thematic review

Thematic review series: Patient-Oriented Research

Imaging atherosclerosis: state of the art

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Abstract The ability to image obstructive arterial disease brought about a revolution in clinical cardiovascular care; the development of newer technologies that image arterial wall thicknesses, areas, volumes, and composition allows valid imaging of atherosclerosis for the first time. Development of noninvasive imaging of atherosclerosis has further led to a quantum shift in research in the field by enabling the study of asymptomatic populations and thus allowing investigators to focus on preclinical disease without the many biases associated with the study of symptomatic patients. These noninvasive investigations have broad implications for clinical care as well. Coronary angiography, computed tomographic (CT) imaging of coronary calcium, intravascular ultrasound, multidetector CT angiography, B mode ultrasound of the carotid arteries, and MRI of the carotid arteries all have unique strengths and weaknesses for imaging atherosclerosis. Certain of these techniques are extremely useful as outcome variables for clinical trials, and others are uniquely useful as predictors of the risk of cardiovascular disease. All are informative in one way or another with regard to the role of plaque remodeling and composition in disease causation. CT and MRI technology are advancing very rapidly, and research and clinical uses of these imaging modalities promise to further advance our understanding of atherosclerosis and its prevention.— Crouse, J. R., III. **Imaging atherosclerosis: state of the art. *J. Lipid Res.* 2006.** 47: **1677–1699.**

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WHY IMAGE ATHEROSCLEROSIS? REMODELING AND THE VULNERABLE PLAQUE

Although investigators have studied atherosclerosis at the autopsy table and its consequences in the clinic and hospital for well over a century, its quantification in vivo is a more recent advance. As is well known, atherosclerosis (and its progression) is the key substrate for the development of arterial vascular symptoms. As such, it represents a rational outcome variable for studies of risk factors, a rational independent variable for studies of clinical outcome, and a rational end point for clinical trials. Within the last 20 years, investigators have developed methods, some of them noninvasive, for imaging this process in vivo. The development of noninvasive methods for imaging atherosclerosis has resulted in a paradigm shift in our understanding and management of vascular disease by enabling its identification at a preclinical stage (1). Early identification is critical for the prevention of a condition that is clinically silent during prolonged development and that manifests 50% of first events as either myocardial infarction or sudden death. Noninvasive investigation of healthy individuals additionally avoids the several biases associated with the study of symptomatic patients (2). Atherosclerosis may be defined in terms of wall thickening, stenosis, plaque, and plaque composition and dynamics, and the associations between these risk factors and symptom development are complex. Modern imaging methods are capable of studying all of these structural manifestations of atherosclerosis.

Angiographic imaging of obstructive (>50% stenotic) arterial narrowing antedated the imaging of atherosclerosis by ~25 years, but in 1982, Blankenhorn and Curry (3) reviewed comparisons of angiography with pathology dating back to 1962 and concluded that there was "general agreement that angiography underestimates disease when compared with pathologic study." The large disparity between atherosclerosis as quantified at autopsy and stenosis quantified at coronary angiography provided an early indication of the need to distinguish between these two and to understand the source of the discrepancy. Around the same time, Clarkson et al. (4) made the novel observation of expansive arterial "remodeling" in nonhuman primates under the influence of atherosclerosis (dynamic enlargement of the artery without constriction of the lumen), further underscoring the need for greater understanding of atherosclerosis as well as stenosis. In 1987, Glagov et al. (5) extended this observation to humans through the observation of pathologic specimens.

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The observation that considerable atherosclerosis could exist without severe lumen stenosis led several investigators to question the role of stenotic disease in symptom development, and in 1993, Brown et al. (6) summarized information derived predominantly from a careful study of coronary angiographic data that suggested that most nonfatal coronary events resulted from sudden rupture of a previously mildly obstructive (<50% stenotic) plaque rather than from plaques with ⩾50% stenosis. Investigators now believe that, in addition to plaque rupture, plaque erosion and calcified nodules can cause thrombosis and acute events and that even stable plaque without thrombosis may be related to events (7–9). Although it is generally agreed that lesions resulting in <50% lumen stenosis are more frequent causes of events than those resulting in ⩾50% stenosis, the proportion of fatal lesions with ⩾50% stenosis observed at autopsy may be somewhat greater than the proportion associated with nonfatal events (8, 9). Since originally proposed, it has become evident that, in addition to the expansive remodeling described above, "constrictive remodeling" (i.e., a decrease in arterial diameter in association with plaque) can also occur and that remodeling is not uniform, although the literature is inconsistent in some instances (10, 11). Discrepancies likely arise from the difficulty of interpreting a dynamic process based on observations from a single point in time and from differences in the definition of remodeling. Pasterkamp, Galis, and de Kleijn (12) summarized the variability of remodeling between individuals and between arterial beds within the same individuals, noting that femoral arteries often (59%) exhibit constrictive remodeling (**Fig. 1**). Several lines of evidence suggest that the dramatic, frequent, and catastrophic restenosis that accompanied angioplasty before the development of coated coronary stents was largely a consequence of inadequate remodeling (13).

Complementing the concept of arterial remodeling, pathologists and others have shifted focus from the study of stenotic disease to the investigation of plaque characteristics that relate to acute events. Chapman (14) noted a relation of plaque rupture to thrombosis in 1965, and in 1985, Tracy, Devaney, and Kissling (15) compared the histopathology of lesions with overlying thrombosis and "stable" lesions and noted an "inflammatory" process in the former. Falk (16) coined the term "vulnerable plaque" in 1992, characterized by a soft lipid core and thin fibrous cap, although Davies and Thomas (17) and Falk (18) noted that rupture with thrombus was not infrequently observed over plaques that were clinically silent. It is now well accepted that atherosclerosis is a dynamic inflammatory process initiated by, among other factors, lipoprotein infiltration into the subendothelial space. Intraplaque hemorrhage secondary to angiogenesis is another important factor in atherosclerotic plaque growth, inflammation, and destabilization (19). Products of the inflammatory process, matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of MMPs, are likely involved in weakening of the cap of the atherosclerotic plaque with subsequent rupture and healing or development of an acute event. Of interest, this same dynamic process is also probably involved in remodeling: hemorrhage into a plaque and MMP activity promote expansive remodeling, whereas frequent plaque rupture, healing, and accumulation of collagen may contribute to constrictive remodeling (20). It is likely that remodeling is more a function of plaque dynamics and composition than of location, although the two may be intertwined.

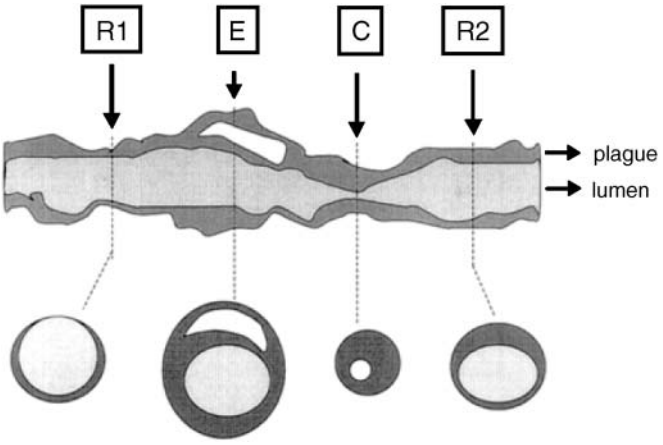

Fig. 1. Schematic presentation of the different remodeling modes. The mode and extent of arterial remodeling are mostly based on comparisons with one or two reference sites. In postmortem studies, often the vessel area in the section with the least amount of plaque (R1) is used as a reference. In intravascular ultrasound (IVUS) studies, the average of the vessel areas of a proximal (R1) and a distal (R2) site with an angiographic normal lumen is used as a reference. Expansive remodeling (E) is then found present when (vessel area R1 + R2)/2 > vessel area culprit lesion. However, constrictive remodeling (C) is evident when (vessel area R1 + R2)/2 < vessel area culprit lesion. Expansive remodeling is often associated with the presence of atheroma and inflammatory cells (see text). Reproduced with permission from Pasterkamp et al. (12).

Recent advances in imaging permit the visualization of arterial dimensions (expansive and constrictive remodeling) and the quantification not only of the extent and severity of plaque but also of its composition as well. Current research with intravascular ultrasound (IVUS), multislice computed tomography (CT) and multislice CT angiography of the coronary arteries, and both B mode and MRI of the carotid arteries may further advance our ability to identify the "culprit lesion" and follow its progress under the influence of therapy.

