Clinical Use of Carotid Intima-Media Thickness: Review of the Literature

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Carotid intima-media thickness (CIMT) is a simple and inexpensive tool to assess the cumulative effect of atherosclerotic risk factors and is an independent predictor of future cardiovascular risk. CIMT is commonly used as a surrogate end point in research trials as a marker of atherosclerosis. However, new software programs have made CIMT a clinically practical examination for risk evaluation. CIMT correlates with cardiac risk factors and is an independent predictor of future myocardial infarction and stroke risk. Tests for subclinical atherosclerosis, such as CIMT, will help clinicians to more effectively identify the vulnerable patient who would benefit from aggressive prevention intervention.

Prevention of CV Disease

The risk stratification of an individual patient without clinically apparent atherosclerosis (primary prevention) is oftentimes complex. Judging the relative contribution of various risk factors to the extent of atherosclerosis, determining the risk of future CV events, and assessing the risks and benefits of various pharmacologic prevention interventions is commonly based on incomplete information. When there is uncertainty as to the optimal treatment plan, incremental data can add conviction to the provider's recommendation and possibly improve patient compliance. The clinical scenario where the measurement of CIMT is of most apparent benefit is in the patient who is judged to be at intermediate risk for future CV events (estimated at 40% of the population) based on risk assessment tools such as the Framingham Risk Score. In addition, there are also patient scenarios where an individual is judged to be at low risk of future CV events by traditional risk stratification scoring but because of young age, the presence of a strikingly abnormal single risk factor, or of an emerging risk factor, the incremental information provided by a CIMT may more accurately assess this risk. Attractive features of CIMT as a noninvasive measure of atherosclerosis are that it is safe with no known adverse biological effects, relatively inexpensive, and does not require radiation exposure for the patient. The results are highly reproducible, normal values are known, and it is an independent predictor of CV events in a variety of populations. In addition, CIMT adds incremental information to traditional risk assessment algorithms. In the Paroi Arterielle et Risque Cardiovasculaire study of 6416 patients, a significant correlation between all components of the Framingham Risk Score and CIMT was found, but variations in one parameter only explained a modest proportion of variance in the other suggesting that CIMT provides additional information to the Framingham Risk Score. Similar results were shown in a prospective study of 229 patients with diabetes who were followed up over 5 years. The authors found that the combination of the Framingham Risk Score and CIMT significantly improved risk prediction. More recently, Gepner et al found that more than...
50% of a moderate or moderately high-risk group as determined by Framingham Risk Score changed risk category when CIMT results were included in the analysis.

CIMT and Atherosclerosis Risk Factors

Multiple established and emerging risk factors for atherosclerosis are associated with CIMT. Traditional CV risk factors such as age, hypertension, diabetes, hyperlipidemia, and smoking correlate with increased CIMT. CIMT has also been shown to correlate with emerging risk factors such as lipoprotein(a), oxidized low-density lipoprotein, and homocysteine. Wang et al found an association between common CIMT and C-reactive protein in women in the Framingham Heart Study, which remained significant even after adjustment for traditional CV risk factors. The Rotterdam Study also found C-reactive protein to be associated with CIMT and predict its progression. Scuteri et al, using data from the Baltimore Longitudinal Study of Aging, found a disproportionate increase in CIMT in patients with metabolic syndrome, even after adjusting for each component. In a young population (mean age 32 years), those with metabolic syndrome had a higher CIMT measurement in the Bogalusa Heart Study compared with control subjects.

CIMT and Other Measures of Atherosclerosis Burden

B-mode measurement of the intima-media thickness has been shown to reliably correlate with that of pathological specimens. However, a theoretic limitation of CIMT is that the artery being imaged is not a coronary artery. In other words, is carotid atherosclerosis indicative of coronary or intracerebral atherosclerosis? The general concept that atherosclerosis is a systemic disease is well supported. CIMT has been found to correlate with coronary artery atherosclerosis as assessed by both computed tomography coronary calcification and coronary angiography. The Rotterdam Calcification Study quantified coronary calcification and performed B-mode ultrasound measurement of the carotid arteries in 2013 patients. After adjustment for traditional CV risk factors, CIMT was still associated with computed tomography coronary calcium score. The Muscatine Study extended these findings to a young group of patients (age 33-42 years). The authors found that although CIMT is statistically correlated with computed tomography coronary artery calcium score, CIMT remains significantly associated with cardiac risk factors even when coronary artery calcium was included in the multivariate model. Thus, the association of CIMT and coronary artery calcium may not be solely a result of shared risk factors and both examinations may be helpful in assessing risk in a younger population. Kafetzakis et al found a correlation between significant coronary artery disease (CAD) (defined as stenosis > 50%) as assessed by coronary angiography and CIMT. This association increased with the increasing number of coronary vessels affected. Kablak-Ziembicka et al evaluated 558 patients who had undergone coronary angiography with CIMT. They found a strong correlation between CIMT and significant (>50% stenosis) coronary artery stenosis. An individual with a CIMT of greater than 1.15 mm had a 94% chance of significant CAD in this study.

