Clinical value of carotid intima-media thickness testing

Patrick J. Devine, MD, Daniel W. Carlson, MD, and Allen J. Taylor, MD

Carotid intima-media thickness (CIMT) testing is recognized as a valid method for the noninvasive assessment of atherosclerosis. In addition to its association with known cardiovascular risk factors and both prevalent and incident coronary heart disease, the rate of CIMT progression is directly related to the risk for future cardiovascular events. Subsequently, CIMT has been a valuable research tool in clinical trials in the assessment of therapeutic agents directed against atherosclerosis. An overview of CIMT testing including its precise measurement, establishment as a surrogate for atherosclerosis by epidemiologic trials, role in clinical trials, and potential applications in both primary and secondary coronary heart disease prevention is presented. (J Nucl Cardiol 2006;13:710-8.)

Carotid intima-media thickness (CIMT) testing has emerged as a valuable tool in monitoring atherosclerosis. Its relationships with coronary heart disease (CHD) risk factors, future cardiovascular events, and atherosclerosis elsewhere in the vascular system allow for it to serve as a suitable surrogate for underlying coronary atherosclerosis. Although it is currently primarily used as a research tool in trials assessing the therapeutic effect of antiatherosclerotic drugs, it has the potential for a clinical role in both the primary and secondary prevention of CHD.

DEFINITION OF CIMT

The arterial wall consists of 3 layers: the intima, the media, and the adventitia. Atherosclerosis begins in childhood with the development of a fatty streak. This first phase in atherosclerosis histologically presents as a focal thickening of the intima with an increase in smooth muscle cells and extracellular matrix. During progression of the disease, arterial wall vessel changes are characterized by gradual thickening of the intima and media layers (Figure 1). Through direct visualization of the arterial wall of a superficial artery such as the carotid artery, B-mode ultrasound can measure this thickening. The *intima-media thickness*, defined as the thickness between the intimal-luminal and the medial-advential interfaces, is measured. Ultrasound imaging cannot discriminate between the intima and media layers because of insufficient axial resolution. Therefore an elevated CIMT may be the result of an increased intima layer from atherosclerosis, an increased media layer due to vascular hypertrophy as seen in hypertension, or both. For this reason, some researchers argue that CIMT, when measured in the absence of intrusive plaque, should be considered as a marker of early arterial wall changes rather than as a true surrogate for atherosclerosis.[1]

MEASUREMENT OF CIMT

Sonograms are generally obtained with the patient in the supine position and his or her head turned slightly to the contralateral side. Longitudinal images of the carotid artery focusing on the imaging target of interest (eg, the far wall of the common carotid artery) are acquired with linear digital ultrasound probes at high frequency ($\geq$10 MHz). Because of systolic arterial expansion and the resultant CIMT thinning, digital images are acquired from an end-diastolic frame of the cine-loop recording, electronically stored, and transferred to a workstation for quantification. The near-field (intimal-luminal surface) and far-field (medial-adventitial surface) arterial wall borders can be manually or automatically traced (by use of edge-detection software) to measure the CIMT (Figure 2).

Measurement of the far wall of the carotid artery is preferred. Studies comparing ultrasound measurements with histology suggest that far-wall CIMT measurements are more indicative of the true thickness of the arterial wall.[2-4] Near-wall CIMT measurements, in comparison, are limited by their dependence on the axial resolution and gain settings of the equipment used and show greater variation between repeated measurements.[5]

From the Cardiology Service, Walter Reed Army Medical Center, Washington, DC.

