhibitory proteins such as matrix gla protein likely play a role in the degree of atherosclerotic plaque calcification in the coronary arteries (55), and polymorphisms for tumor necrosis factor, and inflammatory cytokines, may also influence coronary artery calcification (56). It has been estimated that a large proportion of variation in coronary artery calcification is not due to traditional risk factors (57), and

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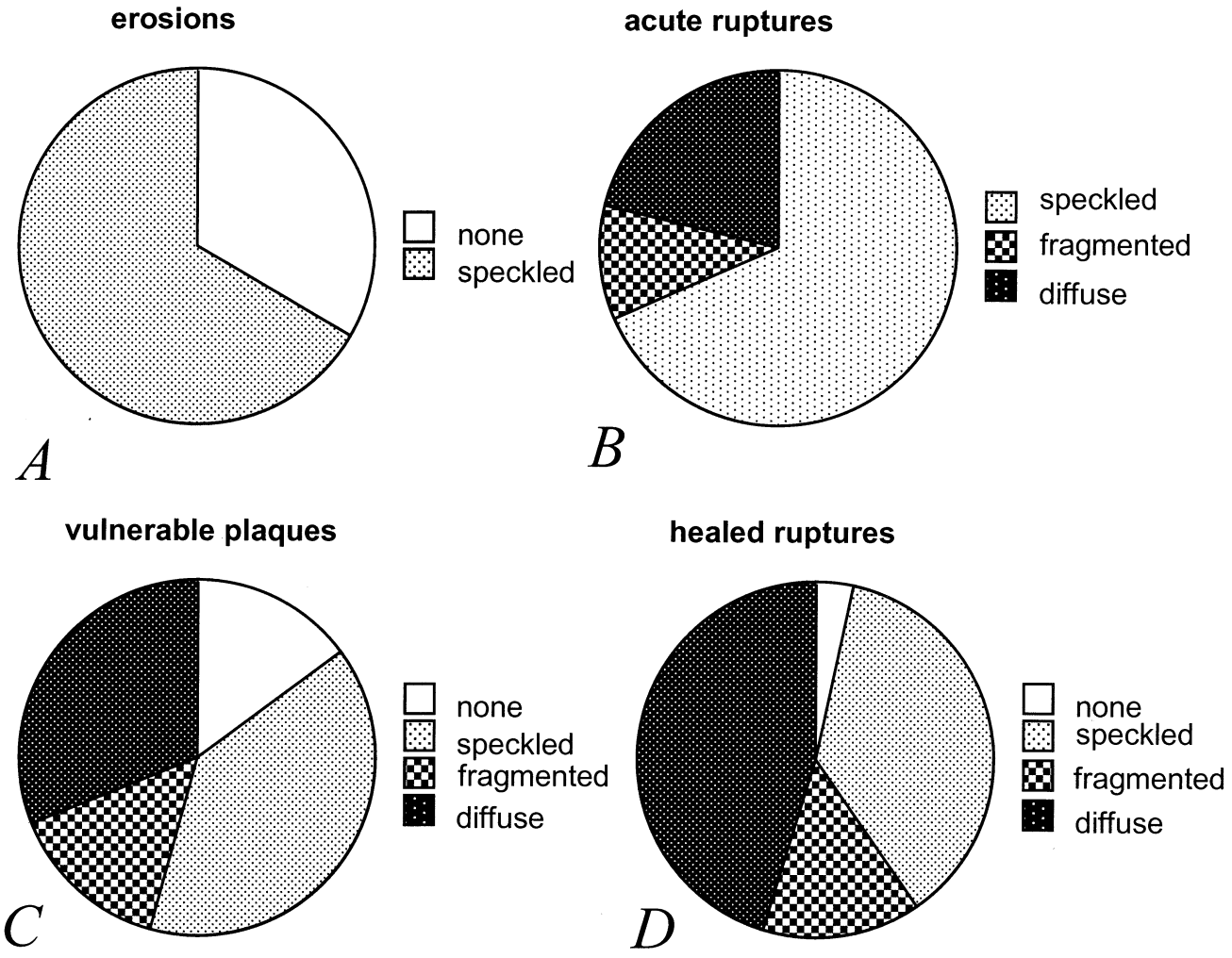

Figure 6. Relationship between plaque morphology and radiographic calcification, autopsy arteries. Reproduced with permission. Burke AP, et al. Pathophysiology of Calcium Deposition in Coronary Arteries. HERZ 2001;26:239–44. (Copyright Urban & Vogel. Reproduced with permission.)

genetic linkage studies have pointed to chromosome 6p21.3 (58). One could foresee the crude total calcium score eventually replaced with one weighted for calcium distribution in the coronary arteries, other metabolic markers, and genetic profiles in order to more accurately predict risk of coronary events.

