Atherosclerosis Imaging
Prognostically Useful or Merely More of What We Know?

Prashant Kaul, MD; Pamela S. Douglas, MD, FAHA

Despite the epidemiological insights from the Framingham Study in the early 1950s and the resulting significant advances in the diagnosis and management of coronary heart disease (CHD), it remains the leading cause of death in the United States. In part, this is because sudden cardiac death is the first presentation of CHD in 50% of men and 64% of women, and therefore, the only available strategy for reducing mortality in these patients is primary prevention. This is the target population for atherosclerosis imaging, which has been proposed as a strategy for the earlier and more accurate identification of individuals at risk for CHD so that lifesaving preventive strategies can be more optimally targeted in those at risk.

**Limitations of Current Primary Risk Assessment Strategies**

Current guidelines for primary prevention recommend initial assessment and risk stratification based on traditional risk factors (eg, the Framingham Risk Score [FRS] in the United States and the Systemic Coronary Risk Evaluation in Europe), followed by goal-directed therapy as necessary to modify those risk factors. However, these traditional prevention strategies can be inadequate, as cardiovascular events do occur in patients without known risk or in low and intermediate risk groups in whom an aggressive treatment strategy would not be indicated. This is highlighted by a study of 222 young adults (men \( \geq 55 \) years and women \( \geq 65 \) years) without known prior CHD, hospitalized for acute myocardial infarction, of whom 70% were in a low-risk category with a 10-year risk of CHD\(<10\%\) based on their FRS. Furthermore, when the 10-year risk of these patients was stratified by number of risk factors and low-density lipoprotein cholesterol level, three quarters did not meet National Cholesterol Education Program III criteria to be identified as “low risk” by FRS. For example, in multivariate analyses, women aged <65 years rarely exceed 20\% 10-year risk with any combination of risk factors and only exceed 10\% risk if they are smokers with low high-density lipoprotein levels. Instead, the prevalence of risk factors in the United States is actually quite high, which gives rise to another limitation of traditional risk factor–based models, such as the FRS. As the prevalence of risk factors increase, they themselves become less discriminatory in predicting a CHD event, despite their apparent causal relationship.

This is analogous to the concept that if almost everyone in a given population smokes, smoking itself will fail to predict the risk of lung cancer. Likelihood ratio analysis using the combined data from 3 large epidemiological studies has been used to highlight this problem. The predictive power of having 1 or more risk factors in predicting CHD events was remarkably low, with a likelihood ratio \(<1.4\), where a likelihood ratio of 2.0 or less denotes low predictive power.

All risk assessment strategies are complicated by the pathophysiology of atherosclerosis and acute coronary events, two thirds of which are a result of angiographically insignificant atherosclerotic lesions or those that appear insignificant due to remodeling (Glagov phenomenon). Such lesions are also largely silent on provocative stress testing, the major modality used to diagnose CHD today. Thus, significant atherosclerosis may be present in the absence of inducible ischemia or even luminal narrowing and, therefore, be undetectable using conventional risk assessment strategies. Efforts to differentiate stable plaque from vulnerable plaque prone to disruption and thrombosis show promise but are not yet ready for widespread clinical use.

Additional limitations of the FRS in identifying primary risk are demonstrated by National Health and Nutrition Examination Survey data that classifies 85\% of healthy adults between ages 20 and 79 years as low risk by FRS, and only 2\% as high risk, although epidemiological data suggests that more than one third will die from cardiovascular disease (CVD). It is important to note that although there are a large proportion of “low-risk” individuals based on the National Health and Nutrition Examination Survey data, this does not imply that the prevalence of risk factors in the general population is low. Individuals may have risk factors but still be classified as “low risk” by FRS. For example, in multivariate analyses, women aged <65 years rarely exceed 20\% 10-year risk with any combination of risk factors and only exceed 10\% risk if they are smokers with low high-density lipoprotein levels. Instead, the prevalence of risk factors in the United States is actually quite high, which gives rise to another limitation of traditional risk factor–based models, such as the FRS. As the prevalence of risk factors increase, they themselves become less discriminatory in predicting a CHD event, despite their apparent causal relationship.

This is analogous to the concept that if almost everyone in a given population smokes, smoking itself will fail to predict the risk of lung cancer. Likelihood ratio analysis using the combined data from 3 large epidemiological studies has been used to highlight this problem. The predictive power of having 1 or more risk factors in predicting CHD events was remarkably low, with a likelihood ratio \(<1.4\), where a likelihood ratio of 2.0 or less denotes low predictive power.

