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?

Rita F. Redberg, MD, MSc, FACC, *Co-Chair*, Robert A. Vogel, MD, FACC, *Co-Chair*, Michael H. Criqui, MD, MPH, David M. Herrington, MD, FACC, Joao A. C. Lima, MD, FACC, Mary J. Roman, MD, FACC

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.

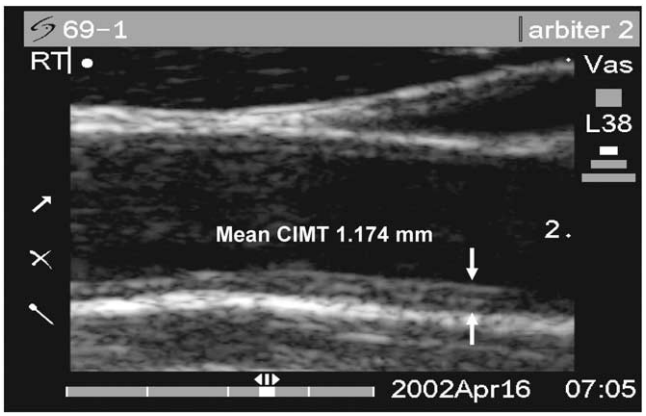

Figure 1. An example of an ultrasound image from the distal common carotid artery with quantification of intima-media thickness. CIMT = carotid intima-media thickness.

SPECTRUM OF IMAGING METHODS

Carotid ultrasonography. METHODOLOGY. Carotid ultrasonography has traditionally been used clinically in the setting of symptomatic cerebrovascular disease or asymptomatic carotid bruit to identify significant obstructive disease, quantified using Doppler technology. More recently, carotid ultrasonography has been used to assess atherosclerosis in epidemiologic studies or in risk stratification by measuring the combined intima-media thickness (IMT) (example shown in Fig. 1) and determining the presence or absence of focal atherosclerotic plaques (2–5). Because the velocity of blood flow does not substantially increase until significant obstruction (greater than 50%) occurs, Doppler quantification of carotid disease detects significant obstruction uncommonly in population-based or screening studies.

Carotid IMT is most commonly measured from B-mode (two-dimensional) images with commercially available linear ultrasound transducers typically utilizing frequencies between 7.5 and 10 MHz. The measurement of IMT is rapid, completely noninvasive (no ionizing radiation), and has the advantage of focusing only upon the intended target (the carotid artery), thus avoiding problems of incidental scan findings. An alternative approach is to use two-dimensionally-guided M-mode images that provide comparable spatial resolution but superior temporal resolution—for example, in the assessment of vascular function. Electrocardiographic (ECG) gating to determine the minimum end-diastolic diameter is optimal with either approach because of cyclic variation in IMT diameter due to pulsatile changes in distending pressure. The most preferable site for the measurement of IMT is the far wall rather than the near wall of the carotid artery because acoustic reflection of the echo-dense intima into the lumen and/or to high gain setting in near wall measurements may lead to overestimation of IMT. Because the common carotid artery (CCA) is tubular and can be aligned perpendicular to the transducer beam, reproducibility and yield of CCA IMT is superior to that of IMT of the carotid bifurcation (bulb) or internal carotid artery (ICA) (5,6). The small size of the carotid IMT (usually less than 1 mm) necessitates computer-assisted measurement using electronic calipers; when measurements are taken from M-mode images, full-screen display is necessary. Semiautomated measurement may be performed of a selected segment (usually 1 cm in length) using an edge detection algorithm (7).

Discrete plaques, commonly defined as focal thickening at least 50% greater than the surrounding wall, can be reliably detected and localized by thorough scanning of the extracranial carotid arteries. However, because the overwhelming majority of plaques are nonobstructive and cannot be quantified using Doppler technology, precise quantification of plaque burden is problematic. Although plaque diameter (maximum excursion into the vessel lumen) is readily measurable, the diameter may correlate poorly with plaque size or volume given the variable and complex three-dimensional morphology of plaques. Semiquantitative approaches include averaging of plaque diameters, the number of segments (CCA, bulb, ICA, external carotid artery [ECA]) containing plaque, or plaque number.

DEFINITION OF ABNORMAL IMT. In general, greater IMT values are associated with greater cardiovascular risk. For example, the Kuopio Ischaemic Heart Disease Risk Factor Study found myocardial infarction (MI) risk increased by 11% for each 0.1 mm increase in common carotid IMT (8). Despite this continuous relationship between IMT and risk, an absolute definition of an abnormally high IMT (measured in the absence of plaque) is problematic due to the strong influence of age on arterial wall thickness in both normotensive and hypertensive individuals (5,9). Furthermore, hypertension increases IMT, probably because of medial hypertrophy, independent of typical atherosclerotic changes (9,10). Thus, the use of an absolute threshold to define an abnormal IMT may result in systematic underdetection in younger individuals and overdetection in older individuals. An alternate approach has been to establish nomograms or ratios of observed to predicted IMT based on age and other potential covariates depending upon the population and application. The approximate age-adjusted 75th percentile values for common carotid IMT are shown in Figure 2 (5,11,12). These values establish a level of age-adjusted relative risk, and may be appropriate thresholds indicating the need for increased attention to cardiovascular risk factors and risk-reduction therapies.

REPRODUCIBILITY AND VARIABILITY. Because of the ease of performance, low risk (no ionizing radiation), and relatively high degree of reproducibility of IMT measurements, IMT has been a common surrogate end point epidemiologic studies (2–5) and in clinical trials (13–15) to assess the effects of various interventions on atherosclerosis burden. These trials demonstrate the potential utility of serial measurements of IMT in individuals. The Cholesterol Lowering Atherosclerosis Study established that both the absolute value and rate of progression of IMT are markers

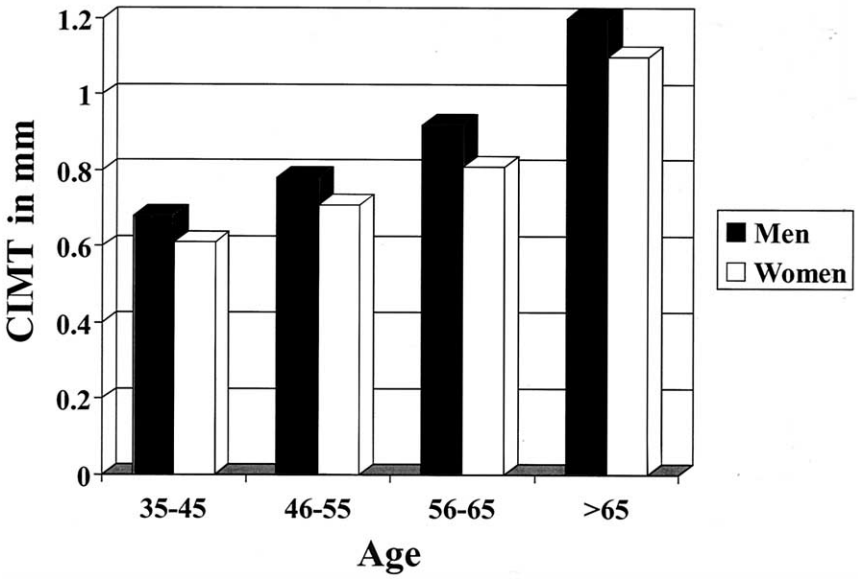

Figure 2. Approximate age and gender values for common carotid intima-media thickness (CIMT) representing the approximate 75th percentile value (4,12). Note that intima-media thickness increases with advancing age, and that the intima-media thickness of men is generally greater than that seen in women.

of adverse cardiovascular outcomes among groups of patients (16). Such assessments in individual patients will be highly dependent on the reproducibility of IMT measurements from any particular laboratory. Reproducibility studies have indicated that absolute intrareader differences in common carotid IMT are in the range of 0.04 mm; however, these differences may be somewhat reduced by the use of more modern imaging equipment (operating at a higher imaging frequency), digital image acquisition and analysis, and the use of automated edge detection devices for quantitation (7). Because even small changes in IMT can alter cardiovascular risk predictions, the accuracy of serial IMT assessments would be enhanced by either a greater interval between scans or multiple assessments across time showing consistent results.

