Screening for Subclinical Coronary Artery Disease Measuring Carotid Intima Media Thickness

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Traditional coronary risk assessment is based on major cardiovascular risk factors using the Framingham risk score. Carotid intima-media thickness (CIMT) measured by ultrasonography is a noninvasive test used to assess for the presence of coronary atherosclerosis. CIMT has been shown to be an independent predictor of future cardiovascular events and is used in research trials as a surrogate for the presence as well as regression of coronary artery disease. The objectives of this report are to review the published reports on CIMT and to help establish the role of CIMT as a screening tool for coronary artery disease in selected patients. CIMT measurement can modify cardiovascular risk prediction in patients initially classified with the Framingham risk score, with reclassification into higher or lower risk categories. It is most useful for refining risk assessment in patients at intermediate risk. The Screening for Heart Attack Prevention and Education (SHAPE) Task Force recommends screening all asymptomatic middle-aged and older men and women using noninvasive imaging. The American Society of Echocardiography established a consensus on the methodologic aspects of CIMT measurement. Sequential scanning of CIMT to assess atherosclerosis is currently not recommended, because of interscan variability and small expected changes over time. In conclusion, in the primary prevention of coronary artery disease, CIMT measurement reclassifies patients into higher or lower risk categories, allowing early appropriate management. **(Am J Cardiol 2009;104:1383–1388)**

The use of noninvasive imaging with direct visualization of atherosclerotic plaque can help refine risk assessment in selected patients. Reclassifying intermediate-risk patients as either low risk or high risk allows early appropriate management. Low-risk patients do not need treatment, whereas high-risk patients could be treated with secondary prevention.[1] Electron-beam computed tomography and computed tomographic coronary angiography are techniques used to assess for the presence of atherosclerosis, but they expose patients to radiation.[2] Carotid intima-media thickness (CIMT) measured by ultrasound is simple and safe, uses no radiation, and is an inexpensive test[3] to assess indirectly for the presence of coronary atherosclerosis. Cardiovascular risk factors correlate well with increased CIMT, and patients with increased CIMT have higher mean values of cardiovascular risk factors than those with normal CIMT.[4] More important, CIMT is an independent predictor of future cardiovascular events and has been used as a surrogate end point in many research trials.[5–9] Some consensus statements have recommended the use of noninvasive imaging for patients at intermediate risk for further clarification of coronary artery disease (CAD) risk assessment, such as CIMT measurement[2,10,11] or coronary artery calcification (CAC) score.[2,12,13] We review the current knowledge about CIMT establishing its role in preventive cardiology as a screening test in at-risk patients.

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Methods

We reviewed published reports describing CIMT, its correlation with coronary atherosclerosis, and its clinical use in current practice. English-language reports published from 1986 to 2009 were collected using Medline. Keywords included "carotid intima media thickness," "subclinical atherosclerosis," "coronary artery disease," and "screening." The bibliographies of identified reports were also explored for additional sources of information.

Results

In 1986, Pignoli et al[14] demonstrated that ultrasound can be used to measure CIMT. CIMT measured by ultrasound was compared to CIMT measured on microscopic examination, and ultrasound measurements were closely correlated with histology.[14,15] Geroulakos et al[16] compared patients who had undergone coronary angiography and CIMT measurement by ultrasound and demonstrated that patients with significant stenoses on coronary angiography had greater common CIMT compared to patients with normal results on angiography.[16]

CIMT measurements by ultrasonography are obtained with the patient in the supine position with slight hyperextension and rotation of the neck to the contralateral side. Images of the carotid artery are obtained with linear-array transducers with frequencies ≥7 MHz. Temporal resolution is best with M-mode ultrasound measurement, but measurement precision may be reduced. B-mode ultrasound is therefore preferred over M-mode ultrasound.[11] Measurements are best acquired at the end-diastolic phase, because the systolic expansion of the lumen causes CIMT thinning.[17]