INFLAMMATORY ACTIVITY

Is inflammation a marker of plaque bioactivity? Inflammation in coronary and aortic plaques has long been associated with plaque "instability" (37,59–61). The relationship between inflammation and acute coronary syndromes has been highlighted by recent correlations between markers of systemic inflammation, especially C-reactive protein, and CHD (62). Relevant to potential imaging for inflammatory components, it is evident that inflammation in atherosclerotic plaques is heterogeneous, consisting of various cells types (including monocytes, macrophages, T-cells, B-cells (63), neutrophils, and mast cells) and occurring in various sites of the plaque, including the adventitia, shoulder region of the atheroma, and within the fibrous cap.

Most ruptured plaques are characterized by a large pool of lipid within the necrotic debris and a thin fibrous cap with a dense infiltration of macrophages. The nature of the inflammatory infiltrate within the cap region has been extensively studied. The release of matrix-digesting enzymes by these cells is believed to contribute to plaque rupture. Also, experimental evidence shows that macrophage myeloperoxidase (MPO) may be responsible for the disruption of the fibrous cap in plaque rupture (64) and that MPO-containing macrophages within the mural thrombus may be associated with occlusive acute plaque ruptures (33). Subsets of macrophages rich in myeloperoxidase are present in the fibrous cap and constitute approximately 13% of the total population at sites of rupture (33). Some evidence that there is more thermal heterogeneity in plaques from patients with unstable angina and acute MI, than in plaques from patients with stable angina (65). Thus, imaging techniques that are able to detect enzymatic pathways that alter temperate or pH have the potential, yet unproven, to identify incipient plaque rupture.

Prevalence and distribution of inflammatory cells. Inflammatory cells, in particular macrophages, are a component of all plaque types in all arterial trees and in young and elderly patients (13), and they have a broad relationship with other pathology and clinical correlates of CHD risk. The degree of intimal and adventitial inflammation increases with increased luminal narrowing (1). Features associated with culprit lesions, namely plaque area and lipid core area, correlate positively with macrophage content (25). Virmani et al. (32) have shown that the degree of macrophage infiltration is greater in acute plaque rupture than in thin-cap atheromas or fibrocalcific plaques. Moreno et al. (66) have shown that the area composed of macrophages and tissue factor is greater in atherectomy samples from patients with unstable syndromes versus stable angina. In human aortic samples, Felton et al. (37) demonstrated that the plaque area occupied by macrophages is significantly greater in disrupted plaques than in nondisrupted segments taken from the same aortas.

The distribution of macrophage infiltration may be as important as total macrophage content in assessing plaque vulnerability. Macrophage infiltrates within a thin cap have been considered an important component of the vulnerable plaque. In comparison, fatty streaks, or intimal xanthomas, are rich in macrophages, but they are not rupture-prone lesions. Surface foam cells overlying an intact fibrous cap, described to be common in saphenous vein graft atheromas (67), are also frequent in coronary plaques but are not likely to be a signal of impending disruption.

Macrophages and monocytes are not the only inflammatory cells in atherosclerotic plaques. The T-cells modulate the progression of the atherosclerotic plaque by the elaboration of growth factors and cytokines that affect endothelial cell regulation, smooth muscle cell proliferation, and macrophage differentiation (68). Neutrophils frequently accompany MPO-positive macrophages at the site of plaque disruption (33). Mast cells, which contain neutral proteases and tumor necrosis factor-alpha, have been implicated as a mechanism of rupture and have been shown to be located in the shoulder regions.