All risk assessment strategies are complicated by the pathophysiology of atherosclerosis and acute coronary events, two thirds of which are a result of angiographically insignificant atherosclerotic lesions or those that appear insignificant due to remodeling (Glagov phenomenon). Such lesions are also largely silent on provocative stress testing, the major modality used to diagnose CHD today. Thus, significant atherosclerosis may be present in the absence of inducible ischemia or even luminal narrowing and, therefore, be undetectable using conventional risk assessment strategies. Efforts to differentiate stable plaque from vulnerable plaque prone to disruption and thrombosis show promise but are not yet ready for widespread clinical use.

Further, much of this effort is necessarily focused on symptomatic patients, as current care paradigms generally eschew noninvasive or invasive diagnostic testing in the absence of a clinical syndrome suggestive of CHD. An ideal strategy...
would detect risk before the appearance of clinical disease or symptoms.

The Rationale for Atherosclerosis Imaging

The concept of primary prevention derives from the knowledge that atherosclerosis develops over decades and has a prolonged asymptomatic phase during which it is possible to modify the course of disease. Thus, earlier detection of anatomically or metabolically significant, but “subclinical” or “preclinical” atherosclerosis may allow for more timely intervention that in turn may prevent progression to and symptomatic illness, vulnerable plaque formation or sudden death. Adoption of this idea significantly extends our concept of CHD prevention and management. The practical implications of this would be a new model in which healthy individuals would be screened for the earliest manifestations of the development of atherosclerosis. Such screening is currently used for the early detection and prevention of breast cancer and colon cancer and has recently been recommended for abdominal aortic aneurysm. However, it would represent both a substantial change in practice as well as a tremendous new cost to an already burdened healthcare system. Further, implementation of such a major change in practice would require the support of a strong evidence base.

In the absence of such evidence, consideration of the World Health Organization criteria for screening may be helpful (Table 1). As can be seen, CHD screening meets many of the requirements, but there is still controversy over whether screening will actually lead to improved outcomes over the traditional method of risk assessment and modification.

Central to the possible effectiveness of a screening strategy is the availability of suitable tools for early detection. Most efforts have focused on the visualization of plaque or its components and a number of imaging modalities to detect atherosclerosis are currently available. Two modalities, coronary artery calcium (CAC) score, often measured by computed tomography (CT), and carotid intima-media thickness (CIMT), measured by B-mode ultrasound, have the most potential and the largest body of supporting data. They will form the focus of this review. Other anatomy-based modalities such as aortic and carotid plaque detection by MRI are less well developed, whereas still others such as measurement of brachial vasoreactivity by ultrasound or vascular compliance measured by radial tonometry detect abnormalities in vascular function and may eventually prove useful but are less well investigated.

CAC Measured by CT

During the past 20 years, much has been learned about the mechanism of coronary arterial calcification. In general, vascular calcification is observed almost exclusively in the setting of atherosclerotic lesions, especially those that are advanced or in older patients, and is rarely seen in a normal coronary artery. Conversely, atherosclerosis may be present without visible calcium.

In this respect, it is important to note that there is some evidence to suggest that unstable plaques are less likely to be calcified. It is, therefore, significant that the presence of CAC has neither been associated with plaque vulnerability nor with the probability of plaque rupture.

Description of the Technology

The potential for using coronary artery calcification to screen for coronary artery disease was suggested as early as the 1970s. Current technologies use thin slice CT imaging and fast scan times to decrease motion-induced artifact. The quantitative CAC score using the Agatston method is an estimate of total plaque burden and is based on the x-ray attenuation coefficient, or CT number measured in Hounsfield units and the area of calcified plaque. CAC measurement can be completed within 15 minutes with only a few seconds of scanning time and without the need for intravenous contrast. The technique has been validated without the need for heart rate control and uses a relatively low-effective radiation dose in the 1.0 to 1.8 mSv range. It is considered a mature technology.

Data Supporting the Use of CAC for Screening

The best primary data regarding the use of CAC comes from the multiethnic study of atherosclerosis. This longitudinal, prospective cohort study was initiated by the National Heart, Lung and Blood Institute in 2000 to investigate the characteristics and progression of subclinical atherosclerosis using a variety of imaging modalities in a population-based sample of 3601 women and 3213 men between the ages of 45 and 84 years without known CVD. The subjects of this study represent a significantly more diverse population than have previously been studied (38% white, 28% black, 22% Hispanic, and 12% Asian [of Chinese descent]). Emerging data reveal close associations between atherosclerosis imaging and subsequent CHD events. Detrano et al found that patients with a CAC score >300 had a hazard ratio of 9.67 (95% CI, 5.20 to 17.98, P < 0.001) compared with those with a CAC of 0. Discriminant accuracy for all CHD events increased significantly from a c-index of 0.77 for risk factors alone to 0.82 for risk factors plus CAC scoring. The mea-