CIMT as a Surrogate Marker of CAD

Atherosclerosis is a disease that begins at a young age and progresses over decades. Because of this,
studies of clinical adverse CV end points often require long-term follow-up and extensive resources. Because of its ease of performance, safety, availability, high reproducibility, and correlation with CAD and CV events,\(^5\) CIMT has been commonly used to assess pharmacologic agents of use in the treatment of CV disease (Table 1). Amlodipine\(^{37}\) and ramipril\(^{13}\) have been shown to decrease CIMT, whereas verapamil\(^{38}\) and probucol\(^{39}\) have been shown to slow progression. Long-acting metoprolol has been shown to significantly decrease CIMT compared with placebo with a trend toward decreased CV events.\(^{12}\) Thiazolidinediones, such as pioglitazone, have also been shown to decrease CIMT. In the Pioneer Study, 173 patients with type 2 diabetes mellitus were found to have a significant reduction at 6 months ($-54 \pm 59 \mu m, P < .001$ vs baseline), with no statistical change in the glimepiride group. This result was independent of long-term glucose control.\(^6\) Folic acid did not significantly affect CIMT or events in patients with chronic renal failure who were followed up for a mean of 3.6 years.\(^{40}\)

The data for 3-hydroxy-3-methyl glutaryl-CoA reductase inhibitors (statins) have been the most impressive in regard to their effect on CIMT. The Asymptomatic Carotid Artery Progression Study studied 919 asymptomatic men and women with hypercholesterolemia. In this study, lovastatin decreased mean CIMT ($P < .001$) and significantly decreased CV event rate and mortality.\(^{41}\) MacMahon et al\(^{11}\) extended these findings in 522 patients with a history of CAD but average or below average cholesterol levels. After 4 years of follow-up, the group treated with pravastatin had a 0.014-mm decrease in CIMT whereas the placebo group had a 0.048-mm increase in CIMT. Two separate studies have shown a comparably larger decrease in CIMT with aggressive lipid lowering using high-dose statin therapy. In 325 patients with familial hypercholesterolemia, atorvastatin (80 mg) decreased CIMT ($-0.031$ mm [95% confidence interval $-0.007$ to $-0.055$]; $P = .0017$), whereas simvastatin (40 mg) resulted in an increased CIMT (0.036 [0.014-0.058]; $P = .0005$) after 2 years.\(^{10}\) In the Arterial Biology for the Investigation of the Treatment Effect of Reducing Cholesterol Trial, atorvastatin (80 mg) induced CIMT regression ($-0.034 \pm 0.021$ mm) as compared with pravastatin (40 mg) (0.025 ± 0.017 mm; $P = .03$) at 12 months.\(^{42}\) These studies were published before evidence that aggressive cholesterol lowering with high-dose statin therapy results in a decrease in adverse CV events in patients with recent acute coronary syndrome as compared with less aggressive statin use.\(^{43}\) In contrast to the data for statins, fibrate therapy does not appear to have the same effect in decreasing CIMT.\(^{44}\)

**CIMT as a Clinical Predictor of CV Events**

The most clinically relevant and promising aspect of CIMT measurement is that it is predictive of future risk for myocardial infarction and stroke. CIMT and CV event rate risk has been evaluated in large prospective trials with long-term follow-up in patients with known CAD, and in individuals 45 years of age and older without clinically apparent CAD. Consistently, CIMT is associated with risk of CV event in these populations. In the Atherosclerosis Risk in Communities Study, 7289 women and 5552 men age 45 to 70 years with no history of coronary heart disease were followed up for 4 to 7 years. They found that hazard rate ratios for myocardial infarction or coronary heart disease death for high versus low tertiles were 6.69 for women and 2.88 for men.\(^2\) The Cardiovascular Health Study studied 5858 individuals older than 65 years without clinically apparent coronary heart disease for a median of 6.2 years.