Could inflammatory plaque imaging identify at-risk patients? Currently, several methods are under investigation for detecting intimal macrophages, either using tracers attached to photodynamic compounds (69), or tracers that are ingested by surface macrophages and labeled with magnetic resonance (MR)-sensitive iron (70) or other radiolabeled antibodies directed toward macrophage cell receptor or matrix metalloproteins. Recently, annexin-based radionuclide imaging of apoptotic macrophages has been suggested as a means for identifying plaques prone to rupture. A study comparing matched segments of atherosclerotic plaques from bilateral femoral arteries demonstrated that, unlike plaque burden and percent lipid core, inflammation was not distributed homogeneously, suggesting that local identification of inflammation should provide information as to local vulnerability in excess to that of systemic factors (71). The heterogeneity of inflammatory infiltrates within atherosclerotic plaques and the surrounding adventitia suggests that imaging techniques developed for detection of macrophages should embrace other lesion characteristics, such as lipid pools or biochemical changes, before assigning an increased risk for vulnerability.

CORRELATION OF RISK FACTORS AND PLAQUE TYPES, AND RELEVANCE TO SCREENING STRATEGIES

What is the variability of the atherosclerotic process in clinically relevant subgroups who are candidates for atherosclerosis imaging? GENDER. The relationships between traditional risk factors and culprit plaque morphology, including plaque rupture and cholesterol, and plaque erosion and smoking, are similar in both men and women (27). However, several gender-based differences exist in plaque morphology. In general, the coronary plaques of women have been shown to be more cellular than those of men, possibly because of decreased lipid, especially in the premenopausal years (28,29). Mean plaque burden and plaque calcification is less in women up to age 70 who die with severe coronary atherosclerosis. Plaques of premenopausal women demonstrate relatively little necrotic core and calcification in comparison to men and postmenopausal women (30), possibly reflecting the protective effect of estrogen on the formation of large necrotic cores. The proportion of fatal atherothrombosis in premenopausal women that is due to plaque erosion is much higher than in men (22,27,30). The cause for this relative increase is likely due to a decrease in the rate of plaque ruptures in this age group, but population-adjusted rates of fatal plaque erosion are similar in men and women under the age of 50 years (23).

AGE. A consistent finding in plaque composition is the relationship between calcified atherosclerosis and age. Gertz et al. (31) showed that the coronary artery plaques of nonagenarians are composed primarily of fibrous tissue, suggesting that the lipid content of plaque decreases with age.

ETHNIC GROUP. Relatively little is known about racial differences in plaque composition. A recent study (23) has demonstrated a similar relationship between risk factors and culprit plaque morphology in blacks and whites, although the rate of sudden death in blacks dying without acute thrombus, and in the setting of cardiomegaly, is greater than in whites. Clinical studies have shown that the calcification rate of atheromatous plaque is lower in blacks than in whites, suggesting that screening for calcium in blacks may not be as sensitive as in whites (72,73).

HYPERCHOLESTEROLEMIA AND DIABETES MELLITUS. Several autopsy studies have shown a correlation between increased serum cholesterol and lipid rich plaques, specifically thin cap atheromas and plaque rupture (21,23,30), as well as an association between diabetes and healed plaque ruptures and plaque with large necrotic cores. A possible positive correlation exists between calcification and diabetes, especially in women (5). These data suggest that, in groups

with specific risk factors, a negative screening test for lipid-rich or calcified plaques may have a higher predictive value for the absence of disease than in patients without these risk factors.

PUTTING IT ALL TOGETHER: VULNERABLE PLAQUE SCORING SYSTEM? IS THE SUM GREATER THAN THE PARTS?

It is difficult to prove a substantial incremental value for imaging atherosclerotic components (above and beyond assessing plaque burden) in predicting acute coronary events. The majority of patients with acute coronary events have two- or three-vessel disease and substantial plaque burden. However, young patients with premature disease often have relatively little plaque burden. Furthermore, imaging of the lumen is not particularly helpful in identifying plaques prone to rupture. Once lesion-targeted intervention is shown to be efficacious, plaque component imaging will become routine, as is risk factor targeting today. Another possible benefit of plaque component imaging will be the anatomic characterization of coronary artery atherosclerosis, which is a heterogeneous pathologic entity. For example, if a patient is identified as having numerous lipid-rich plaques, approaches to prevent rupture will form the prevention strategy, whereas if there are few lipid-rich plaques, prevention of plaque erosion, or strategies to prevent progression of fibrous-rich plaques will be of paramount concern.