IMAGING OF CORONARY ATHEROSCLEROSIS

Because of its link to myocardial infarction, angina, and coronary death, coronary imaging has a long history. It has only recently become possible, however, to image coronary atherosclerosis, a task made difficult because of the motion of the heart, the small size of the coronary vessels, and their distance from the body surface. Truly valid and reliable noninvasive imaging of atherosclerosis of the coronary arteries is not yet possible.

ANGIOGRAPHIC IMAGING OF STENOSIS

Coronary angiography is the most mature and most widely used invasive technology for risk assessment in acute and chronic coronary disease. Its strengths include the ability to directly image the coronary lumen associated with the lesion of interest; drawbacks include the procedure's invasive character, the ability to image lesions only at a late stage of development, radiation exposure, and the need for the use of contrast with attendant potential for renal damage. Only lumens of arteries are visualized; thus, the method precludes the ability to evaluate wall thickness or plaque composition.

Method

Sones et al. (21) first reported on the use of selective coronary cinearteriography in 1959 and transformed the field of cardiology. The technology is well known and involves intra-arterial injection of contrast into lumens of coronary arteries followed by imaging in multiple planes, capture on video film, and interpretation by experienced readers. For clinical purposes, cardiologists and radiologists generally quantify arterial narrowing by comparison of lumen diameter at a stenotic site with that at a proximal "normal" reference site. For research purposes, investigators obtain quantitative lumen measurements (22).

Stenosis: a manifestation of atherosclerosis

Numerous approaches to the quantification of stenosis have been proposed (1). However, in light of the discussion above, it is evident that considerable atherosclerosis can exist without impinging on the lumen of the artery at all, and factors that precipitate clinical events may have more to do with plaque composition than stenosis. Nonetheless, the power of angiography to provide surprising insight into the relation of stenosis to atherosclerosis and events was summarized by Brown et al. (6) in 1993. They reviewed data showing that the underlying lesions of patients undergoing lysis of thrombosis in the setting of acute coronary events were most often only mildly obstructive and data from sequential angiographic studies showing that minimally obstructive lesions often led to clinical events. They also pointed out the discrepancy between the minimal effect of HMG-CoA reductase inhibitors (statins) to reduce stenosis and their profound ability to reduce incident coronary events, and they reviewed information that suggested that statin treatment did little to retard the progression of severely stenotic plaques but rather reduced the clinical danger of mildly obstructive plaques, thus supporting the concept that the reduction of clinical events by lipid-lowering therapy was likely more related to changes in plaque composition than to changes in stenosis.

Risk factors and stenosis

Pearson (2) summarized several epidemiologic studies that related risk factors to stenosis in 1984. In this landmark article, he noted the significant relation between age, male sex, cholesterol, HDL cholesterol, LDL cholesterol, decreasing prebeta lipoprotein, smoking, diabetes, physical activity, and multiple risk factors with coronary stenosis. Triglycerides, hypertension, obesity, and type A personality had more complex relationships. Fried and Pearson (23) identified the pitfalls of relying on stenotic disease as a marker for the impact of risk factors. They noted that risk factor patterns of patients with intermediate levels of stenosis ($<50\%$) more closely mirrored those of patients with $\geq 50\%$ stenosis than those of patients with normal-appearing coronary arteries, as would be inferred from the relation of atherosclerosis and remodeling described above.

Coronary stenosis and clinical outcome

After the early demonstration of the technique of coronary angiography, several important publications demonstrated the clinical importance of obstructive coronary artery disease (CAD) [reviewed by Fraser (24)]. Early serial coronary angiography studies demonstrated disease progression in vivo, providing evidence that the severity of stenosis was directly associated with the rate of progression (24). Also, these seminal trials provided the initial evidence that obstructive stenoses of $\geq 50\%$ and the involvement of multiple vessels were associated with clinical prognosis (24). For example, in 1973, Bruschke, Proudfit, and Sones (25) demonstrated the incremental decline in prognosis associated with single vessel, double vessel, and triple vessel disease (7 year survival of 76, 55, and 32%, respectively) and the poor survival of patients with left main CAD (37% 7 year survival).

Clinical trials with stenosis as end point

Despite the limitations described above, coronary angiography has been used extensively to define outcomes for clinical trials. The Food and Drug Administration has identified change in stenosis as a valid index of atherosclerosis change. The technique has been used in several studies to quantify retardation of progression or regression of stenosis under the influence of lifestyle or pharmacologic modifications (26–36). One recent study demonstrated congruence between a reduction in stenosis progression and a reduction of events associated with treatment with niacin and statin (36).

CT IMAGING OF CORONARY ARTERY CALCIFICATION

CT evaluation of coronary artery calcium (CAC) is attractive because it is noninvasive and directly images disease of coronary arteries. CT is automated and reliable and widely available. Disadvantages include radiation exposure, lack of ability to image walls of arteries, and the unique nature of calcium as a manifestation of arterial disease. The clinical utility of CT stems from its potential for use in risk stratification (see below). Whereas coronary angiography visualizes only the lumen of the artery, CT without contrast does not visualize the lumen; therefore, neither method visualizes the artery wall accurately.

Method

The early communications (1979 ff) that described the use of CT to image CAC used electron beam computed tomography (EBCT) (37). Initially, this technology was used to the exclusion of conventional CT; however, in 1995, Shemesh et al. (38) reported on the utility of conventional helical computed tomography (HCT) for imaging CAC. Subsequent studies that directly compared EBCT with HCT (39, 40) and the development of multiple-row detector helical computed tomography (MDCT) validated the use of the latter (**Fig. 2**). This was an advance because EBCT was available at only ~100 sites in the country, whereas MDCT is nearly universally available. The MDCT technique depends on (prospective or retrospective) electrocardiographic gating of images to avoid motion artifacts in systole and breath-holding. Early scanners required 20–40 s breath-holds, but with 64 detector MDCT, breath-hold time is reduced to 10 s. The quantification of CAC depends on summing the calcium densities from all of the coronary arteries (41).

Coronary calcium: a manifestation of atherosclerosis

With few exceptions vascular calcification occurs only in the setting of atherosclerosis, although atherosclerosis can occur without visible calcium. A great deal has been learned about the mechanism whereby arteries calcify during the last 20 years. As reviewed by Abedin, Tintut, and Demer (42) in 2004, it is evident that vascular calcification is a generalized active process arising in areas of chronic inflammation and intimately involved with the inflammatory condition of the intima now believed to be central to atherogenesis. Multiple key regulators of bone formation and bone structural proteins are expressed in atherosclerotic plaques, and basic calcium phosphate crystals can be internalized into macrophages and augment the inflammatory response (43). This process depends on the uptake of microscopic rather than macroscopic deposits of calcium, and the latter may not be as pro-inflammatory. Similarly, associations have been observed between calcification and the neovascularization that is prominent in atherosclerotic plaque (44). A strong case can be made for the initiation of calcification through pericyte action (44); however, it is also possible that calcification promotes neovascularization, or, alternatively, that some third factor is responsible for both.

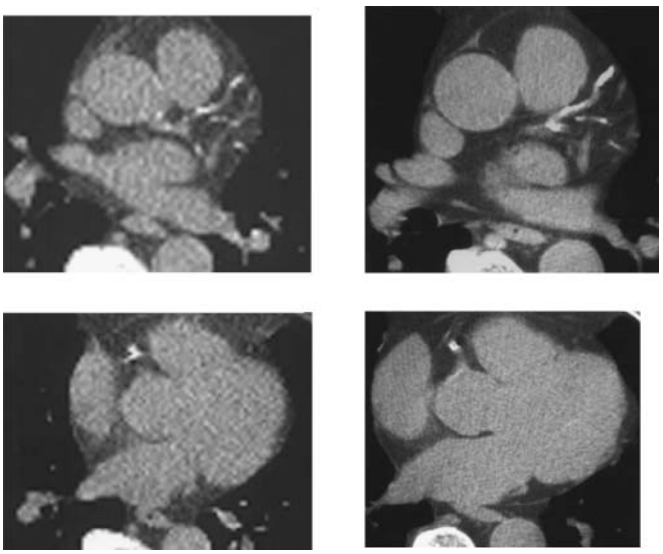

Fig. 2. Electron beam computed tomography (left) and helical computed tomography (right) of a 72 year old man. Top, calcium in the left anterior descending coronary artery and circumflex; bottom, calcium in the proximal right coronary artery. Reproduced with permission from Carr et al. (39).