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Reprint requests: Patrick J. Devine, MD, Cardiology Fellow, Cardiology Service, Walter Reed Army Medical Center, 6900 Georgia Ave NW, Bldg 2, Room 3L28, Washington, DC 20307-5001; *patrick.devine@na.amedd.army.mil.*

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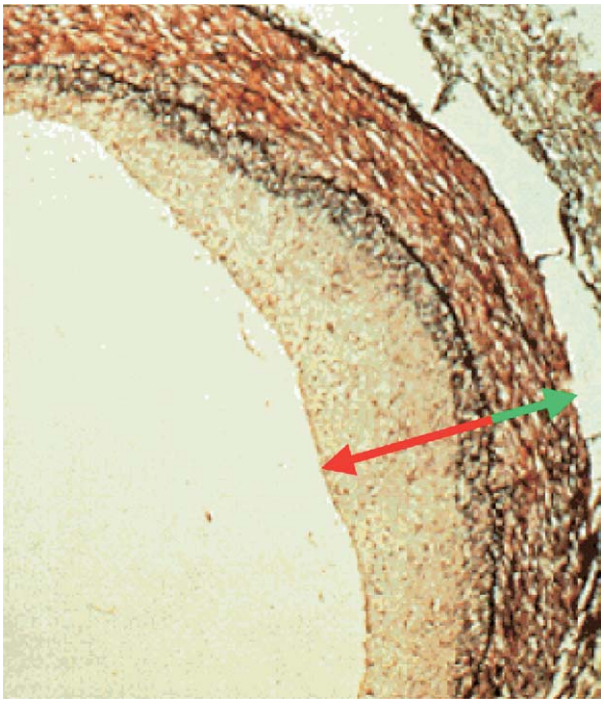

Figure 1. Photomicrograph of arterial layers including media (*green arrow*) and intima (*red arrow*). The histologic correlate of ultrasonographic intima-media thickness is the total span of the red andgreen arrows combined. (H&E stain).

Several portions of the carotid artery are amenable to ultrasonography, including the common, internal, and bulb segments. Laboratories differ in the B-mode measurement of CIMT in terms of the particular segment assessed and the type of measurement reported (eg, mean maximum, mean random, or mean >1 cm). In the Atherosclerosis Risk in Communities (ARIC) study, the reported CIMT was a combined measurement of the far wall of the common and internal carotid artery, whereas other investigators have reported the maximum thickness measured in the common carotid artery.[6] Most laboratories, including ours, report the mean of the distal 1 cm of both common carotid arteries. This approach is preferred because the common CIMT can be assessed in a more reproducible manner and is more predictive of future cardiovascular events and the data collection is more complete.[7-11] Measurements of the internal carotid and bifurcation segments tend to have many more missing values.[8,11] In a call for the standardization of CIMT testing, the Mannheim Intima-Media Thickness Consensus suggested that measurement of the common carotid is ideal.[12]

Several trials have verified the reproducibility of CIMT measurements. Most of the measurement variability in CIMT is caused by differences between observers, whereas the within-observer variability over time appears to be very small.[13] Given this observation, a clinical trial should optimally have the same sonographer obtain all scans for a given patient. Although reproducibility has been established for individual laboratories for particular clinical trials, the current lack of a universal standardized protocol presents an obstacle for the application of CIMT in everyday clinical practice.

WHAT IS NORMAL CIMT?

Because CIMT is a sensitive detector of early atherosclerotic changes within the vessel wall, it is critical that threshold values be defined so that asymptomatic patients can be properly risk-stratified. Normal values have been defined based on their distribution within a general healthy population and have been classified according to age and gender.[6,14] CIMT increases with age and, on average, is larger in men than in women. Slight racial differences have also been reported for CIMT, being highest in black persons, lowest in Hispanic persons, and intermediate in white persons.[8,15,16] The definition of the upper limit of normal is arbitrary but is frequently set at the 75th percentile of CIMT distribution (Figure 3) for the determination of increased relative CHD risk. Alternatively, epidemiologic studies suggest that a value of intima-media thickness at or above 1 mm is associated with a significantly increased absolute risk of CHD.[6] Reliance on a single threshold of abnormality will result in underdetection of disease in younger individuals and overdetection in older individuals.