Coronary CT imaging. METHODOLOGY. Radiographic techniques can detect arterial calcium deposits in any vascular bed. For example, calcified plaques in the thoracic aorta are detectable with the simple chest radiograph, and these were associated with increased cardiovascular risk in the Framingham Heart Study (17). Likewise, coronary CT scans can detect and quantitate the presence of coronary artery calcium deposits with ECG-gated images obtained with either electron-beam computed tomography (EBCT) (example shown in Fig. 3) or helical CT scanners. The EBCT uses an electron sweep of stationary tungsten target rings to generate X-ray images that can detect small amounts of calcium with considerable accuracy, whereas helical CT uses a continuously rotating X-ray source. The EBCT is accomplished by a sequence of subsecond (50 to 100 ms) 3- or 6-mm slices performed during a breathhold sequence of approximately 40 s (dependent on heart rate). In comparison, helical CT scanners have somewhat slower scan times (100 to 200 ms). The entire test takes less than 15 min to complete, and it exposes the patient to a moderate amount of ionizing radiation (less than 200 milliRem [mrem], or approximately 10 to 15 standard chest radiographs) (18).

Both coronary CT methods are highly sensitive and accurate for the detection of coronary calcium based upon comparisons with autopsy samples (19–21). Coronary calcium is most commonly quantitated using a combination of the area and density of calcified atherosclerosis within

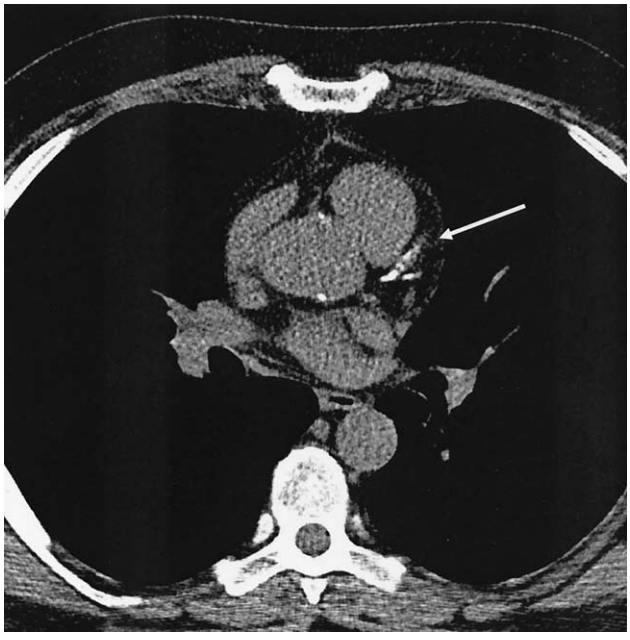

Figure 3. An example of an abnormal EBCT scan taken from a 59-year-old man. The coronary calcium score was 1,101, greater than the 90th percentile value for age and gender. **Arrow** indicates calcified atherosclerosis in the proximal left coronary artery.

regions that exceed a radiographic density of 130 Hounsfield (H) units (22). An EBCT scanner costs approximately $1.5 million and is currently available from only one manufacturer (Imatron). The competing technology, helical CT, requires a helical scanner, which costs $1.5 million to $3 million. The helical scanner also has the advantage that it can be used for other types of CT scanning. In any type of coronary CT, other structures in the upper abdomen and thorax are present in the field of view, and thus incidental scan findings may be encountered. The frequency of incidental findings can be as high as 50% in more elderly or referred populations with comorbid conditions (23).

DEFINITION OF AN ABNORMAL CALCIUM SCORE

The presence of any single focus of calcium (generally defined as a radiographic lesion consisting of at least four contiguous calcified pixels on a CT scan with a given field of view) is considered abnormal, but the prevalence of any detectable calcium becomes very common with aging. For men, the likelihood of having any detectable coronary calcium is roughly equivalent to their age; for women, the probability is 10 to 15 points below their age. In terms of the extent of coronary calcium present, the definition of an abnormal scan varies widely in the published reports. Similar to the prevalence of coronary calcium, the extent of calcium increases with age, and women again lag about 10 years behind men (24,25). Considering age and gender-adjusted relative risk for the development of coronary heart disease, thresholds of risk range from scores above the median to scores above the 90th percentile. In general, higher scores have been equated to higher cardiovascular risk (Fig. 4). A meta-analysis of the published data found that a calcium score above the population median value was associated with an unadjusted odds ratio of 4.2 (95% confidence interval [CI] 1.6 to 11.3) for an MI or death (26). These data have been limited by selection bias within the populations studied, and individual investigations have found widely varying point estimates of risk. An alternative is to establish absolute risk thresholds, although the recommended cut points have varied very widely in the published data from 80 to 640. It remains controversial whether the coronary calcium score will add incremental information over the standard risk-factor assessment (27–29).

Reproducibility and variability. There is much variability noted in the relationship between coronary calcium and atherosclerosis (30) and in the individual relationship between angiographic disease and coronary calcium quantity (30). Studies show significant retest variability in calcium scores obtained from repeated scans. In one study of scans on the same patient on two consecutive days, read by a single experienced reader, variability was 49% ± 45% (31). The investigators caution that use of calcium for screening purposes should report a range of score results to minimize this problem with interpretation.

In another study of interobserver variability, disagreement on calcium scores occurred in 24% of cases by two experienced observers. Potential sources of error include the partial volume effect, respiratory artifact, and errors in calcium measurements. Various solutions have been proposed, such as changing the ECG triggering method (6), volumetric scoring systems (32), averaging results from two or more consecutive scans, using techniques to minimize respiratory motion artifact, and possibly the use of greater CT slice thickness (33). Using such techniques and with current generation CT hardware, variability can be substantially reduced, and test-retest variability of 10% or less is achievable (34). Although the prognostic significance of coronary calcium progression is unknown, serial calcium scores using a three-dimensional (3D) reconstruction technique have been utilized as a surrogate end point of a prospective study evaluating the effects of lipid-lowering therapies (35). The correlation to clinical end points has not yet been tested. The application of serial scanning is not known, but will be of limited value in individuals with low calcium scores in whom small absolute changes in the calcium score are more likely to be due to interscan variability.

CMR. METHODOLOGY. High-resolution CMR has potential as an in vivo modality for atherosclerotic plaque imaging and characterization. The CMR differentiates plaque components (e.g., fibrous cap, calcium, necrotic core) on the basis of biophysical and biochemical parameters such as chemical composition and concentration, water content, physical state, molecular motion, or diffusion (36,37).