The relation of vascular calcification to remodeling and instability is complex. Because calcification is a late manifestation of atherosclerosis, it is nearly inevitably found in association with stenotic CAD. Nonstenotic arteries may also demonstrate calcification, however, as calcification is associated with expansive remodeling. Mautner et al. (45) found that calcification occurred in 93% of arteries with >75% luminal but only in 14% of arteries with <25% stenosis. Whether ruptured plaques are more or less likely to be calcified is unclear (46). Some investigators argue that unstable plaques are less likely to be calcified: cases of sudden death with plaque erosion (as opposed to rupture) were significantly less likely to show calcification (47). An unusual form of medial calcification in peripheral arteries associated with diabetes and chronic renal failure has been described (42). The pathogenesis of medial calcification is unlikely to be the same as that of calcification associated with atherosclerosis related to chronic exposure to the risk factors described above.

Risk factors and coronary calcification

EBCT was first used in 1989 as a clinical tool to detect CAC (48). Since then, numerous communications have identified associations of CAC with CAD risk factors. Age and gender, as would be expected, are the strongest correlates with CAC score, and normative data from population-based samples of older individuals in the United States (49) and Europe (50) and of younger individuals (51, 52) have been published (**Table 1**). CAC scores are highly skewed toward 0. One large epidemiologic study has dealt with this by evaluating associations of risk factors with the presence or absence of CAC and, subsequently, in individuals with calcium, with its extent (49). In general, CAD risk factors are associated with CAC, including hypertension, smoking, and LDL, HDL, and triglyceride concentrations (49–52). Diabetes is a particularly strong risk factor for CAC (53). In the Multi-Ethnic Study of Atherosclerosis (49), area under the receiver-operator curve for a model that related a roster of risk factors to CAC ranged from 0.77 in blacks to 0.82 in whites; risk factor models explained 13–21% of the variability in the amount of CAC. The greater the number of risk factors, the higher the CAC score; however, in a formal test, the Framingham risk score proposed by the Adult Treatment Panel III (ATP III) guidelines (54) was found to underestimate CAC in women (55). Dabelea et al. (56) found insulin resistance to be associated with CAC in

TABLE 1. Distribution of CAC scores in men and women by ethnicity

	Women				Men			
	Age (years)				Age (years)			
Percentiles by Race	45–64	55–64	65–74	75–84	45–54	55–64	65–74	75–84
White, n	379	356	379	194	321	225	375	174
25th	0	0	0	20	0	0	21	103
50th	0	0	13	106	0	28	145	285
75th	0	16	119	370	22	155	540	1,200
90th	8	102	391	9121	110	452	1,245	2,933
95th	31	209	674	1,535	207	742	2,271	4,619
Chinese, n	109	107	103	52	102	94	102	50
25th	0	0	0	0	0	0	0	11
50th	0	0	5	32	0	5	34	81
75th	0	18	70	146	14	67	174	205
90th	12	105	246	.∼8	89	242	487	769
95th	44	213	426	556	184	429	803	1,299
Black, n	274	241	278	110	214	192	206	98
25th	0	0	0	0	0	0	0	23
50th	0	0	0	47	0	0	32	141
75th	0	5	77	214	2	40	191	516
90th	9	74	210	582	45	172	575	1,281
95th	38	173	561	963	105	218	945	2,176
Hispanic, n	218	196	169	86	205	177	149	75
25th	0	0	0	0	0	0	1	36
50th	0	0	1	45	0	3	56	153
75th	0	2	51	5	9	75	247	494
90th	2	50	203	557	88	291	666	1,221
95th	18	118	361	917	195	512	1091	1,943

Reproduced with permission from reference 49.

type 1 diabetic patients and controls independent of CAD risk factors: male controls and diabetic patients had more CAC than females, but this difference was eliminated in diabetic but not nondiabetic patients after control for waist-to-hip ratio, waist circumference, or visceral fat. An association of the polycystic ovarian syndrome with increased CAC did not persist after adjusting for body mass index (57). Hostility (58) and familial hypercholesterolemia (59) have also been related to CAC.

Of interest, older African Americans appear to have less CAC than age-matched Caucasians in most (49, 60–63) but not all (64) studies, even though wall thickness of the extracranial carotid arteries (measured by B mode) is thicker in African Americans (65). This observation poses the question of whether unique features of calcification per se distinguish African Americans. Of interest, several conditions associated with osteopenia (diabetes, aging, menopause, chronic renal failure) are also associated with vascular calcification (42). Doherty et al. (66) reviewed genetic links of CAC with angiotensin 1-converting enzyme, apolipoprotein E, E-selectin, MMP 3, CC chemokine receptor 2, and estrogen receptor α. Recently, investigators have additionally noted associations of CAC with protein tyrosine phosphatase-N1 polymorphisms, paraoxonase 1, lipoprotein lipase, and CD 40 as well as multiple other genes (67–83).

Coronary calcification and clinical outcome

The relation of CAC to clinical outcome has stimulated considerable interest. The association is somewhat complicated by the observation that in some cases, an EBCT or MDCT scan that reveals a large amount of calcium may provoke the patient to seek further diagnostic workup; thus, the diagnostic test becomes, in a sense, an intervention. An American College of Cardiology/American Heart Association consensus document on the clinical utility of CAC testing was published in 2000 (84). Pletcher et al. (85) evaluated the studies reviewed in that document and found only four communications predating 2004 (86–89) that met rigid standards for epidemiologic investigation (asymptomatic populations, documented follow-up for coronary heart disease outcomes, adjustment for multiple other risk factors). Adjustment for multiple risk factors is important because CAC is itself related to multiple CAD risk factors (see above), and the importance of CAC screening lies in its potential ability to increase predictive power for events beyond that provided by the Framingham risk score (54). Although Pletcher et al. (85) felt that the studies reviewed justified further use of CAC for risk stratification, three of the four communications were from referral populations (86, 87, 89) and only one directly measured lipids (88), but that sample included diabetic patients (who would be automatically categorized as at the highest risk by the ATP III guidelines). In addition, that study (88) did not exclude patients with Framingham risk scores > 20%/10 years, for whom ATP III also mandates aggressive treatment. It is important to note that ATP III guidelines identify strata of risk (>20% 10 year risk, 10–20% 10 year risk, <10% 10 year risk), and the important diagnostic and treatment question is to what extent a high CAC score might move a patient to a higher risk stratum. For those already at >20% 10 year risk, a CAC score is unnecessary because they are already at the highest risk level.

Since the Pletcher et al. (85) communication, there have been six other large studies that evaluated the additional predictive accuracy of CAC (90–95). Two of these included referral populations (93, 95) and three included diabetic patients (93–95). In one monograph, CAC added to predictive power in men but not in women and had far greater power if "soft" events were included, heightening concern that CAC screening may provoke events (93). Another study recorded only 11 events over 3 years in 2,000 Army personnel [1.8% 10 year event rate (90)]. Two studies (91, 92) concluded that CAC evaluation added to risk prediction in groups of individuals free of vascular disease and diabetes and at intermediate risk of clinical events (Framingham risk score of 10–20%). Thus, the current evidence supports CAC screening only in intermediate risk individuals (**Fig. 3**).

Clinical trials with coronary calcification as end point

Three clinical trials have failed to show the ability of statin therapy to retard the progression of CAC (96–98), despite a trend for a reduction in clinical events in one of these (98). Several prior observational studies showed reduced risk in association with statin therapy (99–101), but lack of substantiation in clinical trials raises concerns. This is particularly true because clinical trials have generally shown benefits of statin therapy to reduce heart attack and stroke (6) and because trials with B mode- and IVUS-defined atherosclerosis as end points have generally shown that statin treatment retards the progression of atherosclerosis (reviewed below). These negative reports raise questions about the validity of CAC as an end point, at least for clinical trials of statin intervention.