Table 1. World Health Organization Criteria for Screening

| The condition sought should be an important health problem for the individual and community. |
| There should be an accepted treatment or useful intervention for patients with the disease. |
| The natural history of the disease should be adequately understood. |
| There should be a latent or early symptomatic stage. |
| There should be a suitable and acceptable screening test or examination. |
| Facilities for diagnosis and treatment should be available. |
| There should be an agreed policy on whom to treat as patients. |
| Treatment started at an early stage should be of more benefit than treatment started later. |
| The cost should be economically balanced in relation to possible expenditure on medical care as a whole. |
| Case finding should be a continuing process and not a once and for all project. |

Modified from Wilson.
surement of CAC added incremental value to the prediction of CHD above that of traditional risk factors across all 4 ethnic groups sampled and both sexes. Further, the relationship was dynamic, with a 2-fold increase in the CAC score increasing the estimated probability of any coronary event by \( \approx 25\% \) during the 4-year follow-up period.

Women may be at higher risk of misclassification by traditional risk factor assessment. In a previous study of 2447 consecutive, nondiabetic, asymptomatic women undergoing risk assessment, 84% of women with significant CAC (\( \geq 75\text{th} \) percentile) were classified as low risk by the FRS.36 Of the 3601 women enrolled in multiethnic study of atherosclerosis, 90% were classified as “low risk” based on traditional Framingham criteria, although, \( \approx 30\% \) had evidence of coronary calcification.37 Of these, 12% had a CAC score of 300 or higher. These women with advanced CAC scores had a significantly higher relative risk of CHD events than women without detectable CAC and had an absolute CHD event risk of 6.7% over a 3.75-year period.37 However, whether treating this group with more aggressive strategies will reduce CHD events over the longer term is yet to be proven.

The multiethnic study of atherosclerosis findings are similar to and expand on earlier work by Greenland et al38 suggesting that a high CAC score would be of value in modifying the predicted risk obtained from FRS alone, especially among patients in the intermediate risk group. In a prospective observational study of 1461 asymptomatic adults with coronary risk factors, areas under the receiver operating characteristic curves for prediction of CHD death or nonfatal myocardial infarction were 0.63 for FRS alone and 0.68 for FRS plus CAC scoring (\( P<0.001 \)).

Shaw et al39 in a large observational data series of 10 377 asymptomatic individuals, demonstrated that in a risk-adjusted model, coronary calcium was an independent predictor of mortality (\( P<0.001 \)) with a 5-year risk-adjusted survival of 99% for a CAC score of 10 or less and 95% for a score of \( >1000 \) (\( P<0.001 \)). In the largest observational outcome study to date, Budoff et al40 collected mortality data on 25 253 asymptomatic individuals referred for CAC scanning by their primary care physicians. They demonstrated that CAC was an independent predictor of mortality in a multivariable model with a 10-year risk-adjusted survival of 99% for a CAC score of 0 and 88% for a score of \( >1000 \) (\( P<0.0001 \)).

These primary data are extended by a meta-analysis41 of 6 published reports38,42–46 from 2003 to 2005 on the prognostic value of CAC scores. As CAC scores increase, the summary relative risk ratios demonstrate a strong incremental relationship with increasing CAC scores and were associated with higher event rates (Figure 1). In a secondary analysis41 of patients from 4 separate reports38,43,44,46 focusing only on patients with intermediate FRS, annual CHD death, and myocardial infarction rates increased as CAC score increased (Figure 2). Thus, use of CAC in this group would permit reclassification of intermediate FRS patients with CAC scores \( \approx 400 \) into a high-risk category with a \( >20\% \)
10-year risk of estimated coronary events, ie, CHD equivalent risk status, based on the observed annual CHD death or myocardial infarction rate of 2.4% in this group, which in turn would indicate the need for more intensive preventive treatment.

**Limitations**

Widespread adoption of CAC as part of a CHD screening program has the inherent risk of exposing large numbers of healthy individuals to ionizing radiation. The mean effective dose for CAC measurement by CT using prospective gating ranges from 1.0 to 1.8 mSv. The mean effective dose for CT coronary angiography is higher with ranges from 4.0 to 21.4 mSv. For comparison, the average annual background radiation in the United States is 3 mSv, a single-view posteroanterior chest radiograph delivers an effective dose of 0.03 mSv and a dual isotope stress test, up to 29 mSv.47 The effective dose range for a single CAC score scan would, therefore, equate to ≈122 to 219 days of natural background radiation or 33 to 60 posteroanterior chest radiographs. The US Food and Drug Administration suggest that an effective dose of 10 mSv may be associated with an increase in the risk of fatal cancer of ≈1 in 2000.48 When compared with the natural incidence of fatal cancer in the US population (1 in 5), this risk of radiation-induced cancer may appear trivial. However, if large numbers of the healthy population undergo screening procedures of uncertain benefit, even a small increase in radiation-associated cancer risk for an individual can become a more significant public health concern.48 The Food and Drug Administration further notes that the lowest doses received by some of the Japanese survivors of the atomic bombs was in the range of 5 to 20 mSv. These survivors, who are estimated to have experienced doses only slightly larger than those encountered in CT (angiography), have demonstrated a small but increased radiation-related excess relative risk for cancer mortality.