### Table 1: Therapeutic interventions that have been shown to influence carotid intima-media thickness

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Risk factors involved</th>
<th>Finding</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Hypertension</td>
<td>Decreases CIMT</td>
<td>(^{61})</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Hypertension</td>
<td>Decreases CIMT</td>
<td>(^{61})</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Familial hypercholesterolemia</td>
<td>Decreases CIMT</td>
<td>(^{62})</td>
</tr>
<tr>
<td>Diet and exercise</td>
<td></td>
<td>Decreases CIMT</td>
<td>(^{41})</td>
</tr>
<tr>
<td>Intensive diabetes therapy vs</td>
<td>Diabetes mellitus</td>
<td>Intensive diabetes therapy results</td>
<td>(^{63})</td>
</tr>
<tr>
<td>conventional therapy</td>
<td></td>
<td>in less CIMT progression</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin, pravastatin</td>
<td>LDL</td>
<td>Atorvastatin induced regression of CIMT</td>
<td>(^{41})</td>
</tr>
<tr>
<td>Pancreas transplantation</td>
<td>Diabetes mellitus</td>
<td>Regression of CIMT</td>
<td>(^{64})</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Hypertension</td>
<td>Regression of CIMT with lower cardiovascular event rate</td>
<td>(^{37})</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Hypertension</td>
<td>Stops progression of CIMT</td>
<td>(^{37})</td>
</tr>
<tr>
<td>Pioglitazones</td>
<td>Inflammation, atherosclerosis</td>
<td>Reduction in CIMT, independent from glucose control</td>
<td>(^6)</td>
</tr>
<tr>
<td>Rosiglitazones</td>
<td>Nondiabetic CAD</td>
<td>Reduction in CIMT progression</td>
<td>(^{65})</td>
</tr>
</tbody>
</table>

\(CAD\), Coronary artery disease; \(CIMT\), carotid intima-media thickness; \(LDL\), low-density lipoprotein.
Those with the highest quintile of CIMT had a 3.87 relative risk (adjusted for age and sex) of myocardial infarction or stroke compared with those in the lowest quintile. CIMT was as strong a predictor of events as the traditional risk factors and after adjustment for these risk factors, CIMT was the variable most strongly associated with cardiac events. The Kuopio Ischemic Heart Disease Risk Factor Study found risk of myocardial infarction increased by 11% with each 0.1-mm increase of common CIMT. The Rotterdam Study was a single-center, nested case-control study of 7983 patients older than 55 years with a median follow-up of 2.7 years. When adjusted for age and sex, the odds ratio for SD increase in CIMT was 1.41 for stroke and 1.43 for myocardial infarction.

To determine a normal or threshold value for CIMT in an individual, age, sex, and race have to be taken into consideration. Setting an absolute value as a threshold for abnormal CIMT without consideration to age would overestimate the risk of CV event in the older population while underestimating that in the younger population. The most accurate interpretation of a CIMT value is one compared with population databases. There is commercial software currently available that uses available research databases to compare an individual’s result with that obtained from a general population (Figure 2). Such an approach allows for a determination of a vascular age to an individual patient. When this vascular age is incorporated into a traditional risk algorithm, this information can provide an easy-to-understand assessment of risk for patient and provider and may lead to better matching of prevention recommendations to risk level and improved compliance.

Effect of Preventative Interventions on CIMT

Although definitive studies have yet to be published, there are promising data to suggest that CIMT may be useful in evaluating the effectiveness of prevention therapy. Lifestyle changes such as smoking cessation, regular exercise, healthy diet choices, and weight loss are the initial and most important steps in any effective prevention regimen and CIMT has been shown to improve with nonpharmacologic preventative interventions. The Monitored Atherosclerosis Regression Study assessed a multifaceted approach to prevention and found that reducing body mass index by 5 kg/m², quitting a 10-cigarette/day smoking habit, and reducing dietary cholesterol intake by 100 mg/day on average would reduce the annual rate of CIMT progression by 0.13 mm/year. In the Women’s Healthy Lifestyle Project, CIMT progression was accelerated during the menopause transition and a diet/exercise intervention slowed this progression. The Los Angeles Atherosclerosis Study found that increased activity level and increased fiber intake is associated with a decreased progression rate of CIMT. Similarly, good cardiopulmonary fitness as associated by cardiopulmonary fitness (maximal oxygen uptake [mL/kg/min]) is associated with slower progression of early atherosclerosis in middle-aged men. Weight loss after

![Figure 2](image-url)
gastric bypass has also been shown to decrease the rate of progression of CIMT, and improved glycemic control has been shown to slow CIMT progression in patients who are diabetic.

Whether serial CIMT measurement predicts future risk is still to be determined, but there are limited initial data. Hodis et al performed serial CIMT measurement and quantitative coronary angiography on 146 men age 40 to 59 years with history of coronary artery bypass graft surgery for an average follow-up of 8.8 years. For each 0.03-mm increase per year in CIMT there was an increase in the relative risk of coronary event of 3.1. If a change in serial CIMT measurements in an individual proves to be predictive, it would be a powerful clinical tool not only for risk stratification, but also for assessing and optimizing prevention recommendations.

CIMT Technical Considerations

CIMT imaging requires methodic attention to carotid anatomy, ultrasound parameters, and a standardized measurement protocol that is compared with a general population database. The primary objective is to obtain valid and reproducible CIMT measurements. A detailed carotid plaque screen is recommended, with particular attention to the carotid artery bulb and the internal carotid artery. If potentially obstructive plaque is identified, a dedicated carotid duplex flow scan should be recommended. Incidental findings such as a thyroid cyst or nodule should also be noted.