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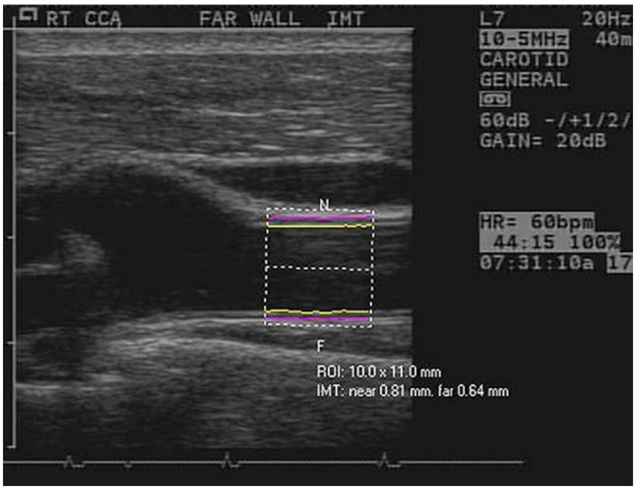

Figure 1. CIMT of the far wall (F) and near wall (N) of the right CCA. HR = heart rate; IMT = intima-media thickness; ROI = region of interest.

Table 1
Carotid intima-media thickness and cardiovascular risk

CIMT in Percentiles Adjusted for Age, Gender, and Ethnicity[11]	Cardiovascular Risk
≤25th percentile	Lower risk
25th percentile–75th percentile	Unchanged risk
75th percentile or ≥1 mm in CIMT[2] or presence of carotid plaque[11]	High risk; adjusted* relative risk of 1.5–4.9 (95% CI) for CAD and stroke[11]

* Adjusted for age, gender, and traditional risk factors.

Roman et al[17] also recommended measuring luminal diameter with CIMT to calculate vascular cross-sectional area. When evaluating CIMT progression, it is important to reexamine the exact same segments, walls, angles, and timing of measurements. The American Society of Echocardiography established a panel to determine methodologic aspects that should be included in protocols for measuring CIMT.[11]

CIMT can be measured from the near wall, closest to the transducer, or the far wall. Measurement of the far wall reflects the true thickness of the arterial wall in comparison to near-wall CIMT because it is more constantly visualized[14,15,18] (Figure 1). Different segments of the carotid artery can be assessed to measure CIMT: the common carotid artery (CCA), the internal carotid artery (ICA), and the carotid bifurcation. The term "segment" usually refers to a 1-cm length of artery. Because of its accessibility, measurement of CIMT of the CCA is more reproducible than that of the ICA or the bifurcation.[19,20] Measurements can be expressed either as the mean CIMT of the right and left CCAs or as the mean CIMT of different sites. The mean CIMT of the CCAs may underestimate the atherosclerotic burden because atherosclerosis is an heterogenous disease that progresses more rapidly in the bifurcation and ICA than the CCA.[20,21] The consensus statement from the American Society of Echocardiography recommends imaging the CIMT of the distal 1 cm of the far wall of each CCA, as well as the plaques of the extracranial carotid arteries, especially in the bifurcation and the ICA, because irrespective of CIMT, patients with coronary plaques are automatically at high risk.[11]

CIMT is a continuous variable. It increases with age and is larger in men.[6,8] CIMT is thicker in blacks, thinner in Hispanic, and intermediate in whites.[20,22,23] Defining abnormal CIMT on the basis of a single threshold would result in underdetection or overdetection of abnormal CIMT depending on patients' characteristics. Therefore, thresholds adjusted for age, gender, and race should be used to detect abnormal CIMT.[20] Also, according to the Committee on Vascular Lesions of the American Heart Association,[24] there are segments of arteries with particularly thick intima related to bifurcations. Increased CIMT can also be seen with hypertension due to medial hypertrophy or fibromuscular hyperplasia associated with aging.[17] In its 2008 consensus statement, the American Society of Echocardiography suggested that CIMT values at or above the 75th percentile of a reference population indicate increased cardiovascular risk[11] (Table 1).