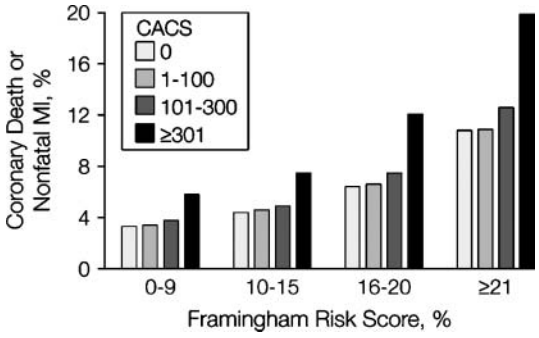

Fig. 3. Predicted 7 year event rates from regression model for coronary heart disease death or nonfatal myocardial infarction (MI) for categories of Framingham risk score or coronary artery calcium score (CACS). The rates are stratified by four levels of Framingham risk score and four levels of CACS. Pairwise analyses compared the highest CACS level (>300) with each of the lower levels of CACS within each Framingham risk score group. ANOVA with pairwise comparisons revealed a statistically significant difference between CACS > 300 and each of the other three CACS groups for a Framingham risk score of >10% ($P < 0.001$) and between CACS > 300 and a CACS of 0 for a Framingham risk score of <10% ($P = 0.01$). Reproduced with permission from reference 92. Reproduced with permisson from Greenland et al. (92).

IVUS IMAGING OF ATHEROSCLEROSIS AND STENOSIS

The development of IVUS has provided additional insight into the pathogenesis of atherosclerosis as well as the impact of various pharmaceutical interventions on atherosclerosis progression. Advantages include the ability to quantify both lumens and walls of arteries, good reproducibility, and the ability to quantify plaque along the length of the artery. Disadvantages include its invasive nature, the ability to image only a portion of the coronary bed, and the inability to image very tight stenosis or arteries with total occlusion. The method requires radiation exposure and exposure to contrast, with potential renal damage.

Method

McPherson et al. (102) first used epicardial ultrasound during surgery to quantify coronary arterial wall thickness in 1987. Yock, Johnson, and Linker (103) described the earliest experience with IVUS in 1988. This invasive technology depends on inserting a catheter equipped with an ultrasound transducer at the tip into a coronary artery and passing it just beyond a distal (fiduciary) branch point. The catheter is then withdrawn at a constant speed with an automatic pullback device, and ultrasound IV measurements of the wall of the artery are taken every 1 mm. The ultrasound image provides accurate identification of the external elastic membrane and lumen areas, and the difference between these defines the wall area. Summation of wall areas at each measurement site allows the calculation of atheroma volume. For progression studies, this process is repeated at follow-up using the fiduciary vessel as a guide. Images are captured and read at work stations where wall volumes are quantified using semiautomated techniques (104).

Definition of atherosclerosis with IVUS

Because of its unique ability to precisely delineate arterial walls and lumens sequentially, IVUS is an excellent tool to investigate atherosclerosis. The earliest communication from (epicardial) ultrasound interrogation of the coronary arteries confirmed the observations from pathology that coronary angiography significantly underestimates the extent of atherosclerosis and that diffuse atherosclerosis may exist in the presence of angiographically normal-appearing lumens (102). Subsequently, a large number of publications have confirmed this observation and enlarged on it by identifying "constrictive" as well as "expansive" remodeling, highlighting the importance of the failure of remodeling as a cause of stenosis (11, 105–112). Although the determinants of these processes are still somewhat obscure, it appears that expansive remodeling is associated with fibrofatty plaque and with small "spotty" calcifications (and perhaps with greater "vulnerability"), whereas constrictive remodeling may reflect more stable lesions with extensive calcification and stenosis (113). Little is known of the risk factors associated

with remodeling; LDL cholesterol was associated with constrictive remodeling in diabetic patients (114). IVUS studies have also shown an association of expansive remodeling with plaque instability (115–117). A few studies have examined associations of remodeling and plaque stability at bifurcations as opposed to nonbifurcation sites. These suggest that the remodeling process may be heterogeneous (118–120).

Risk factors and IVUS-defined atherosclerosis

Because of the invasive nature of this technology, it has generally been used only in symptomatic patients. Nonetheless, a study of IVUS in 262 heart transplant recipients showed atherosclerotic lesions in 52% of hearts, and the prevalence of atherosclerosis varied from 17% in individuals younger than 20 years to 85% in individuals 50 years and older. Intimal thickness was greater in men than in women (121).

IVUS-defined atherosclerosis and clinical outcome

IVUS was first used as a clinical tool for the guidance of angioplasty (122), and although it briefly gained substantial clinical utility, its value has declined with the advent of drug-eluting stents and low restenosis rates (123, 124). Other areas in which IVUS remains useful include lesions with <50% stenosis, certain left main lesions, certain higher risk lesions, and suspected dissections. IVUS continues in clinical use for surveillance in cardiac transplant patients (124).

Clinical trials with IVUS-defined atherosclerosis as end point

Schoenhagen and Nissen (125) reviewed the use of IVUS to define the end point for clinical trials. There have been six trials of statin therapy (126–131). Two of these compared atorvastatin therapy with usual care (126, 127), and one compared more aggressive therapy with atorvastatin with less aggressive therapy with pravastatin (128). In one of these studies (127), the atorvastatin effect was nonsignificant, and in the other two, atorvastatin had a more beneficial effect than either usual care [its use was associated with a reduction in plaque volume (126)] or pravastatin (128). Pravastatin (129), rosuvastatin (130), and simvastatin (131) have also been associated with reductions in plaque volume. An example of the application of IVUS for the clinical trial described in one study (130) is shown in **Fig. 4**. Two other lipid-altering trials have been conducted with IVUS, one showing no effect (or a detrimental effect) of an ACAT inhibitor (132) and one showing a benefit of infusion of intravenous recombinant

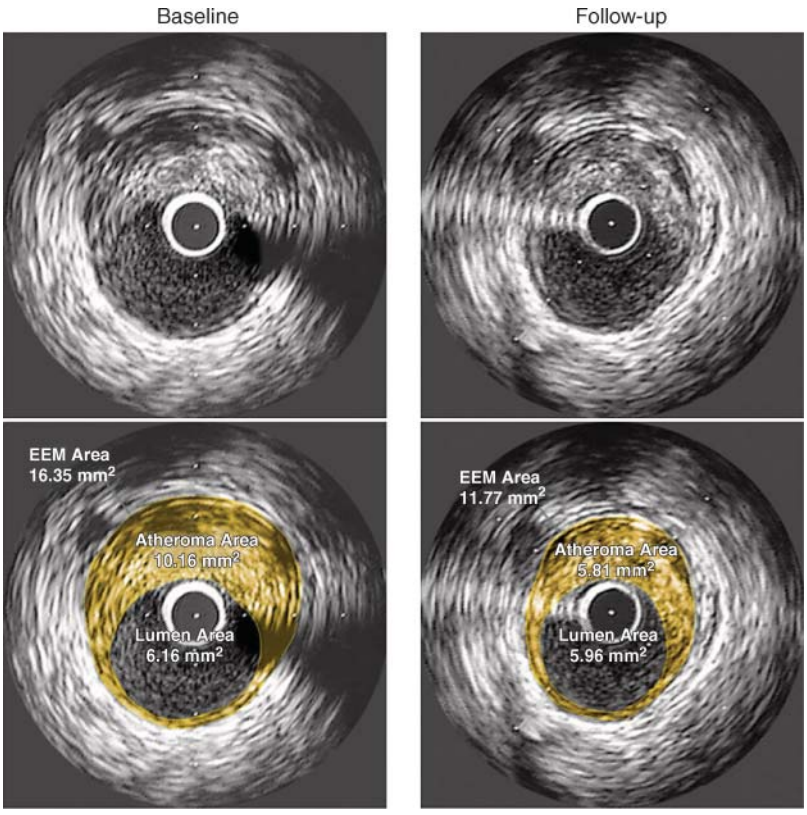

Fig. 4. Example of the regression of atherosclerosis in a patient in the trial described by Nissen et al. (130). The top left panel illustrates the appearance of a single cross-section at baseline IVUS examination, and the top right panel shows the same cross-section after 24 months of treatment. The bottom two panels illustrate the same cross-sections, but with measurements superimposed. Atheroma area was reduced from 10.16 to 5.81 mm^2. EEM, external elastic membrane. Reproduced with permission from Nissen et al. (130).

apolipoprotein A-I_{Milano}/phospholipid complexes (133) on atherosclerosis. Finally, one trial evaluated the effects of antihypertensive agents on atherosclerosis progression with IVUS and found no significant differences between treatment groups (134). The congruence of results of IVUS trials and clinical outcome trials with the same agents provides some validation of the surrogate end point studies (128).