Another major limitation is the failure to detect uncalcified plaque, which may predominate in women, blacks, Asian Indians, and other ethnic groups. Although the high negative predictive value of CAC scoring mitigates against this concern, it may be argued that individuals with uncalcified soft plaques would be falsely reassured by CAC scoring alone. CAC also fails to address the elusive vulnerable plaque.

A final limitation of CAC is the cost required to implement and maintain equipment, particularly in the absence of widespread third party reimbursement.49 The cost of a CT scanner is ≈$1.5 million with other associated expenses such as space, radiation shielding, scan storage requirements, third party image interpretation solutions, etc, amounting to another $500 000. Direct annual operating expenses (including financing of the scanner, space, supplies, personnel, maintenance, etc) can total more than $800 000.49

**Current Clinical Practice Recommendations**

Despite the strong epidemiological evidence linking CAC with CHD events, clinical practice guidelines remain cautious regarding the technique, recommending limited, if any, use in routine practice. In 2007, a Clinical Expert Consensus Document on CAC scoring by CT in global cardiovascular risk assessment was developed by the American College of Cardiology Foundation and the American Heart Association in collaboration with the Society of Atherosclerosis Imaging and Prevention and Society of Cardiovascular Computed Tomography.31 It should be noted that topics are chosen for coverage by expert consensus documents when the evidence base, experience with technology, or the clinical practice are deemed insufficiently well developed to be evaluated by the formal American College of Cardiology/American Heart Association Practice Guidelines process. This document, therefore, represents the best attempt of the American College of Cardiology and the American Heart Association to guide the clinical community in an area where there is perceived to be a paucity of evidence.

The consensus committee judged that in asymptomatic patients with low or high FRS (ie, <10% or >20% 10-year risk of estimated coronary events), there is no role for CAC measurement by coronary CT scanning and its use was not recommended. However, the committee felt it may be reasonable to consider the use of CAC measurements in asymptomatic patients with an intermediate FRS (ie, a 10% to 20% 10-year risk of estimated coronary events). This recommendation was based on the evidence that there is incremental risk prediction information in this patient group and that such patients may be reclassified to a higher risk category and may consequently benefit from a modified management strategy.

The US Preventive Services Task Force currently recommends against routine screening with electron-beam CT scanning for coronary calcium for either the presence of severe coronary artery stenosis or the prediction of CHD events in adults at low risk.50 This is a grade D recommendation, ie, the US Preventive Services Task Force recommends against routinely providing (the service) to asymptomatic patients with at least fair evidence that (the service) is ineffective or that harms outweigh benefits. Fair evidence is defined as “sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies.”50

**CIMT Measured by B-Mode Ultrasound**

The use of B-mode ultrasound for the measurement of CIMT was evaluated and validated in the mid-1980s by in vitro measurements of specimens of common carotid arteries and in vivo measurements in normal human subjects.51 Age-related thickening of both the intimal and medial layers in the absence of overt atherosclerosis is well known in both human and animal models52–54 and can be due to intimal thickening or medial hypertrophy or both. It can occur in the absence of atherosclerotic plaque and is not, as commonly thought, synonymous with atherosclerosis.55 However, intima-medial thickening and atherosclerosis share similar underlying pathophysiologic mechanisms in their development and progression. Thus, CIMT is a risk factor and a marker for CHD risk that most accurately represents subclinical vascular disease but not plaque formation or atherosclerosis per se.