In vivo CMR images of advanced lesions in carotid arteries have been obtained from patients referred for endarterectomy (38–40). The carotid arteries' superficial location and relative absence of motion present less of a technical challenge for imaging than the aorta or coronary arteries. Short T2 components were quantified in vivo before surgery and correlated with values obtained in vitro after surgery (39). Thoracic aortic plaque was assessed with multicontrast CMR and compared to transesophageal echocardiography (TEE) (example shown in Fig. 5) and showed good correlation for plaque composition and mean maximum plaque thickness (41). Although coronary atherosclerosis measurements are currently limited by the spatial and temporal constraints of CMR, CMR represents an area of active investigation (42,43).

In theory, the capability of CMR to identify not only the extent but also the characteristics of atherosclerotic plaque is a potential advantage of CMR techniques. Further improvements in external coils, imaging acquisition, and the use of contrast agents that enhance the different vessel wall components may improve in vivo noninvasive CMR characterization of the plaque. Beyond feasibility, the hierarchy of anatomic targets relative to cardiovascular prognosis for CMR atherosclerosis imaging has not yet been defined.

Definition of an abnormal CMR. Cardiovascular magnetic resonance imaging including multi-contrast CMR (T1-, T2-, proton density-weighted and time-of-flight) has

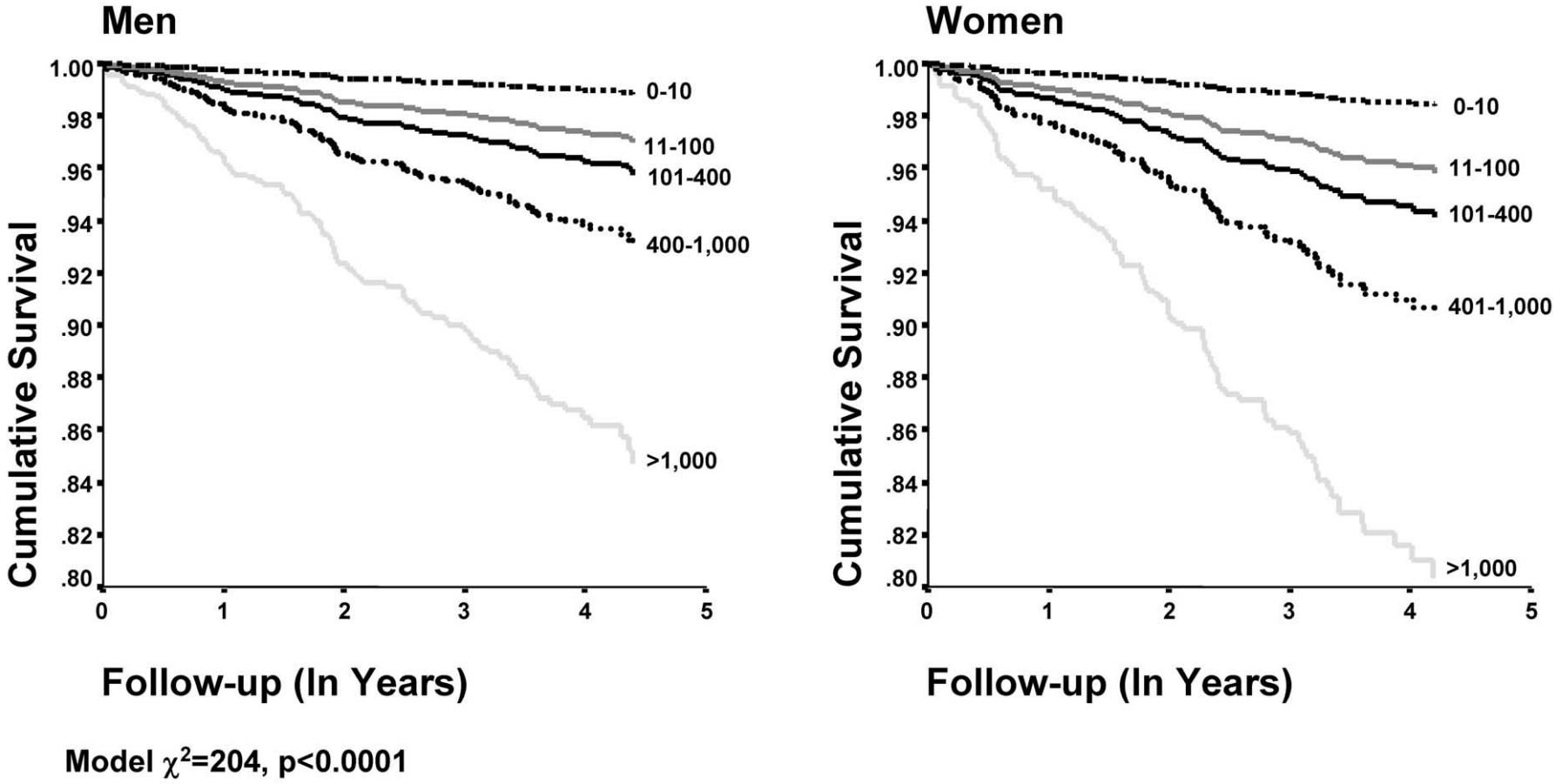

Figure 4. All-cause survival in 4,474 men and 3,219 women with greater than one cardiac risk factor by EBT coronary calcium measurements: Results from a stratified Cox proportional hazards survival model (Model $c^2 = 204$, $p < 0.0001$).

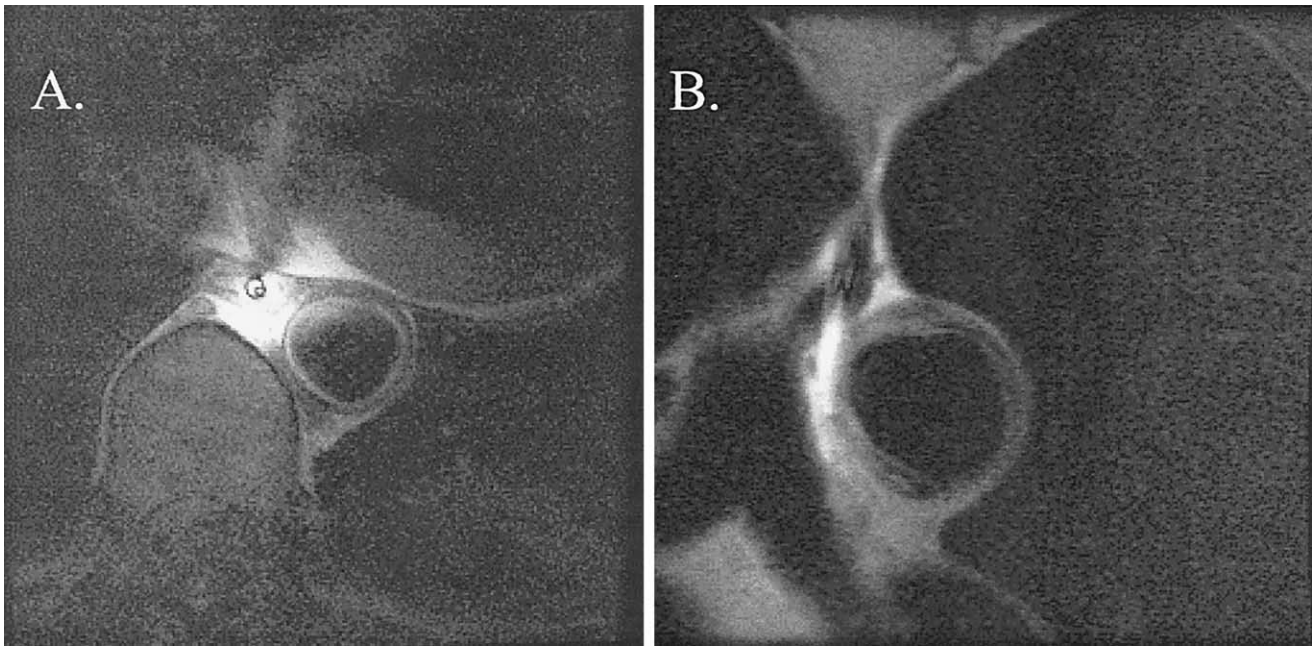

Figure 5. Transesophageal CMR images from two poststroke patients with increased LDL-cholesterol showing **(A)** homogeneous (from a 56-year-old African American hypertensive woman) and **(B)** heterogeneous (from a 72-year-old Caucasian man) CMR signal from thickened aortic walls. The scales are different (in actuality, the aortae have similar diameters), but the nonuniformity of wall thickness and heterogeneous signal, suggesting lipid infiltration from the patient portrayed in **B**, is clearly seen. In addition, these studies revealed the pitfalls of transesophageal echocardiography to assess aortic atherosclerosis caused by its near-field limitations in imaging the anterior aspect of the aortic wall.