CT ANGIOGRAPHIC IMAGING OF ATHEROSCLEROSIS AND STENOSIS

The use of CT with contrast enhancement [CT angiography (CTA), multidetector CTA (MDCTA)] to image atherosclerosis has increased in the last 2 years because of its minimally invasive nature and its increasing ability to measure lumens of arteries with a precision comparable to that of coronary angiography. The technology additionally provides information on CAC (as does HCT and EBCT without contrast; see above), and there is growing interest in validating its use to image walls of arteries by comparison with IVUS (see below). Advantages of the method include its minimally invasive nature (peripheral administration of contrast), its wide availability, and its provision of images of lumens of arteries and of calcium. Disadvantages include radiation and contrast exposure with potential for renal damage, limiting its use in asymptomatic populations. The presence of stents or extensive calcification of arteries limits the ability to accurately determine stenosis at some sites.

Method

EBCT was first combined with contrast injection to image the lumens of arteries by Moshage et al. (135) in 1995, and contrast-enhanced imaging of arterial lumens with conventional HCT was first described in 2000 (136). Early studies showed limited sensitivity and specificity compared with coronary angiography and limited ability to image any but the most proximal arterial segments. Accurate evaluation of lumens with conventional CTA depended on the development of 4 row scanners in 2001, 8 row scanners in 2004, and, more recently, 16 and 64 row scanners (137, 138). These MDCT scanners provide faster acquisition times and coverage of the whole heart in <10 s. Although MDCTA is associated with greater radiation exposure than EBCT angiography (EBCTA), its greater availability has resulted in a larger increase in use compared with EBCTA during the last 2–5 years. Patients with heart rates >60 beats/min are generally premedicated with a β blocker to reduce the heart rate, and immediately before imaging patients receive isosorbide dinitrate to provide maximal vasodilatation. In general, 80–100 ml of iodine contrast is injected into a peripheral vein over 2–5 min, and the operator uses a bolus-tracking technique to ensure the arrival of contrast in the coronary arteries at the same time as the initiation of the scan. Electrocardiographic gating is used as for noncontrast CT. Cross-sectional images are reconstructed with 1.0 mm slice thickness, and coronary segments are identified according to predetermined schema. Multiple projections are reviewed for evaluability by trained reviewers and then categorized according to percentage stenosis (139) (**Fig. 5**).

Definition of atherosclerosis with MDCTA

MDCTA has been used most extensively for the definition of coronary stenosis. In this respect, it shares the strengths and limitations of conventional coronary angiography to image lumens of arteries and to underestimate plaque burden because of remodeling. In addition, however, MDCTA can quantify CAC. More recently, investigators have compared MDCTA with IVUS for the ability to image arterial wall areas and wall composition (140) (**Fig. 6**). Ferencik et al. (141) recently described improvements in vessel morphology measurements through the use of MDCTA with postprocessing of images compared with IVUS. However, because IVUS is generally performed in proximal arterial segments, the ability of MDCTA to quantify atherosclerosis distally is uncertain, and, as mentioned above, the presence of stents or extensive calcification limits the ability of MDCTA to quantify stenosis or wall area. Nonetheless, these data anticipate the future potential for MDCTA to image atherosclerosis as well as lumens and calcium.

CTA atherosclerosis and clinical outcome

Schuijf et al. (137) recently reviewed the sensitivity and specificity of CTA to quantify lumen stenosis as defined by coronary angiography. With the use of 16 slice MDCT, sensitivity and specificity for determining >50% stenosis are 88% and 96%, respectively. The method remains limited in its ability to identify distal stenosis, however, and stenosis that is associated with large amounts of calcium or with coronary stents is poorly imaged. This method is most useful in identifying individuals with normal coronary arteries (138), and although there are currently no guidelines for how the technology should be used, the typical patient now studied is a young woman with nonspecific chest pain and an equivocal exercise test. A normal CTA scan in such an individual would likely enable her to forego invasive cardiac catheterization.

IMAGING OF CAROTID ATHEROSCLEROSIS

The rationale for imaging of carotid atherosclerosis proceeds not only from the obvious relation of atherosclerosis of this arterial bed to clinical events (stroke, transient ischemic attack) but also from the diffuse nature of atherosclerosis: correlations between atherosclerosis of peripheral and coronary arteries translate into correlations between symptomatic cerebrovascular disease and CAD.

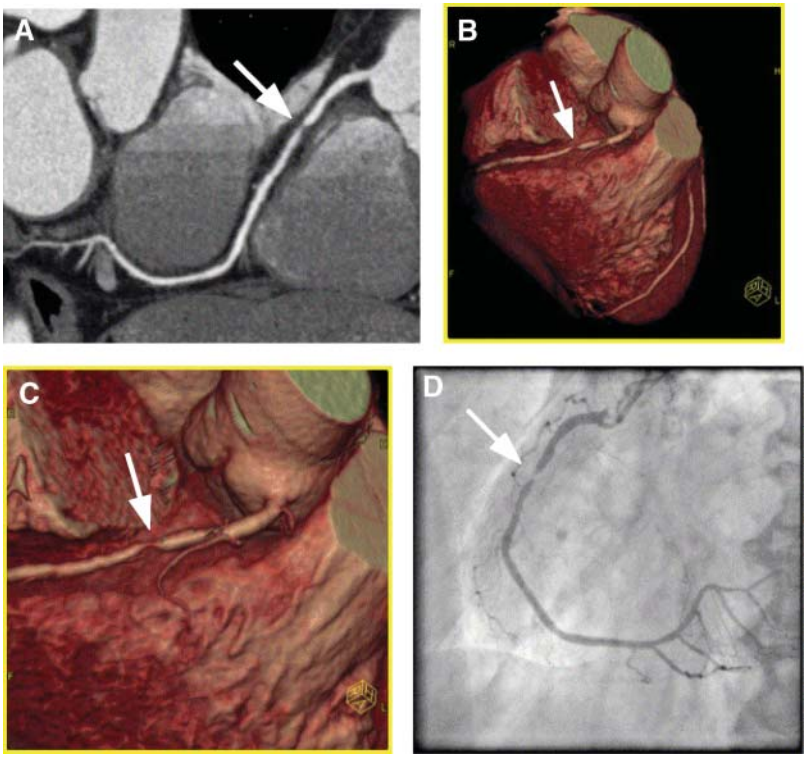

Fig. 5. Stenosis of right coronary artery (arrows). A: Two-dimensional curved multiplanar reconstruction. B, C: Three-dimensional reconstruction of multiple-row detector helical computed tomography. D: Invasive coronary angiography. Reproduced with permission from Achenbach: Cath vs CTA. J. Nucl. Cardiol. 2005; 12: 703.

B MODE ULTRASOUND IMAGING OF CAROTID WALL THICKNESS AND PLAQUE

Doppler ultrasound was validated in the mid 1970s for quantifying rates of flow that translate into percentage stenosis of the extracranial carotid arteries (valid for ⩾50% stenosis) (142). This level of stenosis has been related to a 5.5-fold increased risk of incident stroke and a 3-fold increased risk of CAD compared with individuals without stenosis (143). The focus of Doppler ultrasound on lumen stenosis implies all of the strengths and weaknesses for imaging atherosclerosis described above for coronary angiography or CTA. By contrast, B mode ultrasound accurately images walls of arteries. The noninvasive nature of the B mode technology, in addition to its safety, ready availability, ease of application, reliability, and validity, have justified its use in several large multicenter epidemiologic studies and clinical trials that have expanded our understanding of the pathogenesis and clinical relevance of atherosclerosis enormously since the mid 1980s.

Method

B mode ultrasound was first evaluated in the mid 1980s for its reliability (144) and validity (145) and thus for its utility as a tool for epidemiologic investigation. The B mode equipment is portable and widely available. No special preparation is needed for the examinee, who is generally evaluated while lying comfortably on an examining table. Sonographers use an ultrasound probe with a transducer that produces two to three cycle pulses of ~10 MHz ultrasound, which results in an axial resolution of ~100–200 μm. Images are captured on videotape and reviewed with the use of semiautomated edge detection methods that aid in the definition of the boundaries between the lumen of the artery and the intima and between the media and the adventitia [intimal-medial thickness (IMT)] (146) (**Fig. 7**). Wall thicknesses can be measured at a single site (e.g., far wall of the common carotid artery) or at several sites (e.g., near and far walls of the left and right common carotid arteries, bifurcation, and internal carotid artery). If the latter approach is chosen, the mean of the maximum wall thickness of all sites is generally used as an index of disease (146, 147).