The CIMT is a continuous variable, and the transition to focal plaque is arbitrary. Some investigators have suggested the normal range of CIMT to be 0.5 to 1.2 mm and have arbitrarily defined plaques as CIMT greater than 1.2 mm.[17,18] Another frequently used definition for focal plaque identifies plaque as a focal increase in CIMT greater than 1.5× that of the surrounding CIMT. The most common location of plaque is within the carotid bifurcation, where blood flow is less laminar.[19]

SURROGATE MARKER FOR GENERAL ATHEROSCLEROSIS

Atherosclerosis is a diffuse, systemic disease process that begins long before clinical manifestations emerge. A multitude of cardiovascular risk factors acting in concert contribute to its development. As a marker of structural arterial wall changes, CIMT reflects atherosclerotic progression because of its association with these known cardiovascular risk factors. This relationship allows for its use as a noninvasive marker of early, preclinical atherosclerosis.

This was illustrated in the Muscatine Study, which comprised 725 young and middle-aged adults (aged

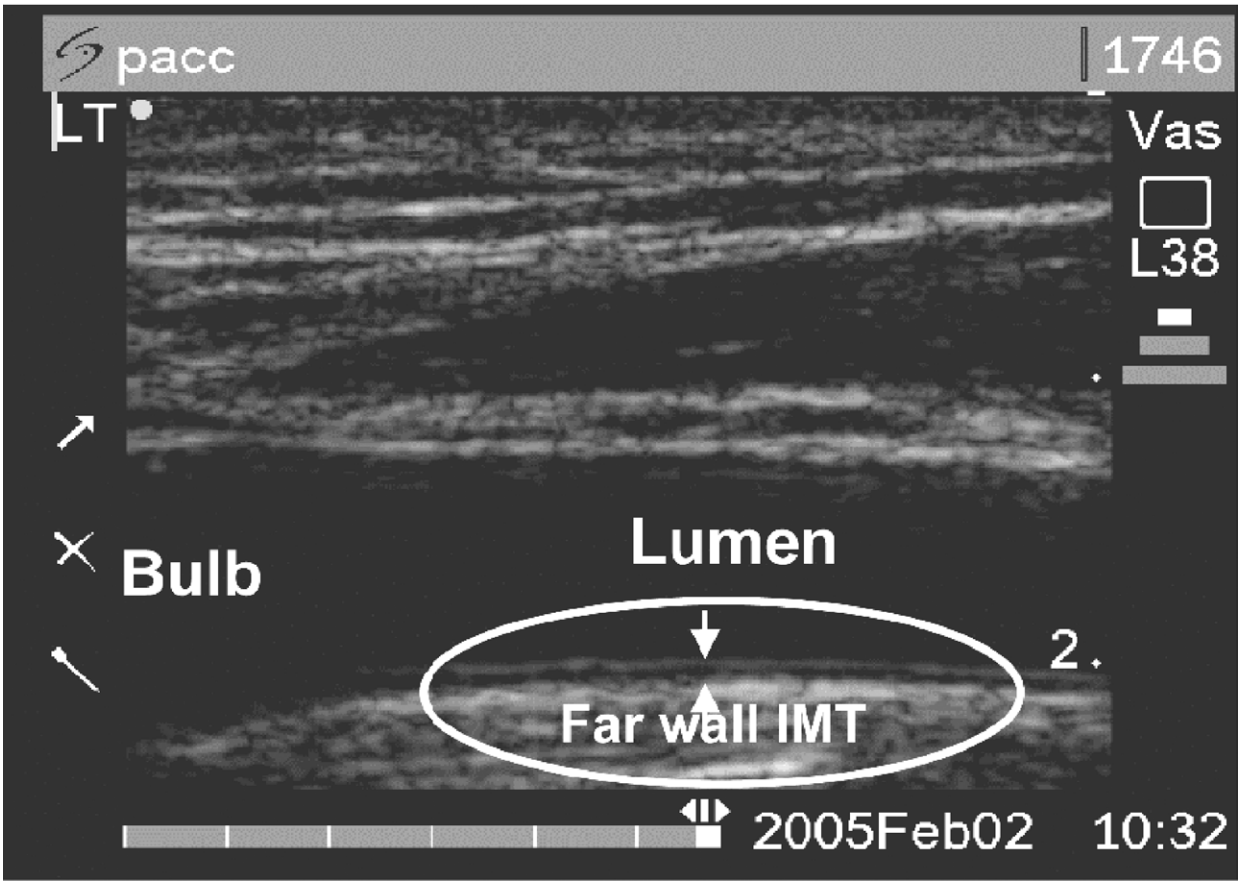

Figure 2. Carotid ultrasound image (10 MHz) of distal common carotid artery. The *2 arrows* represent the intimal-luminal and medial-adventitial interfaces, which collectively border the CIMT. In this example, intima-media thickness (*IMT*) was reported as the mean thickness over the distal 1 cm of the far wall of the commoncarotid artery.

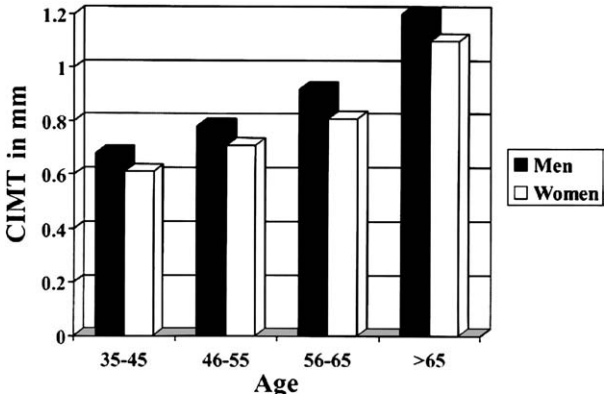

Figure 3. Approximate 75th percentile values for common CIMT by age and gender. *Black bars*, Men; *white bars*, women.

33-42 years) who were followed up from childhood.[20] CIMT was associated with the childhood presence of cardiovascular risk factors, especially total and low-density lipoprotein (LDL) cholesterol in both genders and diastolic blood pressure in women. Raitakari et al[21] also confirmed that there was an association between childhood cardiovascular risk factors—namely, LDL cholesterol, systolic