been shown to accurately image and characterize carotid arterial plaques in vivo (44). Specific capabilities include the quantification of plaque size (45–47), the detection of fibrous cap "integrity" (48), lipid core, and acute intraplaque hemorrhage (49). Data on the extent of aortic thickness within screening populations are beginning to emerge. A cross-sectional study (50) from the Framingham Heart Study offspring cohort found that plaques identified by CMR are two to three times more prevalent in the abdominal than the thoracic aorta. Comparable to quantitative atherosclerosis burden measurements with coronary CT and carotid IMT, the extent of plaque progressively increased with increasing patient age, approximately doubling for each decade. The optimal vascular bed and method for quantifying reported CMR-determined atherosclerosis extent remains to be established in future prospective clinical trials. Further, the prognostic significance of quantitative (e.g., plaque thickness) versus qualitative (e.g., presence of a "thin" fibrous cap) atherosclerosis measures has not been established.

Reproducibility and variability. In one of the lipid-lowering CMR studies of human aortic and carotid plaques (46), the reproducibility of the vessel wall area measurement was assessed after repeated imaging. The error in vessel wall area measurement was found to be 2.6% for aortic and 3.5% for carotid plaques. Similar low measurement errors in plaque area and volume (4% to 6%, respectively) were reported by others, proving that plaque area and volume can be accurately assessed (51,52). Based upon these favorable retest characteristics, CMR has been successfully used as an intermediate end point in interventional trials of antiatherosclerosis treatments. For example, in a study of lipid-lowering therapy (statins) in asymptomatic untreated hypercholesterolemic patients with carotid and aortic atherosclerosis (46,53), regression of atherosclerotic lesions was observed in the aortic and carotid arteries vessel wall at 12 months. These capabilities may extend to serial testing of plaque components with CMR. Patients with coronary artery disease (CAD) who received lipid-lowering therapy (niacin, lovastatin, and colestipol) for 10 years in the Familial Atherosclerosis Treatment Study (FATS) group were shown to have decreased lipid composition (estimated as a fraction of total plaque area) and an increased fibrous tissue composition in the treated group compared to the untreated group.

Brachial artery reactivity testing. METHODOLOGY. Endothelial cells produce nitric oxide, which is the predominant vasodilator in the arterial system. An increase in shear stress on the surface of endothelial cells initiates a signaling pathway that results in phosphorylation and activation of nitric oxide synthase, resulting in an increase in bioavailable nitric oxide (54). Inhibition of nitric oxide synthase reduces, but does not eliminate, vasodilation, suggesting that other vasodilators are also involved. Endothelial-derived nitric oxide inhibits many of the initiating steps in the pathogenesis of CAD, including low-density lipoprotein (LDL) uptake, white cell adhesion to the vessel wall, vascular smooth muscle proliferation, and platelet adhesion and aggregation (55). The degree of arterial vasodilation in the face of a flow-mediated increase in shear stress serves as a

bioassay of endothelial cell capacity to produce and release nitric oxide, and thus, is an indirect indicator of endothelial function. Furthermore, clinical studies show that endothelial dysfunction can become evident well in advance of the development of clinical or anatomic manifestations of atherosclerosis (56,57). For these reasons, impaired flow-mediated vasodilator responses may represent one of the earliest stages of the development of vascular disease. Thus, this technique could be most useful to screen for early stages of arterial disease, especially in children and young adults (58), at a time when risk factor and other interventions might be more effective.

Subject preparation is important, because several factors can affect flow-mediated vascular responses (e.g., smoking, fat or caffeine ingestion, drugs, temperature, sympathetic stimuli) (59–61). Subjects should not smoke or eat for 8 to 12 h before the study, and a quiet, temperature-controlled room should be used for the procedure. In premenopausal subjects, investigators should determine the phase of the subject's menstrual cycle, which can influence flow-mediated dilation (62).

The equipment required to measure brachial artery flow-mediated responses includes a computer equipped with software to measure changes in brachial diameter and a high frequency ultrasound instrument with a vascular transducer and built-in ECG capabilities. The preferred transducer for optimal image resolution is a broad-band linear array model (7 to 12 MHz frequency range). After the subject has rested, the procedure is begun by placing a sphygmomanometric cuff on the forearm or above the antecubital fossa. Baseline ultrasound images are acquired by the sonographer. Then the cuff is inflated (typically to 50 mm Hg above the subject's resting systolic blood pressure) for a standardized period (typically 5 min) to create ischemia and reactive hyperemia in the downstream resistance arteries. Following cuff release, this distal hyperemia produces a transient increase in blood flow through the conduit brachial artery (about six-fold increase). The sonographer acquires additional images following cuff release to document the degree of vasodilation. Most commonly, vasodilation is measured 1 min after cuff release; however, some systems have the capacity to continuously monitor changes in brachial diameter during the entire 1- to 2-min dilation phase. In most studies, subjects are then given a single dose of nitroglycerin (spray or sublingual, 0.4 mg) to assess endothelium-independent vasodilation and thus vascular smooth muscle function.

High-quality ultrasound images are essential for accurate analyses of brachial artery flow-mediated response. Clear visualization of both the near and far wall lumen-intima boundaries is required before the study begins. Boundaries for measurement (either the lumen-intima or media-adventitia interfaces) can be identified with edge calipers by the operator or edge-detection software packages. The response is generally measured as change in poststimulus diameter, as a percentage of the baseline diameter.

Definition of an abnormal brachial artery response. The normal range of vasodilator responses varies, depending on the placement of the blood pressure cuff. In general, in normal individuals, cuff placement on the distal forearm produces vasodilator responses greater than 5%, whereas placement of the cuff above the antecubital fossa results in vasodilator responses greater than 8%. However, many things influence these vasodilator responses. In particular, age is a potent attenuator of vasodilator responses (especially above 40 and 50 years in men and women, respectively) (63,64). Vasodilation is also strongly inversely dependent on baseline arterial diameter (63). Small studies have shown that reduced brachial artery flow-mediated vasodilation is associated with a greater likelihood of CAD and poorer prognosis in individuals with chest pain (approximately three-fold relative risk) (16,47).

Reproducibility and variability. The major limitation to BART is the inherent biologic variability in the measurement. The vasodilator response to forearm ischemia varies greatly within an individual in response to many different variables. For example, changes in dietary patterns (a high-fat meal) and the phase of a woman's menstrual cycle each can alter the results of BART.