**Description of the Technology**

Measurement is typically carried out using high frequency transducers at fundamental frequencies between 7.5 and 10
MHz, resulting in an axial resolution of \( \approx 100 \) to 200 \( \mu \)m. The patient is scanned supine with slight hyperextension and rotation of the neck away from the probe. There have been some suggestions of measuring segments in each common carotid artery bulb, and internal carotid artery bilaterally and then averaging the 6 measurements to establish a composite value.\(^6^6\) However, the current recommended strategy\(^5^5\) is to measure in the common carotid arteries rather than the bifurcation (bulb) or either of the branch vessels due to its almost universal accessibility, perpendicular location relative to the transducer beam, and better reproducibility and measurement yield.\(^5^7,5^8\) Measurements are limited to the far wall of the common carotid arteries because near wall measurements are more technically challenging and less reproducible, partly due to blossoming artifact and acoustic reflection of the echo-dense intima into the lumen.\(^5^9\)

### Data Supporting the Use of CIMT for Screening

The use of CIMT in a number of large clinical trials and epidemiological studies has been facilitated by its speed and ease of use, its noninvasive nature and lack of ionizing radiation, and is justified by its sensitivity and reproducibility in identifying atherosclerotic risk. There have been several autopsy studies that demonstrated statistically significant correlations between atherosclerosis of the carotid and coronary arteries.\(^6^0,6^1\) There is also evidence demonstrating that CIMT adds incremental information to traditional risk factors in predicting angiographically significant coronary artery disease.\(^6^2\)

The rationale for using carotid ultrasound to refine CHD risk assessment is based on at least 8 published prospective studies\(^6^3–7^0\) of CIMT and CHD risk, which have been reviewed in detail in a recent meta-analysis.\(^7^1\) Each of the 8 studies had at least 1000 subjects (2 had more than 12,000 subjects\(^6^4,6^6\)) and demonstrated a statistically significant association between CIMT and the risk for myocardial infarction, CHD death and stroke. The age- and sex-adjusted overall estimate of the risk of myocardial infarction was 1.15 (95% CI, 1.12 to 1.17) per 0.10 mm CIMT difference (Figure 3).\(^7^1\) The fact that the course of CIMT may be changed with risk factor targeted interventions and that such changes are associated with a reduced risk of future CHD events\(^7^3,7^4\) lends strong support to the use of CIMT as a surrogate marker for atherosclerosis and coronary artery disease.

The first clinical trial to investigate the effect of a therapeutic intervention on the progression of CIMT was the Cholesterol-Lowering Atherosclerosis Study in 1993, which demonstrated that placebo-treated patients had significantly increased CIMT measurements over 4 years compared with colestipol-niacin–treated patients who showed significant progressive reduction in CIMT during the same time period.\(^7^5\)

A number of studies demonstrate the effect of cholesterol lowering therapy on reducing and/or reversing the progression of CIMT. The aggressive versus conventional lipid lowering on Atherosclerosis Progression in familial hypercholesterolaemia trial,\(^7^6\) a randomized, double blind study, investigated the effect of atorvastatin 80 mg versus simvastatin 40 mg on CIMT progression in 325 patients with familial hypercholesterolemia. After 2 years, CIMT had decreased (\(-0.031\) mm) in the atorvastatin group but had increased (+0.036 mm) in the simvastatin group (\(P=0.0001\)).

In a separate study, Taylor et al\(^7^7\) reported the results of the ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol trial, comparing the effects of pravastatin 40 mg versus atorvastatin 80 mg. At 1-year follow-up, atorvastatin was significantly more potent for low-density lipoprotein reduction, lowering low-density lipoprotein cholesterol to 76 mg/dL compared with 110 mg/dL in the pravastatin group. Corresponding CIMT measurements showed progressive regression in the atorvastatin group (\(-0.034\) mm) with some increase in the pravastatin group (\(+0.025\) mm; \(P=0.03\)).

In a substudy investigating the role of CIMT in predicting CHD events in those with known CHD, 146 men (40 to 59 years) from the Cholesterol-Lowering Atherosclerosis Study cohort with prior coronary artery bypass graft surgery were selected.\(^7^3\) For each 0.03-mm increase per year in CIMT, the relative risk for nonfatal myocardial infarction or coronary death was 2.2 (95% CI, 1.4 to 3.6) and the relative risk for any coronary event was 3.1 (95% CI, 2.1 to 4.5; \(P<0.001\)). Absolute thickness and progression in thickness predicted risk for coronary events beyond that predicted by coronary arterial measures of atherosclerosis and lipid measurements (\(P<0.001\)).

CIMT has also been integrated into coronary risk assessment models to improve risk prediction by adjusting the chronological age of a patient for their atherosclerotic burden to derive the patient’s vascular age.\(^5^6\) In the population studied, the median chronological age was 56 years with a mean FRS of 9.5%. An average CIMT of 0.806 mm yielded a corresponding average vascular age of 65.5 years, or an increase in this referral population of \(\approx 9.6\) years above the
chronological age. Substituting CIMT-derived vascular age for chronological age also affected predicted coronary risk. Of those at intermediate CHD risk based on their FRS, 36% of patients were reclassified into a higher risk category that would indicate the need for more aggressive therapy. These data provide an indication of the potential incremental value provided by CIMT for risk prediction over conventional FRS.