blood pressure, and smoking—and CIMT measured 21 years later. In this study adolescents with these cardiac risk factors had an approximately 0.1-mm greater CIMT as adults compared with those without risk factors. In the Bogalusa Heart Study metabolic syndrome during childhood was associated with a 2.5-fold increased likelihood of having CIMT in the highest quintile.[22]

In addition to reflecting an individual's past exposure to cardiovascular risk factors, CIMT is associated with prevalent cardiovascular disease and future cardiovascular risk. The ARIC study demonstrated a prevalence of myocardial infarction in individuals in the highest quartile of CIMT of 5%. In the Cardiovascular Health Study (CHS) the odds ratio for symptomatic CHD was 2.8 when the highest quartile of CIMT was compared with the lowest quartile of CIMT.[23,24]

The relationship between CIMT and future CHD events first became evident in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), in which, for

every 0.1-mm increment of CIMT, the risk of future myocardial infarction in Finnish men increased by 11%.[5] For CIMT values greater than 1 mm, there was a 2-fold greater risk for acute myocardial infarction over a 3-year period. The ARIC study provided further support, noting that for every 0.19-mm increment in CIMT, the risk of death or myocardial infarction increased by 36% in middle-aged patients (aged 45-65 years).[6] The CHD risk was almost 2-fold greater in men with mean CIMT greater than 1 mm and even greater in women (risk ratio of 5). Not all studies, however, have shown gender differences in the predictive value of CIMT. For example, the Rotterdam Study found that the risk of CHD events and CIMT was similar among men and women.[25] The association between CIMT and the incidence of myocardial infarction and stroke has been noted in older populations as well. In CHS the adjusted relative risk for myocardial infarction was 3.6. This held true for patients with known cardiovascular disease and those without it[14] (Table 1).