Currently, no vulnerable plaque scoring system is available for imaging applications. The data reviewed here suggest that a potential scoring system should include factors of: 1) fibrous cap thickness, 2) necrotic core size (both percent of cross sectional plaque area, as well as length), and 3) degree of macrophage infiltration, either assessed thermally or by other macrophage localization methods. It is conceivable in the near future that such a 10-point grading system (three tiers for each feature, and all negative) could be applied to stratify plaques in regard to likelihood of future rupture. The degree of positive remodeling of expansion of the internal elastic lamina and extent of vasa vasorum, which has been associated with plaque instability in the coronary arteries and aortic plaque rupture (74) and the degree of proliferation of intimal vessels (vasa vasorum) (75), could also be factored into the scoring system of vulnerable plaques. Because imaging techniques today lack the ability to detect of each of the above parameters it may not be feasible to include all markers of instability into a scoring system, but one can imagine modifications of such a scoring scheme as detection techniques improve.

FUTURE DIRECTIONS

1. The science of pathologically defining the characteristics of vulnerable plaques must be made relevant to the detection of vulnerable patients. For example, as our ability improves to image individual components of atherosclerosis, the accuracy of these determinations must be measured.
2. Because much of our knowledge on vulnerable plaque is derived from referred populations within pathology studies, the applicability of these data to clinical screening populations must be demonstrated.
3. Tight collaborations between experts in cardiovascular pathology and clinicians is encouraged to ensure that proper atherosclerosis "targets" are pursued to improve the detection of at-risk patients.
4. The development of "vulnerable plaque scoring systems," much like considering multiple coronary risk factors in coronary event prediction, is encouraged.

TASK FORCE 2 REFERENCE LIST

1. Baroldi G, Silver MD, Mariani F, Giuliano G. Correlation of morphological variables in the coronary atherosclerotic plaque with clinical patterns of ischemic heart disease. Am J Cardiovasc Pathol 1988;2:159–72.
2. Kragel AH, Gertz SD, Roberts WC. Morphologic comparison of frequency and types of acute lesions in the major epicardial coronary arteries in unstable angina pectoris, sudden coronary death and acute myocardial infarction. J Am Coll Cardiol 1991;18:801–8.
3. Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of atherosclerotic plaques in the four major epicardial coronary arteries in acute myocardial infarction and in sudden coronary death. Circulation 1989;80:1747–56.
4. Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of coronary arterial plaques in isolated unstable angina pectoris with pain at rest. Am J Cardiol 1990;66: 562–7.
5. Burke AP, Weber DK, Kolodgie FD, Farb A, Taylor AJ, Virmani R. Pathophysiology of calcium deposition in coronary arteries. Herz 2001;26:239–44.
6. Mautner GC, Mautner SL, Froehlich J, et al. Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation. Radiology 1994;192:619–23.
7. Srivatsa SS, Edwards WD, Boos CM, et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. J Am Coll Cardiol 1997;29:955–63.
8. Hangartner JR, Charleston AJ, Davies MJ, Thomas AC. Morphological characteristics of clinically significant coronary artery stenosis in stable angina. Br Heart J 1986;56:501–8.
9. Flugelman MY, Virmani R, Correa R, et al. Smooth muscle cell abundance and fibroblast growth factors in coronary lesions of patients with nonfatal unstable angina. A clue to the mechanism of transformation from the stable to the unstable clinical state. Circulation 1993;88:2493–500.
10. Arbustini E, Grasso M, Diegoli M, et al. Coronary atherosclerotic plaques with and without thrombus in ischemic heart syndromes: a morphologic, immunohistochemical, and biochemical study. Am J Cardiol 1991;68:36B–50B.
11. Virmani R, Roberts WC. Extravasated erythrocytes, iron, and fibrin in atherosclerotic plaques of coronary arteries in fatal coronary heart disease and their relation to luminal thrombus: frequency and significance in 57 necropsy patients and in 2958 five mm segments of 224 major epicardial coronary arteries. Am Heart J 1983;105:788–97.
12. Moreno PR, Bernardi VH, Lopez-Cuellar J, et al. Macrophages, smooth muscle cells, and tissue factor in unstable angina. Implications for cell-mediated thrombogenicity in acute coronary syndromes. Circulation 1996;94:3090–7.
13. Vink A, Schoneveld AH, Poppen M, de Kleijn DP, Borst C, Pasterkamp G. Morphometric and immunohistochemical characterization of the intimal layer throughout the arterial system of elderly humans. J Anat 2002;200:97–103.
14. Carr SC, Cheanvechai V, Virmani R, Pearce WH. Histology and clinical significance of the carotid atherosclerotic plaque: implications for endovascular treatment. J Endovasc Surg 1997;4:321–5.