The relation between CIMT and coronary events has been evaluated in several observational prospective studies. Some studies[5,9] of CIMT and cardiovascular events have differentiated CIMT and plaque, whereas others[6–8] have not, considering CIMT a measure of atherosclerosis. Studies that distinguished increased CIMT from plaque defined the former as measuring >1 mm. However, definitions of plaque vary depending on the study. The Kuopio Ischemic Heart Disease Risk Factor (KIHD) study[5] defined plaque as a distinct area of mineralization in the vessel wall or with focal protrusion into the lumen. Belcaro et al[9] defined it as a localized wall thickening and increased density of all ultrasonic layers and intima-media thickness >2 mm. The Mannheim CIMT consensus defines plaque as a focal structure encroaching into the arterial lumen >0.5 mm or 50% of the surrounding intima-media thickness or demonstrating a thickness of >1.5 mm.[25] The definition of nonobstructive plaque in the American Society of Echocardiography report is the presence of focal thickening ≥50% greater than that of the surrounding vessel wall.[17] Studies that have separated increased CIMT and plaque have shown a greater risk for myocardial infarction with plaque. The KIHD study,[5] conducted in 1,257 eastern Finnish men, with a follow-up period of 2 years, evaluated ultrasonographic carotid findings with the risk for acute myocardial infarction. The investigators showed that the presence of plaque was associated with a relative risk of 4.1 (95% confidence interval [CI] 1.8 to 9.2). There was a 2.1-fold increased risk for myocardial infarction with increased CIMT >1 mm, compared to men free of these atherosclerotic lesions, and used as a continuous variable, there was an 11% increase in risk for myocardial infarction with each 0.1-mm increase in CIMT. Belcaro et al[9] followed 2,000 healthy subjects divided in subgroups on the basis of arterial morphology. Cardiovascular event rates associated with each class were studied after 6 years of follow-up. They demonstrated that the presence of nonstenotic plaque was associated with an 18.4% risk for myocardial infarction, angina, cerebrovascular accident, and peripheral vascular disease, whereas CIMT >1 mm increased this risk by 5.5%. Differences between men and women in the association of CIMT and CAD incidence were demonstrated in the Atherosclerosis Risk in Communities (ARIC) study.[6] This study was conducted in

Table 2
Ten-year hard coronary artery disease risk stratification on the basis of Framingham risk score

FRS (points)		Risk Category	10-Year Hard CAD Risk
Men	Women		
>16	>23	High	<20% or cardiovascular disease or diabetes
12–15	20–22	Intermediate	10%–20%
<11	<19	Low	<10%

middle-aged men and women free of disease at baseline, with a follow-up period of 4 to 7 years. Hazard ratios for CIMT >1 mm adjusted for cardiovascular risk factors were 2.62 (95% CI 1.55 to 4.46) for women and 1.20 (95% CI 0.81 to 1.77) for men. The Rotterdam study,[7] however, found that the risk for myocardial infarction in women and men was similar, with odds ratios adjusted for cardiovascular risk factors of 1.26 (95% CI 0.89 to 1.79) and 1.25 (95% CI 0.91 to 1.72), respectively.

Many clinical trials have put emphasis on CIMT regression as a surrogate of CAD regression. Several studies have explored the effects of statin therapy on CIMT. The Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries II (PLAC-II) study[26] demonstrated a lesser progression of CIMT of the CCA with pravastatin compared to placebo, 0.0295 and 0.0456 mm/year, respectively. Similarly, a reduction in the progression of CIMT was found with lovastatin, with a reduction of mean maximum CIMT of −0.009 mm/year compared to the progression of CIMT in the placebo group of 0.006 mm/year.[27] The 2 studies demonstrated that annual reduction in CIMT was also associated with a reduction in the incidence of cardiac events. Yu et al[28] compared the effect of intensive atorvastatin therapy to that of low-dose atorvastatin on the reduction of CIMT in patients with CAD. CIMT was significantly reduced in the high-dose group, whereas the low-dose regimen only prevented the progression of CAD.[28] The Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR) trial demonstrated that rosuvastatin therapy resulted in a reduction of the progression of maximum CIMT compared to placebo in middle-aged adults with low Framingham risk scores (FRS) and subclinical atherosclerosis, with changes of −0.0014 and 0.0131 mm/year, respectively.[29] More recently, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial evaluated the change in CIMT with the combination of simvastatin and ezetimibe compared to simvastatin monotherapy. There was no significant difference between the groups.[30]

However, in clinical practice, assessing for CAD regression or progression using CIMT has not been advocated.[11] Also, the limited prognostic potential of CIMT was demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA).[31] Compared to CAC score, CIMT was less predictive in refining cardiovascular risk assessment in asymptomatic American adults aged 45 to 84 years.