Because CIMT testing at any given moment reflects the integrated effect of cumulative risk factor exposure, it is primarily a reliable predictor of future CHD risk in those patients whose risk factor status (including lifestyle behavior) is stable. However, in patients undergoing risk factor modification, CIMT testing likely will not accurately reflect current risk factor burden and subsequently may be a poor predictor of outcome. It has been proposed that CIMT progression in such individuals might be a better index of risk for future CHD.[26] In the Cholesterol Lowering Atherosclerosis Study (CLAS) men who had undergone previous coronary artery bypass graft surgery were treated with colestipol and niacin.[27] A 0.03-mm annual CIMT increase was associated with a 3-fold increased risk of myocardial infarction, death, or need for revascularization. CIMT and the progression of CIMT predicted CHD risk beyond that predicted by measurements of coronary atherosclerosis by angiography and lipid measurements (Figure 4).[28] However, because of the relatively high interscan variability of CIMT (>0.02 mm), the serial use of CIMT for individual patient assessments is difficult unless performed after an extended time interval to permit discrimination of true CIMT progression from measurement variability.

SURROGATE MARKER FOR CORONARY ARTERY DISEASE

CIMT is a direct measure of atherosclerotic changes in the carotid artery; however, because of the systemic nature of atherosclerosis, as well as the established associations of CIMT with the prevalence and incidence of CHD, it is reasonable to assume that CIMT likely reflects atherosclerotic burden in the coronary arteries as well. Several studies have evaluated the association

Table 1. Summary of prospective trials evaluating CIMT and incident coronary events in patients without known CHD

Study	CIMT measurement	Clinical events	Patient details			CIMT increment (mm)	Odds ratio (95% confidence interval)
			Follow-up	Age (y)	Gender		
KIHD[5]	CCA/carotid bifurcation (mean CIMT)	Fatal/nonfatal myocardial infarction	1 m to 3 y	42–60	Men	0.1	1.11 (1.06–1.16)
ARIC[6]	CCA/ICA/carotid bifurcation (mean far wall, internal carotids, and bifurcation)	Coronary death and myocardial infarction	4–7 y	45–64	Men and women	0.19 and 0.19	1.36 (1.23–1.51) and 1.69 (1.50–1.90)
CHS[14]	CCA/ICA (mean of CCA and ICA)	Myocardial infarction/stroke	6.2 y	>65	Men and women	0.2	1.46 (1.33–1.60)*†
Rotterdam[25]	CCA (mean)	Myocardial infarction/stroke	2.7 y	>55	Men and women	0.163 and 0.163	1.56 (1.12–2.18) and 1.44 (1.00–2.08)‡

CCA, Common carotid artery; *ICA*, internal carotid artery.
*The odds ratio given is risk for myocardial infarction and coronary death only. The odds ratio for myocardial infarction and stroke was 1.47 (1.37–1.67).
†CCA CIMT.
‡The odds ratios given are for risk of myocardial infarction only.

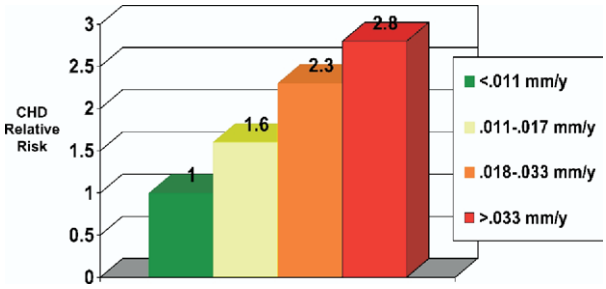

Figure 4. Relative risk for cardiovascular outcomes observed in CLAS trial in subgroups of CIMT progression rates.[28] *Green bar*, Less than 0.011 mm/y; *yellow bar*; 0.011 to 0.017 mm/y; *orange bar*, 0.018 to 0.033 mm/y; *red bar*, greater than 0.033 mm/y.