Ankle-brachial index. METHODOLOGY. The ankle-brachial index (ABI) is the ratio of the systolic blood pressure (SBP) at the ankle divided by the SBP in the arm. The underlying principle is that when a stenosis in a peripheral artery reaches a critical level, a decrease occurs in effective perfusion pressure distal to the stenosis, and this decrease is roughly proportional to the severity of the occlusive disease.

The test is painless, simple to perform, and quite inexpensive. Vascular laboratories often measure limb SBP at multiple levels of the lower extremity (e.g., thigh, above knee, below knee, ankle, and toe), which can help localize any peripheral arterial disease (PAD) present. However, the researcher or clinician screening for PAD typically measures only the ankle pressure, because this will detect proximal as well as distal disease. In addition, the width of the standard arm cuff (12 cm) is particularly compatible with the usual girth at the ankle. A cuff size appropriate for arm size is used for the brachial SBP, and a 12-cm cuff is used at the ankle in all but rare instances. The brachial SBP is taken in both arms using a hand-held Doppler at the brachial artery in the antecubital fossa, and the higher of the two arm pressures is used as the denominator for the ABI calculation for each leg. The higher arm pressure is used to avoid a falsely low arm pressure from subclavian stenosis, which is more common in patients with PAD. At each ankle (right and left), the SBP is measured in both the posterior tibial and dorsalis pedis arteries, using the handheld Doppler. The higher of the two pressures at the right ankle is the numerator for the right ABI, and the higher of the two pressures at the left ankle is the numerator for the left ABI.

Definition of an abnormal ABI. In contrast to cardiovascular imaging methods, the ABI is not an imaging tech-

nique and does not detect early plaque formation or minimal stenosis. The ABI generally is a test that detects individuals with more advanced (although often asymptomatic) vascular disease. An abnormal ABI, defined as a value less than or equal to 0.90, has a sensitivity of about 90% and a specificity of about 98% for moderate or greater obstructive PAD on angiography (65,66). The use of the ABI is particularly important giving the limited sensitivity, specificity, and predictive value of the traditional clinical assessments for PAD (pulse palpation and symptom assessment) (67). The ABI can detect subclinical (asymptomatic) cardiovascular disease (CVD), and up to 40% of patients with abnormal ABI tests have no symptoms (67,68). Some subjects with complaints of claudication may show a normal ABI at rest, but exercise will often uncover a low ABI. A simple pedal plantar flexion test may be substituted for a treadmill in office practice (69).

Reproducibility and variability. The variability in SBP in both the ankle and arm is similar, and the ABI shows fair repeatability, with a 95% CI of ±16% for a single measurement, which improves to ±10 % when taken as the mean of four measurements (70). Based upon these test-retest characteristics, the ABI is generally poorly suited to serial testing, and thus it is more commonly used in cross-sectional population screening.

EMERGING TECHNOLOGIES: NUCLEAR IMAGING OF VULNERABLE PLAQUE

Several novel and emerging technologies are being developed to evaluate subclinical atherosclerosis, including various radiolabeled monoclonal antibodies targeting molecular components of atherosclerosis. Animal studies have demonstrated the feasibility of in vivo nuclear imaging of atherosclerotic plaques using radiolabeled antibodies targeted to oxidized LDL and to components (such as apoptotic cells) of necrotic core. Serial studies in animals have also been performed showing the ability to track the oxidized LDL content in plaque after hypolipidemic treatments. Alternatively, increased inflammation within symptomatic atherosclerosis can be imaged using 19 F-fluorodeoxyglucose, as has been recently demonstrated in carotid atherosclerosis. Feasibility, accuracy, and clinical utility have not yet been demonstrated for coronary lesions or in human subjects.

Validation studies of different imaging technologies. All tests require formal technology assessments so as to be considered a valid clinical tool. Such initial technical evaluations are typically performed using cross-sectional study designs relative to a reference standard. For anatomic screening tests, the reference standards range from autopsy or pathology specimens to another established anatomic imaging test. Animal studies provide an important source of direct anatomic correlations, although an inherent degree of uncertainty exists when translating these studies to human subjects. Analytic variability studies determine the accuracy and reproducibility of a method and also generate technical standards that serve as a basis for vital quality control standards. Overall, the intertest variability appears to be lowest for aortic MR, although all techniques have good reproducibility characteristics. Although older technologies are all currently trying to add quality control techniques (vascular ultrasound, echocardiography) and the pitfalls of lacking quality control are receiving more and more attention (mammography series, *New York Times*, June 27 to 28, 2002), quality control must be part of the development and adoption of any new imaging technology. Finally, biologic variability of the measurement must be considered. Among atherosclerosis tests currently available, brachial artery reactivity is affected to the greatest degree by short-term biologic variability such as menstrual cycle. Biologic variability is also evident within other anatomic imaging tests. For example, a moderate degree of variability exists between carotid ultrasonography performed in the right and left carotid artery (71,72). Similar variability is found in the extent of coronary calcium within different coronary vascular distributions (25).

Cross-sectional intermodality validation studies. Cross-sectional evaluations of the associations between different anatomic atherosclerosis assessments are useful to understand the relationships between the results of different tests performed within specific populations. Such studies provide important data on the relative prevalence of abnormal test results within populations, leading to hypotheses regarding the test performance characteristics of different modalities in screening settings. Several cross-sectional comparisons of coronary CT with carotid ultrasonography (73–77) and the ABI have been reported (73). The Rotterdam Coronary Calcification Study, a population-based investigation of subjects over age 55, recently reported the researchers' experience with EBCT scan, carotid IMT, carotid plaques, ABI, and aortic calcification measurement in 2,013 subjects (73). Using coronary calcium scores as the reference measurement, graded associations were found between coronary calcification and common carotid IMT, carotid plaques, and aortic calcification. The strongest relationship was between coronary calcium score and the number of carotid plaques. The correlation between coronary CT and carotid IMT was weaker, suggesting that IMT is a less specific marker of atherosclerosis than is discrete plaque. A nonlinear association was found between coronary calcification and the ABI, and abnormal values of the ABI (less than 1.0) were seen in association with higher coronary calcium scores.

Prospective intermodality validation studies. Technical validation studies form the foundation for crucial clinical validation studies evaluating the role of these technologies in detecting cardiovascular prognosis. The optimal basis for the comparison of different atherosclerosis imaging modalities is to measure their relative accuracy for the prediction of future cardiovascular events. Because age, race, and gender could dramatically affect the test characteristics of a given modality within a specified population, comparisons of individual studies using single modalities are insufficient.

Valid comparisons will require multiple modalities to be incorporated within a single study, one that optimally includes a broad range of patient demography, including age. Ultimately, new imaging modalities need to be shown to provide incremental information about risk beyond what is available through conventional risk assessment strategies utilizing measured risk factors (e.g., the Framingham risk score).

IS THERE A CLINICAL HIERARCHY OF ATHEROSCLEROSIS IMAGING TESTS?

Several potential considerations in the clinical hierarchical relationship between atherosclerosis imaging tests need to be weighed. These include the biologic foundation of the test, age of the population, the clinical availability of the procedure, its reproducibility, and the extent of prospective data demonstrating incremental information to the global risk assessment (Table 1).