Up to 50% of patients who have first myocardial infarctions have no previous symptoms of atherosclerosis.[2] The primary prevention of CAD is therefore crucial. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III[32] recommended CAD risk assessment on the basis of the FRS in the United States. Absolute 10-year risk is estimated with the summation of risks contributed by each risk factor. The FRS is based on major risk factors such as gender, age, serum cholesterol levels, hypertension, tobacco use, and diabetes. This allows the classification of patients into 3 risk categories (Table 2). Low-risk patients with low FRS constitute approximately 35% of the United States adult population aged ≥20 years. High-risk patients with existing CAD, vascular disease, diabetes, or multiple major risk factors represent approximately 25% of United States adults. The remaining 40% of patients belong to the intermediate-risk group.[33] The NCEP recommended that the intensity of risk-factor management be adjusted by the severity of risk. Akosah et al[34] showed that misclassified patients who developed early CAD did not benefit from cholesterol-lowering therapy.

Risk stratification based on traditional risk factors is limited. Most myocardial infarctions occur in patients in the intermediate-risk group.[2] The FRS uses only the standard risk factors: smoking, blood pressure, serum cholesterol, high-density lipoprotein cholesterol, age, gender, and diabetes. However, other risk factors not included in the FRS can contribute to the development of CAD, such as family history of premature CAD, insulin resistance, overweight and obesity, physical inactivity,[10] and metabolic syndrome, which has been associated with increased atherosclerosis.[35] As a result, patients can be judged to be at low or intermediate risk in the absence of traditional risk factors. Also, risk factors such as smoking and diabetes are considered only as present or absent, although continuous relations between cardiovascular disease risk and tobacco exposure and glucose levels have been described.[11] Similarly, patients with intermediate risk scores may progress to the high-risk category because of the cumulative effect of a single risk factor.[10] On the opposite, a single risk factor, such as age, at high values increases older patients' risk without distinction of atherosclerotic burden among them and may lead to the inappropriate selection of patients for aggressive therapy.[36] These limitations have been recognized by the American Heart Association and the NCEP expert panel.[10,32] CIMT can modify cardiovascular risk prediction. Studies[37–40] that evaluated CIMT in patients classified according to FRS reported changes in risk stratification. Individual CIMT values were compared to CIMT from a population database to determine vascular age.[38–40] The investigators compared vascular age and chronologic age in the 10-year CAD risk estimates. Stein et al[38] found that when substituting vascular age for chronologic age, 35.7% of patients initially in the intermediate category were reclassified as at higher risk, and 14.3% were reclassified as at lower risk. Significant predictors of reclassification were tobacco use, high-density lipoprotein cholesterol, systolic blood pressure, and low-density lipoprotein cholesterol. However, the study did not demonstrate the accuracy of using vascular age in CAD risk assessment above traditional CAD risk assessment. Gepner et al[40] demonstrated similar findings. In their study, 50% of the moderate-risk group and 60% of the moderately high risk group, with 10-year cardiovascular risk of 5% to <10%

Table 3
Screening for Heart Attack Prevention and Education risk stratification on the basis of carotid intima-media thickness and plaque measurement

Risk Category	Atherosclerosis	LDL Cholesterol Target (mg/dl [mmol/L])
Very high	≥50% stenotic plaque	<70 (<1.82)
High	CIMT ≥1 mm or >75th percentile or <50% stenotic plaque	<100 (<2.59)
Moderately high	CIMT <1 mm and <75th percentile and no carotid plaque	<130 (<3.37)
Moderate	CIMT <50th percentile and risk factors	<130 (<3.37)
Lower	CIMT <50th percentile and no risk factors	<160 (<4.14)

Adapted from Naghavi et al.[2]
LDL = low-density lipoprotein.

and of 10% to 20%, respectively, using the FRS, were reclassified.