To begin the CIMT examination, the patient should be supine with the sonographer positioned at the head of the bed. The patient and sonographer should be comfortable during the examination with careful attention paid to safe, efficient, and ergonomic scanning positions to minimize the potential for injury. The time needed for a thorough and complete examination is dependent on the protocol and sonographer experience, but typically is 15 to 60 minutes. During the scan the patient should have minimal support under the neck to aid in neck extension and rotation that will aid in positioning of the carotid artery for optimal imaging. Linear-array transducer frequency is best between 8 to 12 MHz using fundamental frequency only. There should be no harmonic or compound imaging as this will “bloom” the returning signals and can create a falsely thickened CIMT. The far wall CIMT should be seen as a double line representing the lumen-intima and media-adventitia interface. The best image resolution is obtained when the ultrasound beam is perpendicular to the structure being imaged, which may require the scanner to manipulate transducer, ie, heel-to-toe and/or rotation motions, to optimize the intima-media image. Setting the focal position on the far common carotid artery wall and using overall gain, time gain compensation and postprocessing functions (eg, dynamic range, edge, space/time) can further enhance the quality of the images.

Reliability and Reproducibility

The difference in thickness between a normal scan and an abnormal scan can be small and a common concern for those who have not previously performed CIMT measurement is whether the measurement is accurate and reproducible. Data from published research centers that have an expertise at performing CIMT have consistently shown that the measurement is highly reproducible, although this varies somewhat depending on sites measured, number of measurements, and whether mean or maximum values were used (Table 2).

Newer semiautomated border detection programs are available that are less time-consuming and more reproducible for less experienced users (Figure 3). A recent study compared a novice reader with a reference laboratory using a semiautomated border detection program. The novice reader results were bioequivalent to the reference laboratory with small absolute differences (experienced 0.011 ± 0.004 mm, novice 0.022 ± 0.004 mm) in CIMT and high reproducibility (coefficients of variation: experienced 3.1%, novice 7.8%).

Carotid Plaque

As would be expected, the presence of carotid plaque predicts an increased risk of future CV events. In fact, the presence of plaque may be a stronger predictor of future event risk than increased CIMT. In the CAFES-CAVE study,
10,000 individuals at low risk had their femoral and carotid arteries imaged with ultrasound and were followed up for 10 years. The CV event rates were 10 of 7989 in those with normal arteries, 81 of 930 (8.6%) in those with intima-media thickening, 239 of 681 (39.6%) in those with nonstenosing plaque, and 381 of 470 (81%) in those with stenosing plaques. Because plaque is a strong predictor of risk and the primary goal of a test for subclinical atherosclerosis is to identify those at higher than expected risk, it has been suggested that an efficient method to evaluate risk would be complete if carotid plaque is found. If there is no plaque, then determination of the CIMT would be performed.

Future Needs and Direction

Although measurement of CIMT has been correlated with CV risk factors, has become a surrogate marker for the effect of interventions targeting atherosclerosis, and has shown to be predictive of future myocardial infarction and stroke, it has remained primarily a research tool until more recently. The introduction of software that allows for less experienced laboratories to efficiently and reproducibly measure CIMT and compare those results with general population databases has allowed CIMT to become a clinically practical test. Expert guidelines that establish training and competency criteria and that recommend a protocol for obtaining an accurate measure in an efficient and clinically feasible manner is forthcoming from the American Society of Echocardiography. Another factor that has limited more widespread use of CIMT is reimbursement. Lack of reimbursement by traditional health care payers is a common issue with preventative measures in general and this also applies to CIMT. However, a Medicare Current Procedural Terminology code has been created for CIMT, and as the focus of medical care shifts from care of established diseases to a focus on prevention of disease, health care payers may be more likely to reimburse preventative care.

Although the research database for CIMT is one of its strengths, further research is still needed to possibly expand the use of CIMT in clinical practice. Selected areas of investigation may include assessing if the use of CIMT can lead to lower event rates by identifying individuals at higher risk for preventative measures. The role of CIMT in the assessment of the effectiveness of an individual’s prevention regimen will also need to be defined.

CIMT is a safe, reproducible test that is effective in the risk stratification of selected individuals for future CV events. Normal values are known in diverse population studies to allow accurate interpretation of the test results. Software programs with semiautomated border detection capability and that compare the result with the large population databases to render a percentile score and a vascular age combined with an imaging protocol that focuses on the common carotid artery and the presence or absence of atherosclerotic plaque will make CIMT a test that is useful and practical in a clinical setting. Challenges are apparent, but the future of CIMT in CV disease risk stratification is bright.
REFERENCES