Atherosclerosis measurement. Choosing a gold standard for comparative studies on the measurement of atherosclerosis burden is problematic because atherosclerosis severity varies within different vascular beds. However, theoretical considerations can lead to some preliminary hypotheses. Brachial reactivity is sensitive across a broad range of atherosclerosis, extending from risk factors that predispose to atherosclerosis to advanced disease. Its application may be particularly suited to young individuals who generally have the most robust vasodilator responses, and thus enable more accurate separation of normal from abnormal responses. Carotid ultrasonography can produce categorical (plaque) or continuous (IMT) measurements. The current data available on this test support its use principally in middle-aged and older patients. Studies that have clearly distinguished IMT from plaque demonstrate that coronary heart disease (CHD) risk is largely associated with the presence of nonobstructive or obstructive plaque rather than IMT (2,78). Increasing common carotid IMT and mean carotid IMT greater than or equal to 1.0 mm were predictive of future cardiovascular events in women but not in men following adjustment for risk factors in the ARIC study (4). Additionally, CCA IMT did not predict risk of MI in the Rotterdam Study after adjustment for traditional risk factors (3). Although carotid atherosclerosis is a manifestation of cerebrovascular disease, the majority of events predicted by an abnormal carotid ultrasound study are due to coronary disease, underscoring the systemic nature of atherosclerosis. Coronary CT to detect coronary calcium reveals advanced plaques that may be underrepresented in the atherosclerosis of young individuals and overrepresented in the atherosclerosis of older patients. In contrast, the ABI is abnormal only in the setting of peripheral arterial disease, which tends to cluster among patients with more advanced coronary atherosclerosis.

An alternative approach to measurement of atherosclerosis burden is to evaluate qualitative characteristics of atherosclerosis in an effort to distinguish vulnerable from stable

Table 1. Comparison of Atherosclerosis Imaging Modalities

	Test Availability	Test Reproducibility	Magnitude of Prospective Validation for Cardiovascular Events	Incremental Predictive Value Over Office-Based Risk Assessment	Comments
Brachial artery reactivity testing	Widely available	3% (absolute) or ~25% (relative)	Relative risk—3	No data	Equipment widely available; requires specialized training. Biologic variability is high (e.g., can vary with meals, menstrual cycle).
Coronary CT	79 U.S. centers	24% to 49% (absolute for CAC score)	Relative risk—approximately 4 for values above population median	Not proven	Controversy concerning independent predictive value. High incidence of incidental findings. Optimal test characteristics in middle-age individuals.
CMR	Limited	4% to 6% (image-specific absolute SD)*	No data	No data	Current feasibility limited to measurement of peripheral atherosclerosis.
Carotid ultrasonography	Widely available	5% to 11% (relative) for common carotid artery	Approximately 11% relative risk increase for each 0.1-mm increase in IMT	Yes	Limited data on patients below age 45.
Ankle-brachial index	Widely available	16% for single, 10% for multiple measures (relative variability)	Relative risk—5 to 7	Yes	Clinical impact limited by low prevalence of abnormal test results in individuals less than 60 years of age.

*Very limited data available.
CMR = cardiovascular magnetic resonance imaging; CT = computed tomography; IMT = intima-media thickness.

atherosclerosis. Although the utility of such measurements over simple plaque burden assessments has not been demonstrated, CMR, through its capability of direct plaque visualization, has the greatest potential to anatomically distinguish various types of plaques. Soft plaque imaging with contrast-enhanced coronary CT is a technique under development for this purpose. Comparative studies including emerging biomarker techniques (nuclear techniques) are also needed.

Detection of cardiovascular risk. Among anatomic screening tests, IMT, coronary artery calcification (CAC), and CMR assessments of atherosclerosis extent have weak to modest correlations with the Framingham risk score. Except for CMR, for which no data are available, carotid IMT/plaque, CAC, endothelial dysfunction, and ABI all predict cardiovascular events, with risk ratios ranging from two- to eight-fold increased CHD risk for an abnormal test result. The magnitude of this increased relative risk matches or exceeds the typical risk ratio for single risk factors (e.g., hyperlipidemia) in their ability to predict CHD events.

To date, an independent contribution of anatomic screening tests over office-based risk factor assessment has been definitively shown only for abnormal carotid ultrasound and ABI (see Task Force 4 report). Although recent data for CAC are suggestive, considerable controversy exists on the potential independent role of CAC assessment. Additional studies, particularly studies comparing multiple anatomic screening modalities, are needed. Ultimately, the greatest application of these technologies would be to aid in the early detection of cardiovascular disease, which would result in more widespread and effective prevention strategies. None of these imaging technologies have been shown to make prevention more effective, although their integration into office-based risk factor assessment is under active study.

ATHEROSCLEROSIS MEASUREMENT IN SPECIAL POPULATIONS

Diabetes mellitus. Although all patients with diabetes mellitus are generally considered to have an increased risk for cardiovascular events, establishing a gradient of risk among different patients with diabetes is appealing to refine the deployment of cardiovascular prevention resources. Kuller et al. (79) demonstrated in diabetic patients in the Cardiovascular Health Study that the presence of subclinical atherosclerosis, determined through a composite measure including ABI and carotid ultrasonography, confers a greater risk of cardiovascular events even among individuals with known diabetes mellitus. Among modalities, BART may have a specific limitation in diabetes due to augmented vasodilator responses seen in hyperinsulinemic states leading to false negative studies, particularly in early diabetes.

Women. There are no data to suggest gender-based limitations to atherosclerosis imaging. However, notable differences do exist in gender-based distributions of atherosclerosis measurements. Thus, accurate risk assessments will require the application of gender-specific data on atherosclerosis extent and cardiovascular outcomes. Although IMT values are, in general, lower in women, the relationship between IMT and outcomes in the ARIC study was stronger in women than in men (4). Coronary calcium scores on coronary CT are also generally lower for women than for men; however, recent data indicate greater cardiovascular risk for a given calcium score in women (80). The reasons for this are unknown, but this could be due to smaller artery size in women (thus, a given absolute calcium score would represent a greater relative extent of atherosclerosis). The results of BART also require gender adjustment, as women have a greater vasodilator response than do men. The relative risk of an abnormal ABI for cardiovascular events is similar in men and women (81).

Ethnicity. Phenotypic differences in atherosclerosis imaging exist between races, although for many modalities the extent and implications of these differences is yet to be fully defined. This has been most clearly demonstrated in coronary CT imaging. After adjustment for cardiovascular risk factors, blacks have less prevalent and less severe coronary calcium (82) but a proportionately greater number of coronary events than do whites (83). Although the biologic foundation for this finding is unclear, these data do indicate that ethnic group-specific distributions of coronary calcium scores are needed, and the relationship between these data and cardiovascular outcomes must be individually defined. Black individuals are also known to have worse vasodilator responses on BART, again indicating the need for ethnic-specific data. Black individuals, in comparison with other ethnic groups, are twice as likely to have an abnormal ABI (84,85). In comparison, the reported ethnic differences in carotid ultrasonography have generally been minor (86,87).

Age. Patient age is an important consideration within atherosclerosis imaging, although additional cross-sectional and longitudinal studies with broad age demography are needed to fully define the limitations of individual imaging modalities. Theoretically, BART is an optimal technique for use in young individuals in whom endothelial dysfunction should precede the development of advanced atheroma. Similarly, MR, which can detect total aortic atheroma extent may have a specific advantage in the young. In contrast, imaging modalities that rely upon the detection of advanced atheroma (coronary CT and ABI) are more likely to have a limited role in younger individuals, in whom advanced atheroma has a relatively low prevalence (leading to underdetection of cardiovascular risk) and in older individuals in whom advanced atheroma is too prevalent.