between CIMT and the extent of coronary atherosclerosis as visualized on angiography, with conflicting conclusions. Wofford et al[29] observed a strong relationship between the extent of coronary atherosclerosis as assessed by plaque severity on angiograms and CIMT. Moreover, Kablak-Ziembicka et al[30] noted that in patients with mean CIMT greater than 1.5 mm, there was a 94% likelihood of having obstructive coronary artery disease (CAD). A significant, nearly linear correlation between CIMT and advancing CAD was observed, with 1-vessel CAD being associated with a mean CIMT of 1.01 mm and 3-vessel disease corresponding to 1.47 mm. However, the bivariate relationships between atherosclerosis in different vascular beds are limited. For example, Adams et al[31] found only a weak correlation between CIMT and CAD severity on angiograms, with correlation coefficients of 0.26 between mean CIMT and severity of CAD (number of coronary arteries with >70% stenosis) and 0.23 between mean CIMT and extent of CAD.

In interpreting these mixed results, it should be noted that the ability of coronary angiography to identify atherosclerosis at an early stage is imperfect. Thickness in carotid and coronary arteries is known to precede the onset of stenosis in atherosclerosis.[32] Because angiography is a measure of stenosis, it is a marker of more advanced atherosclerotic change. The limited ability of coronary angiography to detect significant nonobstructive mural atherosclerosis may explain the weak correlations seen with CIMT, a much more sensitive marker of early atherosclerosis throughout the arterial wall.

ROLE IN PRIMARY PREVENTION

Atherosclerosis remains clinically silent for many years before manifesting later in life as myocardial infarction, stroke, claudication, or even sudden death.[33] Multiple risk factors have been identified, and subsequent therapies such as statins have been developed. To effectively make an impact on atherosclerosis, the identification of patients at high risk in the subclinical phase is critical to allow for modification of cardiovascular risk. Coronary angiography is currently considered the gold standard for detecting obstructive coronary atherosclerosis through the detection of coronary vessel stenoses. However, its inability to detect early atherosclerotic change, its invasive nature, and its high cost, as well as the exposure to ionizing radiation, make it an unappealing primary screening tool in preventive cardiology.

CIMT represents an alternative technique for assessing atherosclerotic burden and future cardiovascular risk. CIMT meets the criteria for an ideal screening tool in CHD. It is noninvasive and quantitative and correlates with clinical outcome. Furthermore, it is repeatable and demonstrates satisfactory interscan and interobserver reproducibility to allow for assessment of atherosclerotic progression over time.[34] Similarly, electron beam computed tomography, another noninvasive atherosclerosis screening modality for the detection of calcified coronary atherosclerosis, has also been shown to accurately assess atherosclerotic burden and predict future cardiovascular risk.[35] However, coronary calcium detection has limited application in young adults because plaque calcification represents a more advanced stage of the atherosclerosis. CIMT testing offers better sensitivity for detecting atherosclerotic change in this patient group.

Currently, the most established means of assessing cardiovascular risk is the Framingham risk score (FRS). This has been used by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in deciding whether patients at intermediate cardiovascular risk should be targeted for more intensive lipid reduction.[36] Many patients, particularly young adults, are classified as being at low to intermediate risk despite the presence of metabolic syndrome, which has clearly been shown to be associated with increased CIMT and risk for atherosclerotic progression.[22] In patients classified as having low or intermediate cardiovascular risk by FRS, CIMT might be clinically useful as a supplement to the FRS in making decisions regarding the modification of cardiovascular risk. This was assessed by Baldassarre et al,[37] who investigated whether CIMT could be combined with the FRS to improve the predictability of cardiovascular events in dyslipidemic patients who are at low or intermediate risk. Both FRS and CIMT proved to be independent outcome predictors, with a hazard ratio of 6.7 in patients with an FRS of 10% to 20% and elevated CIMT (>60th percentile for men or 80th percentile for women). This category of patients, who currently are not aggressively treated based on current guidelines, proved to have a risk similar to that in

patients with an FRS of 20% to 30%. These findings are consistent with recommendations from Prevention Conference V, which stated that CIMT measurement can be considered for further clarification of CHD risk.[38]