Limitations
A potential limitation of IMT measurements for predicting CHD risk is the fact that the carotid artery is being imaged to extrapolate the presence of disease in a different arterial bed. However, a reliable correlation has been shown between B-mode ultrasound measurements and pathological specimens and a number of studies have shown correlation between CIMT measurements and coronary angiographic findings.

All ultrasound techniques are operator dependent and measuring CIMT requires adequate training. In one study assessing the ability of nonsonographer clinicians to measure CIMT, the misidentification of plaques during screening and difficulty discriminating between the internal and external carotid artery was noted. Other technical considerations that may be potential sources of error include the dynamic range, gain and probe distance, all of which can significantly alter lumen diameter and CIMT measurements made using image analysis software. These variables need to be documented and standardized for reliability and reproducibility. Finally, although comparatively cheap and easy to implement, CIMT, like CAC, has yet to receive widespread third party reimbursement.

Current Clinical Practice Recommendations
The American Society of Echocardiography Carotid Intima-Media Thickness Task Force, with the endorsement of the Society of Vascular Medicine, has published the only consensus statement on the use of carotid ultrasound to identify subclinical vascular disease by a professional body. Their consensus recommendation for the use of CIMT measurement by ultrasound in asymptomatic patients is limited to those with an intermediate FRS, with a goal of predicting future CHD events. CIMT measurements are not recommended for individuals in low or high FRS groups. This mirrors the American College of Cardiology Foundation/American Heart Association philosophy, as outlined in the expert consensus document, on CAC scoring by CT.

What Is the Clinical Role of Atherosclerosis Imaging?
The earlier descriptions demonstrate that both CAC and CIMT are mature technologies with both biological plausibility and abundant epidemiological evidence linking them to atherosclerosis and CHD risk. This is necessary, but insufficient to recommend their use in guiding preventive treatment. A host of other considerations and conditions must be met before this can be done, including determining whether a strategy of CHD screening using either test is clinically preferable to current standard of care, which test is preferable, whether atherosclerosis imaging changes care, and whether testing is cost effective in any group. Evidence is needed on all of these questions before atherosclerosis imaging can truly enter the mainstream of preventive cardiology.

Is Screening for CHD Using Atherosclerosis Imaging a Viable Strategy?
The fundamental question is whether imaging atherosclerosis for coronary risk assessment as measured by CAC scoring or CIMT measurement of clinical value? Second, does the determination of clinical value rest on the performance of randomized, controlled trials showing improved clinical outcomes in terms of a reduction in future CHD events and improved health status? The evidence-based, 21st century medical community would certainly demand this scientific approach. An alternative view, however, is that given the significant public health burden of atherosclerosis and CHD and the limitations of the FRS, an exception is justified. This argument hinges on the conclusion that current practice inappropriately classifies patients as low risk and, therefore, fails to properly guide the implementation of lifesaving treatment.

The Screening for Heart Attack Prevention and Education Task Force report in 2006 offers such a challenge to the existing paradigm. The authors suggest noninvasive screening in the form of an “atherosclerosis test” (either CAC scoring or CIMT measurement) for most asymptomatic men 45 to 75 years of age and asymptomatic women 55 to 75 years of age (except those defined as very low risk) to detect and treat those with subclinical atherosclerosis. Because its publication, the report has been met with criticism due to a lack of peer review, sparse evidence regarding cost effectiveness, potential conflicts of interest, and the lack of endorsement by any professional society. However, this has not stopped the introduction in Texas, by state Representative René Oliveira, of legislation that would mandate that health insurers reimburse atherosclerosis imaging studies in asymptomatic populations as suggested by the Screening for Heart Attack Prevention and Education proposal. Although the outcome of this effort is still unknown, the transformation of unproven practice recommendations into legislative mandates may limit research on alternative options and may be potentially disruptive to the scientific process that fosters professional debate when evidence is limited or ambiguous.

A critical question is whether medical strategies are even appropriate for primary prevention in low-risk individuals. Although population studies have yet to demonstrate an effect, advocates for a personalized cardiovascular care approach, such as the Screening for Heart Attack Prevention and Education paradigm, suggest that an individual may benefit from medical therapy despite a relatively minor effect on overall population incidence of disease. However, such an approach borders on the anecdotal, given the current lack of evidence in favor of a treatment effect for imaging-guided prevention. It also fails to take into account Bayesian principles, which dictate that a positive result in a low risk population (ie, low-pretest probability) is more commonly a false positive than a true positive when compared with positive test results in an intermediate risk population. Finally, given the results of the recent Justification for the Use of statins in Primary prevention: an Intervention Trial Eval-
CVD incidence. This prospective analysis of the multiethnic compared with CIMT measurements in the prediction of CHD risk. Recently, CAC scoring was directly associated with the risk of incident CVD, independent of preexisting coronary risk factor status. However, the only prospective, randomized, controlled trial of CAC scoring in CHD found that in an asymptomatic population, the addition of the diagnosis of subclinical coronary disease did not affect CHD risk profile or impact motivation to change risk-related behaviors.