Definition of atherosclerosis with B mode ultrasound

Most investigators use wall thickness to define atherosclerosis. On interrogation of carotid arterial walls, the sonographer may identify sites where wall thicknesses are considerably greater than adjacent sites or where encroachment on the lumen can be identified. Such areas ("plaques") have been the focus of some investigators (148), whereas others feel that the overall wall thickness is an adequate indicator of disease (146, 147). In addition to

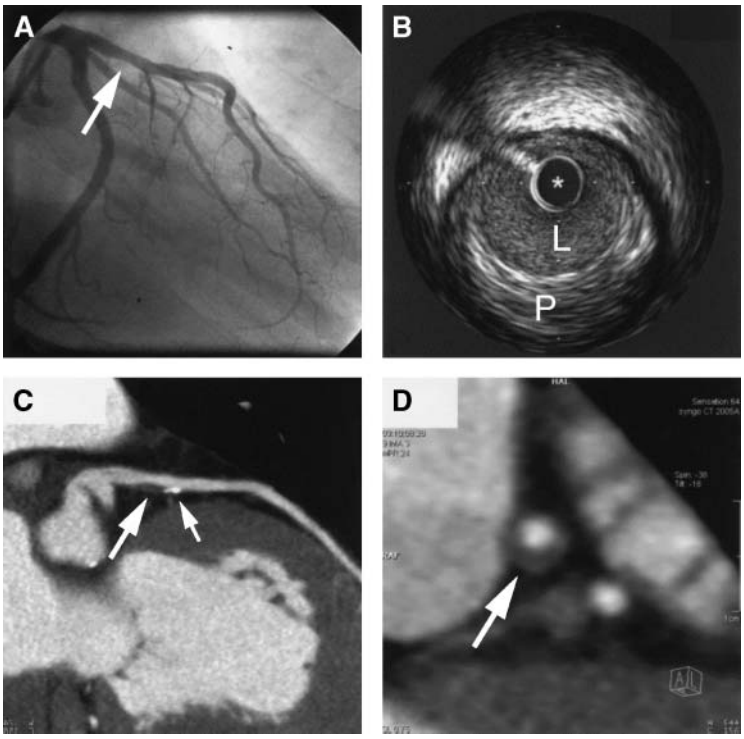

Fig. 6. Visualization of coronary atherosclerotic plaque by 64 slice computed tomography (CT). A: Coronary angiography shows mild eccentric lumen reduction in the proximal left anterior descending artery (arrow). B: IVUS demonstrates the presence of eccentric noncalcified coronary atherosclerotic plaque. L, lumen; P, plaque. The asterisk indicates the IVUS catheter. C: Contrast-enhanced 64 slice CT shows the proximal left anterior descending artery in a multiplanar reconstruction. At the site of lumen reduction, a coronary atherosclerotic plaque with positive remodeling can be seen (large arrow). A small calcification is present toward the distal border of the plaque (small arrow). D: Cross-sectional view of the lesion at the site of maximum plaque area by CT, demonstrating the bright, contrast-enhanced lumen and the eccentric plaque (arrow). Reproduced with permission from Achenbach Ed Comment, JACC 2005; 46: 156.

IMT, B mode ultrasound is capable of defining arterial lumen diameter and interadventitial diameter. Increased IMT is associated with expansive remodeling of the common carotid artery (149), and most risk factors that are associated with increased IMT (aging, male gender, cigarette smoking, hypertension, diabetes) are also associated with expansive remodeling of the common carotid artery (LDL cholesterol is the exception and is associated with smaller arterial lumens in the common carotid artery) (150–152). Of interest, these relations do not seem to apply to the internal carotid artery, in which increased IMT is associated with no change or even constrictive remodeling (149, 152). These observations were recently extended to compare patients with and without defined CAD: although associations of lumens and IMT are similar between CAD patients and controls in the common carotid, CAD patients appear to have a greater tendency for lumen compromise with increasing IMT in the internal carotid compared with CAD-free controls (153).

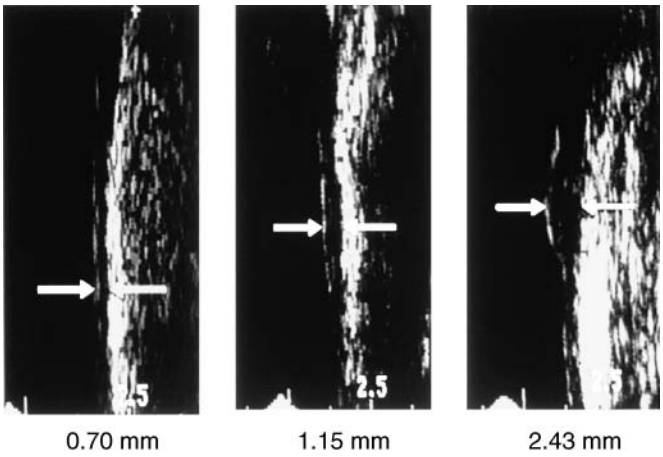

Fig. 7. Examples of B mode ultrasound images captured on videotape. In each panel, arrows represent intima and media boundaries. Wall thickness between each set of arrows is indicated below the panel. From left to right, panels present normal wall thickness, thickened wall (1.15 mm), and plaque extending into the lumen (2.43 mm).

Risk factors and B mode ultrasound-defined atherosclerosis

Normative data have been developed for wall thickness of the extracranial carotid artery (**Table 2**) (154). All of the traditional risk factors for CAD have been associated with increased IMT as well as numerous nontraditional risk factors, as outlined in **Table 3** (155–201), which additionally lists risk factors associated with IMT progression. Several investigators have noted strong associations between antecedent risk factors and future IMT, in some cases stronger than concurrent risk factor associations (158, 202, 203). Sharrett et al. (204) noted only a weak association of high density lipoprotein cholesterol and triglycerides with IMT but a strong association with incident cardiovascular events, leading them to speculate that these risk factors might be involved in the transition from atheroma to atherothrombosis. Patients with CAD have been shown to progress their IMT more rapidly (30 μm/year) than patients free of CAD (10 μm/year). Of interest, the impact of risk factors on progression was greater in patients with CAD than in those free of CAD (201).

TABLE 2. Normative distribution of IMT

Race	Percentile	Women Age (years) 45	55	65	Men Age (years) 45	55	65
White	25th	0.48	0.55	0.61	0.51	0.60	0.67
	50th	0.56	0.66	0.75	0.61	0.73	0.85
	75th	0.66	0.79	0.94	0.73	0.92	1.10
	90th	0.79	0.99	1.26	0.90	1.21	1.50
	95th	0.94	1.19	1.60	1.09	1.48	1.85
Black	25th	0.51	0.55	0.62	0.52	0.60	0.70
	50th	0.59	0.68	0.76	0.63	0.73	0.86
	75th	0.69	0.83	0.95	0.74	0.89	0.93
	90th	0.84	1.06	1.25	0.91	1.12	1.49
	95th	0.97	1.10	1.50	1.09	1.34	1.87

IMT, intimal-medial thickness. Reproduced with permission from reference 154.

A number of genetic variants have been studied for their relation to carotid IMT, including those associated with angiotensin 1-converting enzyme, apolipoprotein E, angiotensinogen and angiotensin II type 1 receptor, methylene tetrahydrofolate reductase, paraoxonase, nitric oxide synthase, various genes related to lipid and lipoprotein levels (e.g., hepatic lipase), and genetic variants related to hemostatic and inflammatory factors, interleukins and immune response, platelet receptors, and oxidative pathways and MMPs (205–207). Manolio et al. (206) have summarized data confirming the heritable nature of IMT.

B mode ultrasound-defined atherosclerosis and clinical (carotid and coronary) outcome

Numerous studies have linked carotid IMT and IMT progression with prevalent symptomatic CAD (159, 200, 201, 208–212) and cerebrovascular disease (159, 208–210) as well as with cerebral white matter lesions (213, 214).