Another potential role of CIMT in primary prevention of CHD is patient motivation. By visualizing the presence of plaque, carotid ultrasound has been shown to be a useful adjunct in smoking cessation in middle-aged men.[39] Unfortunately, the prevalence of well-developed carotid plaque in this age group is relatively low, thereby limiting its applicability. The low prevalence of calcium in young adults also likely compromised the ability of electron beam computed tomography to motivate patients in modifying their cardiovascular risk profile.[40] However, CIMT is readily visualized by patients and easily quantified regardless of age, thereby increasing its potential in patient motivation. Despite this potential, its role in patient motivation has not yet been established.

ROLE IN SECONDARY PREVENTION

Despite the advances in percutaneous revascularization therapies, mechanical treatment of focal lesions in patients with CAD does not affect the underlying systemic process of atherosclerosis.[41] Rather, the identification and treatment of risk factors that contribute to the development of atherosclerosis, including age, smoking, dyslipidemia, diabetes mellitus, and hypertension, have proven most effective in preventing ischemic cardiovascular events.[42-44] Currently, the effect of interventional therapy on known cardiovascular risk factors with drugs such as statins, niacin, and antihypertensive agents is assessed through the measurement of the specific risk factor in question and not based on the overall atherosclerotic disease process. As a surrogate for atherosclerosis, CIMT could potentially serve in this role.

In patients with known CHD the relationship between CIMT and future CHD risk has been shown in several trials. In the aforementioned CLAS trial the risk of myocardial infarction or coronary death increased not only with increments in CIMT but also with the rate of progression of CIMT.[28] Therefore, by attenuating CIMT progression in patients with known CHD, therapies directed toward atherosclerosis, such as statins, fibrates, and niacin, would improve future cardiovascular risk (Table 2).[27,45-50] In the Monitored Atherosclerosis Regression Study (MARS) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trials, lovastatin and pravastatin, respectively, led to reductions in the rate of CIMT progression.[46,47] Significant effects of statins on CIMT are seen as early as 6 months after the initiation of therapy. Other lipid-modifying agents and cardiovascular medications besides statins have slowed the rate of CIMT progression in patients with known CHD. In addition to the significant changes in CIMT progression seen with colestipol and niacin in the CLAS trial and with extended-release niacin in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) trial, significant effects have also been noted with cilostazol, amlodipine, and ramipril.[49-51]

It should be noted that, in most of these trials, treatments associated with a significant effect on CIMT progression also conferred a significant reduction in the incidence of cardiovascular events. In the Regression Growth Evaluation Statin Study (REGRESS), a 0.05-mm annual reduction in mean carotid and femoral artery intima-media thickness led to an absolute risk reduction of 10% over a period of 2 years in the incidence of cardiac events.[52] This reduction in both CIMT and future risk of CHD events implies that the therapeutic drug exerts an antiatherosclerotic effect on the carotid wall and further validates the use of CIMT as a surrogate marker of atherosclerosis and CHD risk. Despite the numerous trials using CIMT as a means of assessing therapeutic effects in patients with known CHD, in clinical practice the role of CIMT in secondary prevention is currently undefined. For example, should titration of statin therapy be influenced by the target LDL level alone, or should a "target" CIMT be achieved? In patients with known CHD, this can be problematic because a "target" CIMT has yet to be defined. Moreover, other likely concomitant therapies in CHD such as niacin, metoprolol, and ramipril have all been shown to have an effect on CIMT progression.[49,53,54] Finally, although CIMT measurements have been standardized in well-controlled research settings, protocols have not been implemented in clinical practice to allow for the monitoring of CIMT over time in a reliable and valid manner.