Some consensus statements have recommended the use of CIMT measurement by ultrasound for coronary risk stratification.[2,10,11] In 2000, considering the limitations of risk stratification using traditional cardiovascular disease, the American Heart Association's Prevention Conference V recommended the use of CIMT measurement for further clarification of CAD risk assessment.[10] In 2006, the Screening for Heart Attack Prevention and Education (SHAPE) Task Force compared screening for CAD on the basis of risk factors only and screening for subclinical atherosclerosis. They showed the benefit of screening for CAD measuring subclinical atherosclerosis and estimated decreases of 10% in cardiovascular disease deaths and 25% in myocardial infarction prevalence, with an increased number of patients eligible for aggressive therapy. The potential reductions in costs associated with these decreases in cardiovascular disease death and in myocardial infarction prevalence have been estimated at $1.2 billion and $18 billion, respectively. The SHAPE Task Force presented new practice guidelines for cardiovascular screening in the asymptomatic at-risk population using noninvasive imaging such as computed tomography for the measurement of CAC score or ultrasound for CIMT measurement. This screening strategy is based on the principle that the major determinant of risk for atherosclerotic cardiovascular disease in asymptomatic patients is the presence of the underlying disease, subclinical atherosclerosis. The task force recommended screening all asymptomatic men aged 45 to 75 years and asymptomatic women aged 55 to 75 years in addition to the traditional risk-factor assessment to detect and treat those with subclinical atherosclerosis. Using CIMT measurement, ultrasound considered to have positive results when CIMT is ≥75th percentile or a carotid plaque is present. Patients are then classified into moderately high, high, or very high risk categories depending on CIMT and the severity of atherosclerotic plaque (Table 3). Patients with positive results should be retested within 5 years. Patients with negative atherosclerotic test results should be treated according to the NCEP Adult Treatment Panel III guidelines with reassessments every 5 to 10 years. In that report, in the absence of subclinical atherosclerosis, diabetes is not considered a CAD risk equivalent. Recently, the American Society of Echocardiography consensus statement[11] recommended refining risk assessment in patients with intermediate cardiovascular risk, such as young patients aged <60 years with severe abnormalities on a single risk factor who would not be classified as at high risk and women aged <60 years old with ≥2 cardiovascular risk factors, because they tend to develop cardiovascular disease at older ages. In patients with diabetes, carotid ultrasonography can add further information by establishing a gradient of risk among them, although they are already classified as at high risk for CAD.[11] Other investigators have pointed out specific patient populations that could benefit from the early detection of atherosclerosis. The 34th Bethesda Conference Task Force Number 4[41] suggested that noninvasive imaging of atherosclerotic burden could be useful in young patients at risk for atherosclerosis but in whom risk factors are not taken into account in the FRS, such as end-stage renal disease or family history of premature CAD. Patients at risk for accelerated atherosclerosis with inflammatory disease such as systemic lupus erythematosus or rheumatoid arthritis also could be tested with noninvasive imaging.[9]

Some associations, however, do not support screening for CAD using noninvasive testing. In 2004, a United States Preventive Services Task Force systematic review studied rest electrocardiography, exercise treadmill testing, and electron-beam computed tomography as screening tools for CAD. Although these tests could provide information about future CAD events, the effect of screening for asymptomatic CAD on cardiovascular events and mortality in asymptomatic patients was unclear.[42] Studies on the impact of noninvasive imaging including CIMT on behavioral changes have yielded conflicting results.[43] Wyman et al[44] demonstrated that although the presence of plaque increased patients' perception of cardiovascular risk, it did not motivate patients to make lifestyle changes. Also, there are no convincing data that atherosclerosis imaging improves medication adherence.[43] Limitations of CIMT measurement include the need for a good technician, because variability in CIMT measurements is caused mostly by interobserver variability,[5,19] and the lack of consensus on measurements. Frequently observed carotid ultrasound imaging pitfalls are due to patient position, gain and focus adjustment, and image stabilization. The importance of standardization of instrument calibration and imaging protocol is outlined in the American Society of Echocardiography consensus.[11] Another limitation is the definition of abnormal CIMT on the basis of a relative measure (percentile for age, gender, race), whereas directing treatment should be based on absolute risk.

Comparing CIMT measurement and CAC score, there are different data regarding their accuracy in the prediction of cardiovascular disease. In 2008, Newman et al[45] found that CAC score and common CIMT similarly predicted cardiovascular disease and CAD in adults aged ≥70 years. However, on the basis of the MESA study, CAC score may be better than CIMT in refining cardiovascular risk assessment in asymptomatic American adults aged 45 to 84 years. There were ethnic differences in CAC score and to a lesser degree in CIMT.[31] A 2009 study suggested that CIMT may be more sensitive than CAC score for the determination of cardiovascular disease risk in young to middle-aged patients.[46] Lester et al[46] conducted their study in men and women aged 36 to 59 years. They found that 47% of patients with no CAC (low risk) had evidence of atherosclerosis in the form of carotid plaque or CIMT >75th percentile for age, gender, and race (increased risk). Conversely, only 15% of those with CIMT <50th percentile (low risk) had CAC (increased risk).[46] CIMT measurement might be best used in younger patients, because CAC has low prevalence in younger patients.

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