Increased IMT as identified by B mode ultrasound of the extracranial carotid arteries is also a predictor of incident coronary events (215–222) and stroke (216, 218, 223, 224) as well as all-cause mortality (225). O'Leary and colleagues (216) reported that age- and sex-adjusted risk of incident stroke or myocardial infarction increased >2-fold among Cardiovascular Health Study participants whose common carotid IMT exceeded 1.06 mm. However, the ability of IMT to improve on risk prediction above that provided by traditional risk factors might be described as only modest. In the most recent analyses from the Atherosclerosis Risk in Communities study, the addition of IMT together with several other "nontraditional" risk markers to a roster of traditional risk factors improved the area under the receiver-operator curve for incident coronary heart disease in men but not in women [and IMT was also important when not combined with other nontraditional risk factors (219)]. In the Cardiovascular Health Study, IMT was also independently related to incident coronary events (222). In a recent head-to-head comparison, CT-identified CAC discriminated CAD patients from controls considerably better than IMT (226).

IMT is also logically related to incident stroke. In the Atherosclerosis Risk in Communities study, the addition of IMT to a basic model including traditional risk factors increased the area under the receiver-operator curve for stroke, but this was only statistically significant when combined with a marker of peripheral vascular disease (224).

TABLE 3. Risk factors shown to be related to wall thickness of the extracranial carotid by B mode ultrasound

Risk Factors	IMT (Reference)	IMT Progression (Reference)
Age, male gender, menopausal status, smoking, diabetes, hypertension, high LDL cholesterol, depressed HDL cholesterol	154–166	181–186
Passive smoking	167	187
Ethnic factors	168	188
High homocysteine	169	
Diet saturated fat/fiber	170	196
Postprandial lipemia	171	
Thrombosis, thrombolysis	172, 173	182–189
Chlamydia	174	
E-selectin, ICAM	175	
C-reactive protein	176	190, 191
Psychosocial factors	177	192
Asymmetric dimethylarginine	178	
Metabolic syndrome	179	193–195
Insulin sensitivity	160	
Inflammatory disease	180	
Cardiorespiratory fitness		197, 198
Antioxidant vitamins		199
Coronary disease	200	201

Clinical trials with B mode ultrasound-defined atherosclerosis as end point

The Food and Drug Administration has accepted change in progression of IMT measured by B mode ultrasound as an index of reduction in atherosclerosis burden (227). A recent publication summarized the associations between IMT change and clinical events (228).

Several trials have evaluated the effects of lipid-lowering regimens on IMT progression. The Cholesterol-Lowering Atherosclerosis Study in 1993 was the first clinical trial to evaluate the effect of a pharmacologic intervention on the progression of IMT (229). This study compared colestipol-niacin therapy with placebo over 4 years. Placebo-treated patients progressed more rapidly than colestipol-niacin treated patients. Subsequently, an additional 12 studies have been reported. Eleven of these evaluated statin treatment compared with placebo (230–237), probucol (238), or in a comparator manner [atorvastatin vs. pravastatin (239), atorvastatin vs. simvastatin (240)], and one evaluated the incremental impact of niacin added to statin treatment (241). These trials have consistently shown that decreasing cholesterol retards the rate of progression or is associated with a net regression of IMT. In two of these trials (239, 240), more intensive lipid lowering was associated with more dramatic reductions of IMT progression. The addition of niacin to underlying statin therapy resulted in the absence of progression in the group ad-

ministered niacin, whereas the group not taking niacin showed progression (241). LDL apheresis also retards the progression of carotid atherosclerosis (242).

In addition, 10 clinical trials have evaluated the effects of antihypertensive therapy on IMT progression compared with diuretic or placebo (237, 243–252). In general, these trials have shown that antihypertensive treatment slows progression; however, these trials are more difficult to interpret than lipid-lowering trials because antihypertensive therapy often acutely changes intravascular volume. Because IMT varies inversely with acute changes in intravascular volume, it becomes difficult to distinguish between acute changes in IMT caused by physiologic alterations in blood volume and long-term changes in atherosclerosis burden.

Intensive diabetes management retards the progression of IMT in patients with type 1 diabetes (253), and metformin, acarbose, and the thiazolidinediones have shown benefit in patients with type 2 diabetes (254–256). Hormone replacement has been associated with variable effects on IMT progression (257–260).

Lifestyle intervention with weight loss, exercise, and stress reduction (210–264) has been shown to retard the progression of IMT, but treatment with ω-3 fatty acids has not (265). Two of three studies evaluating the effects of antioxidant or B complex vitamins have shown a beneficial effect on IMT (266–268). Treatment with aspirin (269) or other antiplatelet agents (270) has also been shown to have a beneficial effect.

MRI OF CAROTID ATHEROSCLEROSIS AND PLAQUE COMPOSITION

MRI has very recently been used to define disease in the carotid arteries. Exploration of the use of this modality is still evolving, but it holds great promise to increase our knowledge of the pathogenesis of disease. Advantages of MRI include its noninvasive nature and the ability to quantify the full range of pathologic abnormalities associated with atherosclerosis: wall dimensions, plaque composition, remodeling, and stenosis. Disadvantages include the expense and time involved in capturing and analyzing images, the lack of wide availability of the technique, and limited spatial resolution (300 μm), which partly limits the reliability and validity of the technique.

Method

Berr et al. (271) were among the first to use MRI (1995) to image extracranial carotid atherosclerosis. For the examination, a technician questions the participant about potential indwelling metal objects that would preclude imaging. Patients with claustrophobia are also excluded. The participant disrobes and removes all metal-containing objects. For quantitative imaging of carotid plaque components, a specially designed carotid coil is used (272). One point five tesla scanners are in general use at present, although the first experience with 3 tesla scanners for imaging the carotid arteries was recently described (273). In general, both time-of-flight and black blood (T1, T2, and proton density) images are acquired, and plaque composition is determined by comparing images from the various modalities (274). Image time is ~45 min. For greater contrast, gadolinium may be administered (275). Digital images are transferred to a work station, where skilled readers quantify wall, lumen, and vessel area and area of calcium, soft plaque, and fibrous tissue (276).

Definition of atherosclerosis with MRI

Of all the imaging modalities discussed, MRI is best suited for the characterization of atherosclerosis. Investigators can use this to characterize not only wall and lumen areas and volumes (in two or three dimensions) but also cap thickness, plaque rupture, and plaque area involved with calcium, fibrous tissue, hemorrhage, lipid/necrotic core, and neovasculature (**Figure 8**). The technology is eminently suited to identify remodeling through sequential noninvasive studies. To date, investigators have explored the reliability of the technique (277), and several communications have reported on its validity for the quantification of wall areas through comparison of in vivo MRI measurements with pathology of endarterectomy specimens (273, 278, 279). Saam et al. (280) have recently shown good correlations between areas of plaque components (dense fibrous tissue, lipid/necrotic core, loose matrix, and calcification) measured by MRI in vivo and pathology after endarterectomy in 40 subjects. Kerwin et al. (281) have published quantitative data defining neovasculature volume in carotid plaque. Takaya et al. (282) observed more rapid progression of atherosclerotic plaque after intraplaque hemorrhage. Options for imaging after the administration of ultrasmall superparamagnetic iron oxide to highlight macrophages also exist (283). MRI can also image coronary vessels, but at present the ability to accurately quantify arterial wall dimensions and characteristics is limited (137).

Risk factors and MRI-defined atherosclerosis

MRI of carotid atherosclerosis has been used almost exclusively in clinical samples to date. One study comparing symptomatic Chinese and American patients with carotid stenosis identified greater lipid/necrotic core and less calcium in Chinese compared with Americans (284). Several ongoing studies (e.g., the Multi-Ethnic Study of Atherosclerosis) will provide information about this in the future.