15. Carr S, Farb A, Pearce WH, Virmani R, Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. J Vasc Surg 1996;23:755–65.
16. Little WC. Angiographic assessment of the culprit coronary artery lesion before acute myocardial infarction. Am J Cardiol 1990;66:44G–7G.
17. Muller JE, Tofler GH. Triggering and hourly variation of onset of arterial thrombosis. Ann Epidemiol 1992;2:393–405.
18. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–71.
19. Janowitz WR. CT imaging of coronary artery calcium as an indicator of atherosclerotic disease: an overview. J Thorac Imaging 2001;16:2–7.
20. Guthrie RB, Vlodaver Z, Nicoloff DM, Edwards JE. Pathology of stable and unstable angina pectoris. Circulation 1975;51:1059–63.
21. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336:1276–82.
22. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93:1354–63.
23. Burke AP, Farb A, Pestaner J, et al. Traditional risk factors and the incidence of sudden coronary death with and without coronary thrombosis in blacks. Circulation 2002;105:419–24.
24. Arbustini E, Dal Bello B, Morbini P, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 1999;82:269–72.
25. Bezerra HG, Higuchi ML, Gutierrez PS, et al. Atheromas that cause fatal thrombosis are usually large and frequently accompanied by vessel enlargement. Cardiovasc Pathol 2001;10:189–96.
26. Burke AP, Farb A, Liang YH, Smialek J, Virmani R. Effect of hypertension and cardiac hypertrophy on coronary artery morphology in sudden cardiac death. Circulation 1996;94:3138–45.
27. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;97:2110–6.
28. Dollar AL, Kragel AH, Fernicola DJ, Waclawiw MA, Roberts WC. Composition of atherosclerotic plaques in coronary arteries in women less than 40 years of age with fatal coronary artery disease and implications for plaque reversibility. Am J Cardiol 1991;67:1223–7.
29. Mautner SL, Lin F, Mautner GC, Roberts WC. Comparison in women versus men of composition of atherosclerotic plaques in native coronary arteries and in saphenous veins used as aortocoronary conduits. J Am Coll Cardiol 1993;21:1312–8.
30. Burke AP, Farb A, Malcom G, Virmani R. Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis. Am Heart J 2001;141:S58–S62.
31. Gertz SD, Malekzadeh S, Dollar AL, Kragel AH, Roberts WC. Composition of atherosclerotic plaques in the four major epicardial coronary arteries in patients greater than or equal to 90 years of age. Am J Cardiol 1991;67:1228–33.
32. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–75.
33. Burke AP, Kolodgie FD, Virmani R, Farb A, Weber DK. Role of circulating myeloperoxidase positive monocytes and neutrophils in occlusive coronary thrombi (abstr). J Am Coll Cardiol 2002;39 Suppl:256A.
34. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92:1355–74.
35. Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1994;89:2462–78.
36. Stary HC. Composition and classification of human atherosclerotic lesions. Virchows Arch A Pathol Anat Histopathol 1992;421:277–90.
37. Felton CV, Crook D, Davies MJ, Oliver MF. Relation of plaque lipid composition and morphology to the stability of human aortic plaques. Arterioscler Thromb Vasc Biol 1997;17:1337–45.
38. Virmani R, Burke AP, Kolodgie FD, Farb A. Vulnerable plaque: the pathology of unstable coronary lesions. J Interv Cardiol 2002;15:439–46.
39. Kolodgie FD, Burke AP, Farb A, et al. The thin-cap fibroatheroma: the major precursor lesion to acute coronary syndromes. Curr Opin Cardiol 2001;16:285–92.
40. Lendon CL, Davies MJ, Richardson PD, Born GV. Testing of small connective tissue specimens for the determination of the mechanical behaviour of atherosclerotic plaques. J Biomed Eng 1993;15:27–33.
41. Rekhter MD, Hicks GW, Brammer DW, et al. Hypercholesterolemia causes mechanical weakening of rabbit atheroma : local collagen loss as a prerequisite of plaque rupture. Circ Res 2000;86:101–8.
42. Galis ZS. Atheroma morphology and mechanical strength: looks are important, after all—lose the fat. Circ Res 2000;86:1–3.
43. Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. Circulation 2001;103:1051–6.
44. Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions. A structural analysis with histopathological correlation. Circulation 1993;87:1179–87.
45. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet 1989;2:941–4.
46. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. Circulation 2002;105:297–303.
47. Pasterkamp G, Schoneveld AH, van der Wal AC, et al. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. J Am Coll Cardiol 1998;32:655–62.
48. Pasterkamp G, Schoneveld AH, Hijnen DJ, et al. Atherosclerotic arterial remodeling and the localization of macrophages and matrix metalloproteases 1, 2 and 9 in the human coronary artery. Atherosclerosis 2000;150:245–53.
49. Sabate M, Kay IP, de Feyter PJ, et al. Remodeling of atherosclerotic coronary arteries varies in relation to location and composition of plaque. Am J Cardiol 1999;84:135–40.
50. Proudfoot D, Shanahan CM. Biology of calcification in vascular cells: intima versus media. Herz 2001;26:245–51.
51. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. J Am Coll Cardiol 1992;20:1118–26.
52. Burke AP, Taylor A, Farb A, Malcom GT, Virmani R. Coronary calcification: insights from sudden coronary death victims. Z Kardiol 2000;89 Suppl 2:49–53.
53. Watson KE, Abrolat ML, Malone LL, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997;96:1755–60.
54. Pfohl M, Athanasiadis A, Koch M, et al. Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene is associated with coronary artery plaque calcification as assessed by intravascular ultrasound. J Am Coll Cardiol 1998;31:987–91.
55. Herrmann SM, Whatling C, Brand E, et al. Polymorphisms of the human matrix gla protein (MGP) gene, vascular calcification, and myocardial infarction. Arterioscler Thromb Vasc Biol 2000;20:2386–93.
56. Keso T, Perola M, Laippala P, et al. Polymorphisms within the tumor necrosis factor locus and prevalence of coronary artery disease in middle-aged men. Atherosclerosis 2001;154:691–7.
57. Valdes AM, Wolfe ML, Tate HC, Gefter W, Rut A, Rader DJ. Association of traditional risk factors with coronary calcification in persons with a family history of premature coronary heart disease: the study of the inherited risk of coronary atherosclerosis. J Investig Med 2001;49:353–61.
58. Lange LA, Lange EM, Bielak LF, et al. Autosomal genome-wide scan for coronary artery calcification loci in sibships at high risk for hypertension. Arterioscler Thromb Vasc Biol 2002;22:418–23.
59. Biasucci LM, Liuzzo G, Angiolillo DJ, Sperti G, Maseri A. Inflammation and acute coronary syndromes. Herz 2000;25:108–12.

60. Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. Am J Cardiol 1989;63:114E–20E.
61. Libby P, Geng YJ, Sukhova GK, Simon DI, Lee RT. Molecular determinants of atherosclerotic plaque vulnerability. Ann N Y Acad Sci 1997;811:134–42.
62. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. Circ Res 2001;89:763–71.
63. Hansson GK. The B cell: a good guy in vascular disease? Arterioscler Thromb Vasc Biol 2002;22:523–4.
64. Sugiyama S, Okada Y, Sukhova GK, Virmani R, Heinecke JW, Libby P. Macrophage myeloperoxidase regulation by granulocyte macrophage colony-stimulating factor in human atherosclerosis and implications in acute coronary syndromes. Am J Pathol 2001;158:879–91.
65. Stefanadis C, Diamantopoulos L, Vlachopoulos C, et al. Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo: a new method of detection by application of a special thermography catheter. Circulation 1999;99:1965–71.
66. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775–8.
67. Farb A, Weber DK, Burke AP, Kolodgie FD, Virmani R. Morphology of stenosis progression and rupture in saphenous vein bypass grafts (abstr). Circulation 1999;100 Suppl:I599.
68. Virmani R, Kolodgie FD, Burke AP, Farb A. Inflammation in coronary atherosclerosis—pathological aspects. In: Mehta JL, editor. Inflammatory and infectious basis of atherosclerosis. Boston, MA: Birkhauser Verlag, 2001:23–46.
69. Tawakol A, Fischman A, Hasan T, Zahra T, Muller J, Hamblin M. Accumulation of a novel macrophage-targeting photodynamic compound within lipid-rich atherosclerotic plaques (abstr). J Am Coll Cardiol 2002;39 Suppl:248A.
70. Azadpour M, Jagannath C, Chan D, et al. Lipid coated SPIO: introducing a novel tracer for MR imaging of macrophage infiltration in vulnerable atherosclerotic plaque (abstr). J Am Coll Cardiol 2002;39 Suppl:389A.
71. Vink A, Schoneveld AH, Richard W, et al. Plaque burden, arterial remodeling and plaque vulnerability: determined by systemic factors? J Am Coll Cardiol 2001;38:718–23.
72. Budoff MJ, Yang TP, Shavelle RM, LaMont DH, Brundage BH. Ethnic differences in coronary atherosclerosis. J Am Coll Cardiol 2002;39:408–12.
73. Newman AB, Naydeck BL, Whittle J, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Racial differences in coronary artery calcification in older adults. Arterioscler Thromb Vasc Biol 2002;22:424–30.
74. Moreno PR, Purushothaman KR, Fuster V, O'Connor WN. Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. Circulation 2002;105:2504–11.
75. Burke AP, Farb A, Malcom GT, Liang Y, Smialek JE, Virmani R. Plaque rupture and sudden death related to exertion in men with coronary artery disease. JAMA 1999;281:921–6.
76. Stary HC. Changes in components and structure of atherosclerotic lesions developing from childhood to middle age in coronary arteries. Basic Res Cardiol 1994;89 Suppl 1:17–32.