The relationships between age and the outcomes associated with advanced atheroma may be complex. For example, the predictive value of vascular calcification for cardiovascular events may diminish with advancing age (17,88). This may explain the apparent discrepancy in the prognostic value of coronary CT described in different reported studies, and it underscores the need for carefully designed longitu-

dinal studies. Most published data for carotid ultrasonography have been from middle-aged and older populations, and the predictive value for this modality in the young (less than age 45) has yet to be demonstrated. Finally, the ABI, which detects more advanced atherosclerosis manifested as peripheral arterial disease, is particularly well-suited to older populations.

IMAGING HORIZONS

What future developments within atherosclerosis imaging can be anticipated? Compared with CMR and BART, carotid ultrasonography and the ABI are mature technologies that will provide useful benchmarks for the development of new techniques. Although the current scope of coronary CT is largely limited to coronary calcium detection, expansion of this technology with contrast enhancement for soft plaque imaging could allow detection of total coronary plaque burden. Once technically feasible and validated, the incremental value of this measurement over coronary calcium assessments must be demonstrated. Use of CMR has likely the greatest potential for future developments in the field. Although the spatial and temporal resolution remains a formidable challenge for coronary imaging, plaque characterization utilizing nanoparticles or gadolinium-tagged molecular imaging is currently being performed in noncoronary vascular beds. In addition, protocols are being developed to use CMR for detection and quantification of atherosclerosis in other territories such as the distal aorta, which may prove useful in the near future. Development of molecular plaque imaging modalities is in its infancy but should be a rich source of knowledge on atherosclerosis bioactivity. Clinical validation of these technical refinements will be necessary, performed in comparison to more established atherosclerosis imaging techniques.

FUTURE DIRECTIONS

1. There is a need for data on the incremental value of new techniques to standard office-based risk assessment in order to determine utility.
2. There is a need to move toward broader standardization of imaging modalities to ensure external validity of the published data, and to enable cross-study comparisons. Once standardized, the reproducibility and variability of a methodology must be defined. This need is particularly evident for newer modalities. The portability of test performance characteristics from research centers to clinical settings must be demonstrated.
3. The currently available atherosclerosis imaging modalities are in different phases of development. Although the data for ABI and carotid ultrasound are most mature, these technologies are also most static, with little room for further development. The effectiveness of more mature modalities as CHD risk-screening tools cannot be generalized to newer modalities (e.g., plaque burden testing with CMR must be independently validated for CHD prognosis).
4. Because atherosclerosis imaging test results can be considered continuous, improved definition of "positive" versus "negative" results is needed.
5. There is a need for data on subgroups (e.g., gender and race) for each modality. Various modalities may perform differently in detecting CHD prognosis among patient subgroups.

TASK FORCE 3 REFERENCE LIST

1. U.S. Preventive Services Task Force. Guide to Clinical Preventive Services, 2nd edition. Washington, DC: U. S. Department of Health and Human Services, 1996.
2. Belcaro G, Nicolaides AN, Ramaswami G, et al. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study). Atherosclerosis 2001;156:379–87.
3. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96: 1432–7.
4. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. Am J Epidemiol 1997;146:483–94.
5. Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993;24:1297–304.
6. Crouse JR III, Craven TE, Hagaman AP, Bond MG. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 1995;92:1141–7.
7. Wendelhag I, Liang Q, Gustavsson T, Wikstrand J. A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. Stroke 1997;28:2195–200.
8. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation 1993;87 Suppl II:56–65.
9. Roman MJ, Pickering TG, Pini R, Schwartz JE, Devereux RB. Prevalence and determinants of cardiac and vascular hypertrophy in hypertension. Hypertension 1995;26:369–73.
10. Roman MJ, Saba PS, Pini R, et al. Parallel cardiac and vascular adaptation in hypertension. Circulation 1992;86:1909–18.
11. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH. Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) investigators. Stroke 1997;28:1693–701.
12. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14–22.
13. Crouse JR, III, Byington RP, Bond MG, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). Am J Cardiol 1995;75:455–9.
14. Furberg CD, Adams HP, Jr., Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Circulation 1994;90:1679–87.
15. Salonen R, Nyyssonen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Circulation 1995;92:1758–64.
16. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998;128:262–9.
17. Witteman JC, Kannel WB, Wolf PA, et al. Aortic calcified plaques and cardiovascular disease (the Framingham Study). Am J Cardiol 1990;66:1060–4.

18. Rumberger JA, Sheedy PF, Breen JF, Fitzpatrick LA, Schwartz RS. Electron beam computed tomography and coronary artery disease: scanning for coronary artery calcification. Mayo Clin Proc 1996;71: 369–77.
19. 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.
20. Detrano R, Tang W, Kang X, et al. Accurate coronary calcium phosphate mass measurements from electron beam computed tomograms. Am J Card Imaging 1995;9:167–73.
21. Mathur KS, Kashyap SK, Kumar V. Correlation of the extent and severity of atherosclerosis in the coronary and cerebral arteries. Circulation 1963;27:929–34.
22. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
23. Hunold P, Schmermund A, Seibel RM, Gronemeyer DH, Erbel R. Prevalence and clinical significance of accidental findings in electron-beam tomographic scans for coronary artery calcification. Eur Heart J 2001;22:1748–58.
24. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87: 1335–9.
25. Wong ND, Kouwabunpat D, Vo AN, et al. Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. Am Heart J 1994;127:422–30.
26. O'Malley PG, Taylor AJ, Jackson JL, Doherty TM, Detrano RC. Prognostic value of coronary electron-beam computed tomography for coronary heart disease events in asymptomatic populations. Am J Cardiol 2000;85:945–8.
27. Detrano RC, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. Circulation 1999;99:2633–8.
28. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000;101:850–5.
29. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–44.
30. Sangiorgi G, Rumberger JA, Severson A, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 1998;31:126–33.
31. Devries S, Wolfkiel C, Shah V, Chomka E, Rich S. Reproducibility of the measurement of coronary calcium with ultrafast computed tomography. Am J Cardiol 1995;75:973–5.
32. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998;208: 807–14.
33. Wang S, Detrano RC, Secci A, et al. Detection of coronary calcification with electron-beam computed tomography: evaluation of interexamination reproducibility and comparison of three image-acquisition protocols. Am Heart J 1996;132:550–8.
34. Mao S, Budoff MJ, Bakhsheshi H, Liu SC. Improved reproducibility of coronary artery calcium scoring by electron beam tomography with a new electrocardiographic trigger method. Invest Radiol 2001;36: 363–7.
35. Achenbach S, Ropers D, Pohle K, et al. Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. Circulation 2002;106:1077–82.
36. Fayad ZA, Fuster V. Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. Circ Res 2001;89:305–16.
37. Yuan C, Mitsumori LM, Beach KW, Maravilla KR. Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. Radiology 2001;221:285–99.
38. Yuan C, Murakami JW, Hayes CE, et al. Phased-array magnetic resonance imaging of the carotid artery bifurcation: preliminary results in healthy volunteers and a patient with atherosclerotic disease. J Magn Reson Imaging 1995;5:561–5.
39. Toussaint JF, LaMuraglia GM, Southern JF, Fuster V, Kantor HL. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. Circulation 1996;94:932–8.
40. Fayad ZA, Fuster V. Characterization of atherosclerotic plaques by magnetic resonance imaging. Ann N Y Acad Sci 2000;902:173–86.
41. Fayad ZA, Nahar T, Fallon JT, et al. In vivo magnetic resonance evaluation of atherosclerotic plaques in the human thoracic aorta: a comparison with transesophageal echocardiography. Circulation 2000; 101:2503–9.
42. Fayad ZA, Fuster V, Fallon JT, et al. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. Circulation 2000;102:506–10.
43. Kim WY, Stuber M, Bornert P, Kissinger KV, Manning WJ, Botnar RM. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. Circulation 2002; 106:296–9.
44. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002;106: 1368–73.
45. Yuan C, Beach KW, Smith LH Jr., Hatsukami TS. Measurement of atherosclerotic carotid plaque size in vivo using high resolution magnetic resonance imaging. Circulation 1998;98:2666–71.
46. Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. Circulation 2001;104:249–52.
47. Neunteufl T, Heher S, Katzenschlager R, et al. Late prognostic value of flow-mediated dilation in the brachial artery of patients with chest pain. Am J Cardiol 2000;86:207–10.
48. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 2000;102:959–64.
49. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation 2001;104:2051–6.
50. Jaffer FA, O'Donnell CJ, Larson MG, et al. Age and sex distribution of subclinical aortic atherosclerosis: a magnetic resonance imaging examination of the Framingham Heart Study. Arterioscler Thromb Vasc Biol 2002;22:849–54.
51. Kang X, Polissar NL, Han C, Lin E, Yuan C. Analysis of the measurement precision of arterial lumen and wall areas using high-resolution MRI. Magn Reson Med 2000;44:968–72.
52. Chan SK, Jaffer FA, Botnar RM, et al. Scan reproducibility of magnetic resonance imaging assessment of aortic atherosclerosis burden. J Cardiovasc Magn Reson 2001;3:331–8.
53. Corti R, Fuster V, Fayad ZA, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. Circulation 2002;106:2884–7.
54. Joannides R, Haefeli WE, Linder L, et al. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 1995;91:1314–9.
55. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–65.
56. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899–906.
57. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.
58. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111–5.

59. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation 1993;88:2149–55.
60. Harris CW, Edwards JL, Baruch A, et al. Effects of mental stress on brachial artery flow-mediated vasodilation in healthy normal individuals. Am Heart J 2000;139:405–11.
61. Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF, Jr., Vita JA. Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 1996;93:1107–13.
62. Hashimoto M, Akishita M, Eto M, et al. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. Circulation 1995;92:3431–5.
63. Herrington DM, Fan L, Drum M, et al. Brachial flow-mediated vasodilator responses in population-based research: methods, reproducibility and effects of age, gender and baseline diameter. J Cardiovasc Risk 2001;8:319–28.
64. Herrington DM, Espeland MA, Crouse JR, III, et al. Estrogen replacement and brachial artery flow-mediated vasodilation in older women. Arterioscler Thromb Vasc Biol 2001;21:1955–61.
65. Yao ST, Hobbs JT, Irvine WT. Ankle systolic pressure measurements in arterial disease affecting the lower extremities. Br J Surg 1969;56: 676–9.
66. Ouriel K, McDonnell AE, Metz CE, Zarins CK. Critical evaluation of stress testing in the diagnosis of peripheral vascular disease. Surgery 1982;91:686–93.
67. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation 1985;71:516–22.
68. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–24.
69. McPhail IR, Spittell PC, Weston SA, Bailey KR. Intermittent claudication: an objective office-based assessment. J Am Coll Cardiol 2001;37:1381–5.
70. Fowkes FG, Housley E, Macintyre CC, Prescott RJ, Ruckley CV. Variability of ankle and brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. J Epidemiol Community Health 1988;42:128–33.
71. Denarie N, Gariepy J, Chironi G, et al. Distribution of ultrasonographically-assessed dimensions of common carotid arteries in healthy adults of both sexes. Atherosclerosis 2000;148:297–302.
72. Schmidt C, Wendelhag I. How can the variability in ultrasound measurement of intima-media thickness be reduced? Studies of interobserver variability in carotid and femoral arteries. Clin Physiol 1999;19:45–55.
73. Oei HH, Vliegenthart R, Hak AE, et al. The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. J Am Coll Cardiol 2002;39:1745–51.
74. Megnien JL, Sene V, Jeannin S, et al. Coronary calcification and its relation to extracoronary atherosclerosis in asymptomatic hypercholesterolemic men. The PCV METRA Group. Circulation 1992;85: 1799–807.
75. Davis PH, Dawson JD, Mahoney LT, Lauer RM. Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults. The Muscatine study. Circulation 1999;100:838–42.
76. Schonbeck U, Mach F, Sukhova GK, et al. Regulation of matrix metalloproteinase expression in human vascular smooth muscle cells by T lymphocytes: a role for CD40 signaling in plaque rupture? Circ Res 1997;81:448–54.
77. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res 2002;90: 251–62.
78. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245–9.
79. Kuller LH, Velentgas P, Barzilay J, Beauchamp NJ, O'Leary DH, Savage PJ. Diabetes mellitus: subclinical cardiovascular disease and risk of incident cardiovascular disease and all-cause mortality. Arterioscler Thromb Vasc Biol 2000;20:823–9.
80. Callister TQ, Schisterman EF, Berman D, Raggi P, Shaw LJ. Risk-adjusted mortality by extent of coronary calcification (abstr). J Am Coll Cardiol 2002;39.
81. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381–6.
82. Lee TC, O'Malley PG, Feuerstein IM, Taylor AJ. The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects. J Am Coll Cardiol 2003;41: 39–44.
83. Doherty TM, Tang W, Detrano RC. Racial differences in the significance of coronary calcium in asymptomatic black and white subjects with coronary risk factors. J Am Coll Cardiol 1999;34:787–94.
84. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation 1993;88:837–45.
85. Criqui MH, Vargas V, Ho E. Ethnicity and peripheral arterial disease: the San Diego population study (abstr). Circulation 2002;105.
86. Chait A, Brazg RL, Tribble DL, Krauss RM. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. Am J Med 1993;94:350–6.
87. Manolio TA, Burke GL, Psaty BM, et al. Black-white differences in subclinical cardiovascular disease among older adults: the Cardiovascular Health Study. CHS Collaborative Research Group. J Clin Epidemiol 1995;48:1141–52.
88. Taylor AJ, O'Malley PG, Detrano RC. Comparison of coronary artery computed tomography versus fluoroscopy for the assessment of coronary artery disease prognosis. Am J Cardiol 2001;88:675–7.
89. Thulesius O. Principles of pressure measurement. In: Bernstein F, editor. Noninvasive Diagnostic Techniques in Vascular Disease. St. Louis, MO: Mosby, 1985.
90. Hundley WG, Hamilton CA, Clarke GD, et al. Visualization and functional assessment of proximal and middle left anterior descending coronary stenoses in humans with magnetic resonance imaging. Circulation 1999;99:3248–54.

Task Force #4—How Do We Select Patients for Atherosclerosis Imaging?

Peter W. F. Wilson, MD, *Co-Chair*, Sidney C. Smith, JR, MD, FACC, *Co-Chair*, Roger S. Blumenthal, MD, FACC, Gregory L. Burke, MD, Nathan D. Wong, PHD, FACC

The coronary heart disease (CHD) risk assessment should begin in the office of the physician or other health care provider. All adults should undergo a standard assessment to help predict future CHD risk. The American College of Cardiology (ACC) and the American Heart Association (AHA) endorse the global risk assessment based on the Framingham risk prediction model, which includes the traditional risk factors of age, gender, smoking, blood pressure, total and high-density lipoprotein (HDL) cholesterol. Once the patient's absolute CHD risk is assessed, the