MRI-defined atherosclerosis and clinical outcome

A small number of studies in symptomatic patients have identified a markedly increased risk of cerebrovascular events associated with a thin or ruptured fibrous cap (hazard ratio 17), intraplaque hemorrhage (hazard ratio 5.2), large lipid-rich/necrotic core (hazard ratio 1.6), and larger maximum wall thickness (hazard ratio 1.6) (**Fig. 9**)

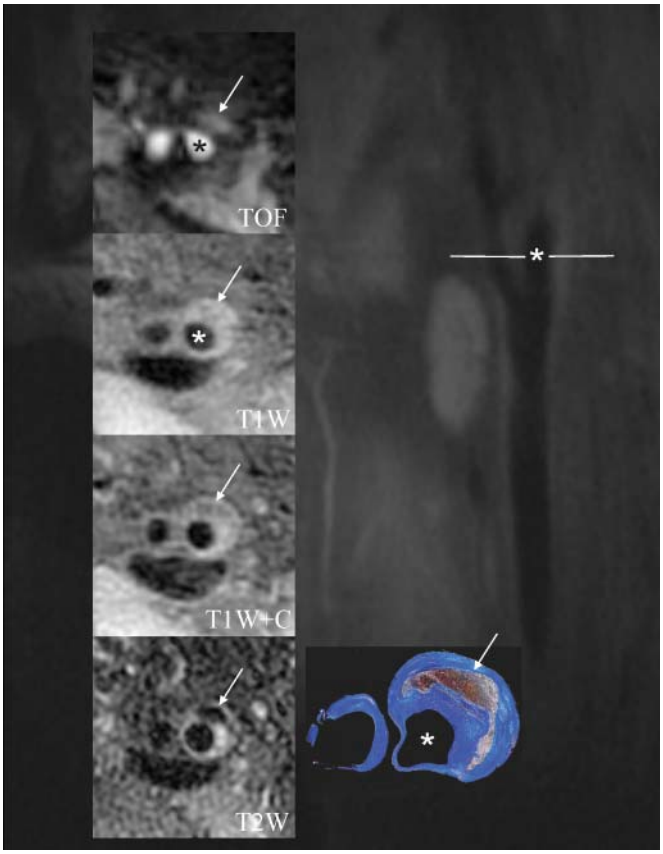

Fig. 8. This 69-year-old male was imaged with a high-resolution magnetic resonance imaging (MRI) protocol at 1.5 T with phase-array carotid surface coils 8 days prior to a right carotid endarterectomy (CEA). The background image is an oblique T1-weighted (T1W) MRI image of the carotid artery. The asterisk indicates the lumen of the internal carotid artery (ICA), and the white line corresponds to the location of the inset axial images to the left of the figure. The inset axial images were acquired from the same location using time-of-flight (TOF), T1W, contrast-enhanced TW1 (TW1-C), and T2W sequences. The color image is a Mallory's trichrome stain from a matched location of the CEA specimen. Present in the lesion is a recent intra-plaque hemorrhage (arrow) within the lipid-rich necrotic core, which is readily apparent on the axial MRI sequences in this atherosclerotic lesion. The following researchers contributed this original figure: Thomas S. Hatsukami, MD, Marina S. Ferguson, MT, Randy Small, HT, Hunter R. Underhill, MD, Chun Yuan, PhD, University of Washington-Seattle, Department of Radiology and Surgery.

(285, 286). Larger population-based studies will provide further insight regarding carotid artery plaque characteristics identified using MRI and their potential relationship with cerebrovascular and cardiovascular events.

Clinical trials with MRI-defined atherosclerosis as end point

We are aware of two published nonrandomized studies of the effects of statin on carotid plaque measured by MRI. In the first, patients treated with statins experienced regression of atherosclerotic lesions (287); in the second,

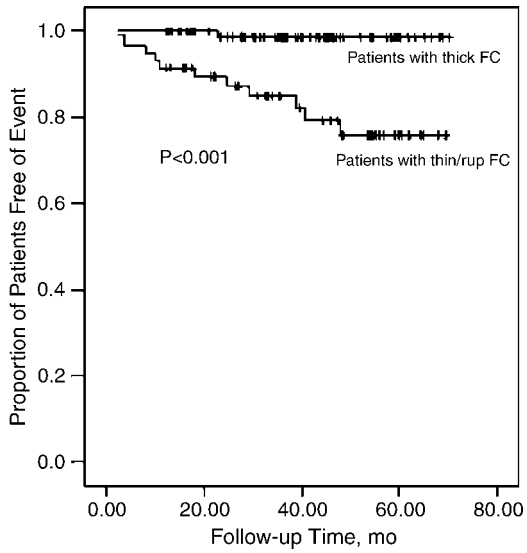

Fig. 9. Kaplan-Meier survival estimates of the proportion of patients remaining free of ipsilateral cerebrovascular events for subjects with (lower curve) and without (upper curve) thin or ruptured fibrous cap (FC). Reproduced with permission from Takaya et al. Stroke 2006; 37: 818.

arteries of patients who had been treated with lipid-altering therapy for 10 years had smaller core lipid areas compared with treatment-naïve patients (288). These uncontrolled studies suggest opportunities for controlled trials in the future.

SUMMARY

Strengths and weaknesses of the various approaches described above are outlined in **Table 4**. Although it has long been appreciated that atherosclerosis was responsible for clinical events, for many decades it was only possible to investigate atherosclerosis at the autopsy table. Coronary angiography was the earliest technology used to image atherosclerosis in vivo (1959), but it is an invasive technique that visualizes only the lumens of arteries. The next generation of imaging studies included invasive techniques that enabled precise definition of walls/areas/volumes of arteries (IVUS, 1988) and minimally invasive techniques that were best suited for imaging arterial lumens (CTA, 1995). Noninvasive techniques were also developed that could be used to visualize either calcium in walls of arteries (CT, 1979) or wall thickness of the carotid arteries (B mode, 1983). The most recent generation of imaging modalities quantifies not only walls, lumens, and areas/volumes of peripheral arteries but also the composition of plaque (MRI, 1995). This approach holds great promise, because investigators now believe that plaque composition is more responsible for clinical events than plaque burden. In addition to plaque composition, arterial remodeling appears to be tightly linked to symptom

TABLE 4. Advantages and disadvantages of various imaging modalities

Modality	Level of Technological Development	Invasive	Images Walls	Images Lumen (Stenosis)	Images Plaque Composition	Advantages		Disadvantages
Coronary angiography	Mature	Yes	No	Yes	No	Clinical utility Importance of stenosis Revascularization Useful for clinical trials	+++++	Contrast exposure Radiation exposure Images atherosclerosis imperfectly
Electron beam computed tomography, helical computed tomography	Mature	No	No	No	No/yes (Ca^{2+})	Clinical utility Automated Wide availability Images calcium	+	Radiation exposure Images atherosclerosis imperfectly Not useful for clinical trials (?)
Intravascular ultrasound	Mature	Yes	Yes	Yes	No/yes	Clinical utility Images atherosclerosis Good reproducibility Useful for clinical trials	+	Contrast exposure Radiation exposure Images selected arterial segments Cannot image tight stenosis Cannot image total occlusion
Computed tomography angiography	Developing	Minimal	No/yes	Yes	No/yes (Ca^{2+})	Clinical utility Sensitive to stenosis Useful for clinical trials (?)	++	Contrast exposure Radiation exposure Images atherosclerosis imperfectly Need for premedication
Doppler ultrasound	Mature	No	No	No/yes	No	Clinical utility Easily accessible	++++	Reflects atherosclerosis imperfectly Not useful for clinical trials
B mode ultrasound	Mature	No	Yes	No/yes	No/yes	Clinical utility Images atherosclerosis Useful for clinical trials	±	Sonographer dependence
Carotid MRI	Developing	No	Yes	Yes	Yes	Clinical utility Images atherosclerosis Useful for clinical trials	(?) (?)	Time-consuming Expensive Not universally available Clinical contraindications Claustrophobia Indwelling metal Limited spatial resolution

development; however, the precise role of remodeling is poorly understood, even though all of the modalities discussed above (pathology, angiography, CT, IVUS, CTA, B mode, MRI) shed light on the process. Most studies of remodeling rely on data drawn from a single point in time, whereas, by definition, remodeling is a dynamic process. One limitation of the use of a structural measure of chronic stable disease to predict future events is that the contemporaneous measure reflects backward on the person's lifetime exposure to risk factors. Recent lifestyle or medication change might not be reflected in the contemporaneous atherosclerosis burden but might affect prognosis. Thus, it is critical to understand how atherosclerosis progression affects outcome when combined with a prognostic algorithm such as the Framingham risk score. It is also important to better understand the role of plaque composition and remodeling in symptom development. If, in the future, sequential imaging of atherosclerosis becomes a means of following patients to determine the benefit of treatment, it will be essential to know which changes in the artery are associated with a favorable prognosis. It may not be possible to identify "the" culprit plaque that leads to an event, because asymptomatic patients likely have multiple plaques in various stages of inflammation, remodeling, rupture, and healing. However, it may be possible in the future to use noninvasive imaging to quantify atherosclerosis progression and thus predict treatment benefit for individual patients, thereby overcoming the challenge of the prolonged clinically silent progress of the atherosclerotic plaque. At present, MRI is the most promising technology to achieve this goal.

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