Task Force #3—What Is the Spectrum of Current and Emerging Techniques for the Noninvasive Measurement of Atherosclerosis?

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This task force reviews the technical status and strength of evidence for the use of carotid ultrasonography, coronary computed tomography (CT), cardiovascular magnetic resonance imaging (CMR), brachial artery reactivity testing (BART), and the ankle-brachial index (ABI) in the noninvasive indication of the functional or anatomic manifestations of atherosclerosis. These methods are either currently used or have potential for use in the cardiovascular risk assessment.

The U.S. Preventive Services Task Force recommended in its 1996 report that any screening test utilized in the assessment of risk can be considered effective if it: 1) provides an accurate determination of the likelihood that an asymptomatic person has the condition (accuracy); 2) if its results are stable when repeated (reliability); and 3) if early intervention is likely to have a beneficial impact (1). As an extension of these concepts, we further recommend that any imaging method for prediction of cardiovascular risk should have incremental value to the risk predicted by office-based risk assessment. This Task Force examined atherosclerosis imaging from the perspective of accuracy and reliability of the technologies, whereas the issue of appropriate intervention and incremental value is more fully discussed in other Task Force reports of this Bethesda Conference. This Task Force urges the adoption of standard methodology for each of the imaging methods so that data can be shared and assessed for quality control measurements. Currently, different protocols and standardization are used by different laboratories, and it is difficult to establish normal and abnormal (age and gender adjusted) values. Also, prior to the widespread adoption of any imaging technique, it is essential that it be shown to be reproducible, have low biologic variability, and to be clinically useful. In addition, the Task Force recognizes that although the literature often refers to test outcomes as dichotomous for purposes of analysis, the test results of all of these techniques are actually on a continuous scale. Consideration of actual results, adjusted for age, gender, and race, adds valuable information to just a positive or negative result.