A subsequent, more recent study, on the other hand, did show that CAC screening motivated the initiation of CHD preventative measures. A similar effect of office-based CIMT screening on physician behavior and patient motivation was demonstrated in a recent study showing that physicians were more likely to prescribe evidence-based, CHD risk-reducing interventions such as aspirin and lipid-lowering therapies if increased CIMT or carotid plaque was documented. In the same study, the act of screening itself increased patients’ stated motivation to make dietary changes and increase exercise. Further, patients with abnormalities were more likely to report increases in plans to take lipid-lowering therapies and had an increased perceived likelihood of having and developing CHD. These results are in keeping with 2 other previous studies demonstrating the feasibility of CIMT measurement by ultrasound in an office setting.

<table>
<thead>
<tr>
<th>Imaging focus</th>
<th>CAC Scoring by Computed Tomography</th>
<th>CIMT by B-Mode Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>Noninvasive</td>
<td>Noninvasive</td>
</tr>
<tr>
<td>Radiation</td>
<td>1.0 to 1.8 mSv</td>
<td>No ionizing radiation</td>
</tr>
<tr>
<td>Sensitivity for the diagnosis of obstructive CHD, %</td>
<td>85%</td>
<td>50 to 70%</td>
</tr>
<tr>
<td>Specificity for the diagnosis of obstructive CHD, %</td>
<td>75%</td>
<td>60 to 80%</td>
</tr>
<tr>
<td>Hazard ratio for incident CVD event per SD increment</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Availability</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ease of use</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Operator dependence</td>
<td>Automated</td>
<td>Sonographer dependent</td>
</tr>
<tr>
<td>Estimated test cost, $</td>
<td>300 to 600</td>
<td>200</td>
</tr>
<tr>
<td>Major payer reimbursement</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cost of implementation, $</td>
<td>Capital: 1.5 million plus renovation; operating: $800 000/year</td>
<td>Capital: 100 000; operating: $50 000/year</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; CT, computed tomography; CIMT, carotid intima-medial thickness.

Table 2. A Comparison Between CAC by CT and CIMT by B-Mode Ultrasound

CAC Versus CIMT: Which Is the Preferred Test?

Both tests have the potential to be clinically useful in the prediction of CHD risk. Recently, CAC scoring was directly compared with CIMT measurements in the prediction of CVD incidence. This prospective analysis of the multiethnic study of atherosclerosis cohort, in which almost 6700 subjects were followed over a maximum of 5.3 years, used the composite risk of incident CVD events (CHD, stroke, fatal CVD) as its main outcome measure. During the follow-up period there were 222 CVD events. CAC was associated more strongly with CIMT with the risk of incident CVD with a hazard ratio for an incident CVD event was 1.3 (95% CI, 1.1 to 1.4) per SD increment of CIMT and 2.1 (95% CI, 1.8 to 2.5) per SD increment of CAC score. Receiver operating characteristic curve analysis also suggested that CAC scoring was a better predictor of CHD incidence than CIMT, with areas under the curve of 0.81 versus 0.78, respectively.

Despite the seeming superiority of CAC scoring over CIMT measurement, the question of which of these imaging modalities is preferable in the detection of subclinical atherosclerosis remains open. In clinical practice, a number of other variables become relevant when choosing a specific imaging test such as the availability and ease of use of the modality, the physician’s familiarity with the technology, cost considerations, and differences in radiation exposure. The relative merits of the 2 imaging modalities are outlined in Table 2.

Does Atherosclerosis Imaging Change Care?

An early study by Wong et al. suggested that CHD risk-reducing behaviors may be reinforced by the knowledge of a positive CAC scan, independent of preexisting coronary risk factor status. However, the only prospective, randomized, controlled trial of CAC scoring in CHD found that in an asymptomatic population, the addition of the diagnosis of subclinical coronary disease did not affect CHD risk profile or impact motivation to change risk-related behaviors.