OTHER POTENTIAL ROLES

Not all plaques result in an acute coronary syndrome. This has fueled research into characterization of the "unstable" plaques so that such patients can be identified and aggressively treated. Assuming that hypoechoic plaques were suggestive of a large lipid-vulnerable core, the investigators in CHS used M-mode ultrasound to identify carotid plaque characteristics that portended vulnerability to rupture.[55] In individuals with greater than 50% stenosis of the extracranial carotid arteries, the stroke event rate was 4.2% per year for individuals with hypoechoic plaques and 1.6% per year for those with nonhypoechoic plaques. Although this may be useful in identifying high-risk patients with more advanced atherosclerosis, it is limited in detecting younger patients

Table 2. Summary of trials demonstrating effects of lipid therapy on CIMT in patients with known CHD

Trial	Details	No. of patients randomized	Intervention	Length of study (y)	Mean change in CIMT (mm/y)		*P* value
					Treatment	Placebo	
PLAC-II[45]	Patients with CAD and elevated LDL cholesterol levels	151	Pravastatin, 10–40 mg/d	3	+0.0295*	+0.0456*	.03
REGRESS[50]	Male patients with CAD and normal to moderately elevated total cholesterol levels	255	Pravastatin, 40 mg/d	2	−0.05†	0†	.0085
MARS[46]	Patients with CAD and moderately elevated total cholesterol levels	188	Lovastatin, 80 mg/d	2	−0.038*‡	+0.019*‡	<.001
LIPID[47]	Patients with CAD and moderately elevated total cholesterol levels	522	Pravastatin, 40 mg/d	4	−0.014‡§	+0.048‡§	<.001
CLAS[27]	Male patients who had undergone coronary artery bypass surgery	188	Colestipol and niacin	4	−0.026§	+0.018§	<.05
ARBITER[48]	Patients with CAD and who met National Cholesterol Education Program II criteria for statin therapy	161	Atorvastatin, 80 mg	1	−0.034*	+0.025*‖	.03
ARBITER 2[49]	Patients with CAD already taking statins	167	Extended-release niacin	1	+0.014*	+0.044*	.08

*CIMT of CCA.
†Mean intima-media thickness of femoral and carotid arteries.
‡Mean change in CIMT during study period.
§CIMT of right CCA.
‖Pravastatin, 40 mg, served as comparison group.

who may not have carotid plaque but are nonetheless considered high risk. Currently, the characteristics of CIMT testing cannot reliably identify high-risk patients who may be harboring vulnerable plaques.

Because several studies have noted an association between CIMT and CAD severity, it has been proposed that CIMT can be used in the preoperative cardiac risk stratification of patients. Belhassen et al prospectively evaluated the use of CIMT as a means of determining the need for invasive coronary angiography in patients scheduled for heart valve surgery.[56] By use of the CIMT criterion of less than 0.55 mm as a predictor of the absence of significant CAD, CIMT had a sensitivity and negative predictive value of 100% in ruling out obstructive CAD. Though an interesting finding, with the advent of 64-slice coronary tomography angiography as an alternative and more direct approach to noninvasive coronary evaluation, the routine clinical application of CIMT testing in preoperative cardiac risk assessment is unlikely.

CONCLUSION

CIMT is a valid marker of early atherosclerosis, as well as its extent and progression, and is a predictor of future cardiovascular events. Because of its quantitative value, CIMT measurement is a valuable instrument in clinical trials to assess the effects of treatments for CHD. Despite this established role in clinical research, its adaptability to routine clinical practice has not yet been realized. It has the potential to be used in both primary and secondary prevention of CHD. Its sensitivity in detecting early atherosclerosis gives it a distinct advantage over coronary calcium measurements, particularly in young adults. Methodologic standardization of CIMT measurement needs to be implemented before CIMT

testing can be used in clinical practice as a tool for stratifying cardiovascular risk in patients with CHD and those without CHD.

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