A subsequent, more recent study, on the other hand, did show that CAC screening motivated the initiation of CHD preventative measures. A similar effect of office-based CIMT screening on physician behavior and patient motivation was demonstrated in a recent study showing that physicians were more likely to prescribe evidence-based, CHD risk-reducing interventions such as aspirin and lipid-lowering therapies if increased CIMT or carotid plaque was documented. In the same study, the act of screening itself increased patients’ stated motivation to make dietary changes and increase exercise. Further, patients with abnormalities were more likely to report increases in plans to take lipid-lowering therapies and had an increased perceived likelihood of having and developing CHD. These results are in keeping with 2 other previous studies demonstrating the feasibility of CIMT measurement by ultrasound in an office setting.

Is Atherosclerosis Imaging Cost Effective?

The economic burden of CHD is immense and the 2008 estimated direct and indirect cost of the disease is $156.4 billion. According to the National Center for Health Statistics, 4 to 6 years of life could be gained by the complete elimination of CHD. For screening to be cost effective, it has to add value to current strategies, ie, risk factor scoring, by producing sufficient additional information to change treatment and hence cardiac outcomes, at an affordable cost per quality-adjusted life year. The randomized, controlled studies necessary for calculating the economic yield of CHD prevention through screening tests do not exist for any cardiovascular test. Instead, decision models, test result and outcome estimates and economic simulations have been used to approximate cost effectiveness.

O’Malley et al assessed the cost effectiveness of CAC scoring as a CHD risk prediction tool and found that its use in an asymptomatic young population is expensive and not cost effective, with a cost per “at risk” case identified of $9789 and a cost per QALY of $86 700. Furthermore, sensitivity analysis suggested that unless earlier intervention could be shown to either increase survival by >1.75 years or there was no deterioration in quality of life as a result of the new diagnosis and medications, CAC screening would not be cost effective in low-risk populations.

At present, there are no studies specifically estimating the cost effectiveness of CIMT in predicting CHD in an asymptomatic population. Two detailed general reviews of the cost effectiveness of screening for subclinical atherosclerosis were inconclusive and unable to determine whether atherosclerosis imaging is cost effective, given the limited clinical and economic data. Thus, there are currently not enough data to convincingly demonstrate cost effectiveness and the
economic advantages, if any, of either modality in screening of CHD are yet to be established.

The Need for Better Evidence

There are no prospective, randomized, controlled trials evaluating the effectiveness of either CAC scoring or CIMT measurement, as strategies to guide modification of preventive measures, which assess a consequent impact on cardiovascular outcomes. Therefore, current published consensus statements are based on observational data and neither modality has received a recommendation for widespread use from professional societies’ guidelines. In this respect, it is interesting to note that the potential outcome benefits of global cardiovascular risk assessment based on risk factors alone have never been validated in a randomized, controlled trial either.103

In recognition of the need for better evidence, National Heart, Lung, and Blood Institute has convened 2 workshops to evaluate the feasibility of performing randomized trials assessing the impact of a screening strategy on clinical outcomes. The first, held in 2004, resulted in a robust trial design to test the hypothesis that “subclinical disease testing will improve patient outcome compared with current standard screening for CHD risk factors” (Michael S. Lauer, MD, personal communication, 2008). Proposed interventions were randomization to screening with CAC and/or CIMT compared with usual care, with primary outcome measures including major morbid and mortal CVD events and total mortality, and quality of life, costs, and physician’s and patient’s behavior as secondary outcomes. Unfortunately, further evaluation of the trial design by National Heart, Lung, and Blood Institute deemed it to be too expensive to fund.

A second National Heart, Lung and Blood Institute Workshop held in 2008 revisited this question and proposed a similar trial design.104 At this writing, it is unclear if such a trial will be funded, but it is clear that, in the absence of randomized, control trial data demonstrating an impact on outcomes, it is unlikely that there would be major changes in clinical practice or in guidelines recommendations.

Conclusion

As we wait for the development of necessary evidence regarding the possibility that a strategy of atherosclerosis imaging to better assess patient risk will lead to more intensive preventive treatment and a reduction in clinical events in the low-intermediate risk population, we are obliged to remember that aggressive management of traditional cardiovascular risk factors has been shown to reduce CHD events. This should, therefore, be the mainstay of contemporary practice. However, given the support of current clinical practice guidelines for the use of CAC scoring and CIMT in selected patients with an intermediate FRS, the path is already clear to more effectively use these techniques to ensure optimal disease prevention in those patient groups for whom there is adequate evidence. After all, primary prevention, by definition, is aimed at avoiding the development of disease and not just its manifestations.

Disclosures

None.

References


57. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echo-


Key Words: atherosclerosis □ imaging □ risk factors □ screening
Atherosclerosis Imaging: Prognostically Useful or Merely More of What We Know?
Prashant Kaul and Pamela S. Douglas

doi:10.1161/CIRCIMAGING.109.850263

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/2/2/150

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/