Carotid Intima-Media Thickness Testing as an Asymptomatic Cardiovascular Disease Identifier and Method for Making Therapeutic Decisions

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Abstract: Cardiovascular disease (CVD) is the leading cause of death and disability in the United States. Although current therapies can reduce the risk for CVD, they are only given to patients who are considered to be at risk, and are therefore only beneficial if a patient’s risk is accurately predicted before he or she sustains a cardiovascular (CV) event. Unfortunately, even relatively accurate risk factor analyses, such as the Reynolds Risk Score algorithm, fail to identify some patients who will sustain a CV event within 10 years. In contrast, the presence of an atheroma is an absolute predictor for the potential of an atherothrombotic event to occur, and it is therefore reasonable to anchor clinical decisions based on this knowledge. Carotid intima-media thickness (CIMT) testing via B-mode ultrasound is a safe, simple, and inexpensive method for evaluating CV risk by measuring the combined thickness of the intimal and medial layers of the arterial wall. Use of CIMT testing can also detect marked thickening of the arterial wall, possibly indicating plaques or atheromas that are associated with accelerated atherosclerotic disease and increased risk for coronary artery disease, myocardial infarction, and stroke. These characteristics make CIMT a practical supplemental method that physicians can use when making decisions. Moreover, the ability of CIMT testing to identify and quantify atherosclerotic disease has led to the adoption of CIMT as a surrogate endpoint in clinical trials, allowing the efficacy of new drugs to be assessed much more rapidly than would be possible by focusing solely on CV event or mortality rates. To date, several trials have provided evidence to indicate that some CVD therapies slow, stop, or reverse the progression of CIMT. Although many of these studies show that changes in CIMT predict future CV events, the value of CIMT testing in CVD risk assessment is still vigorously debated. In this article, we clarify the utility of CIMT testing for risk classification and reexamine its usefulness as a method for assessing therapeutic efficacy.

Keywords: atherosclerosis; carotid intima-media thickness; cardiovascular disease risk assessment; myocardial infarction; stroke

Introduction
Cardiovascular disease (CVD) is the main cause of mortality and a leading cause of disability among men and women in the United States. The most recent statistics show that CVD accounted for 32.8% (almost 812,000) of all US deaths in 2008.1 This implies that > 2200 Americans die of CVD each day, or that 1 death from CVD occurs almost every 40 seconds. Each year, nearly 800,000 Americans experience a new myocardial infarction (MI) and approximately the same number experience a new or recurrent stroke.1 Cardiovascular disease is present in approximately one-third of all US adults and imposes a large financial burden, which was estimated at $448.5 billion in 2008.2 Not surprisingly, comorbidities that contribute to CVD are themselves highly prevalent: 33.5% of US adults aged ≥ 20 years have hypertension, 67.3% are obese
or overweight, 8% have diagnosed diabetes, and 36.8% have abnormal fasting blood glucose levels that indicate prediabetes.\(^1\) Smoking prevalence has declined, but was still at 19.3% in the United States in 2008.\(^1\) Most cardiovascular (CV) events are not limited to the elderly; approximately 150,000 Americans aged < 65 years died of CVD in 2008 and 33% of CVD deaths occurred in those aged < 75 years. Given the frequency of CVD and the even greater presence of risk factors for CVD in US adults, it is evident that the burden of CVD will persist. A continual increase in the prevalence and costs of CVD have been projected for as far as 2030.\(^3\)

Despite this dire situation, it is important to remember that atherosclerosis and CVD are not normal, inevitable consequences of aging, and that there are opportunities to intervene effectively. The course of atherosclerotic disease can potentially begin in childhood as fatty streaks within the arterial wall. Gradual, often silent expansion of these lesions may eventually limit blood flow in the arteries.\(^3\) However, such stenotic lesions are not typically the cause of CV events; rather, either rupture or erosion of the endothelium overlying an atheroma leads to a thrombus.\(^3\) The thrombus may cause enough obstruction to produce a symptomatic event. If the thrombus is small, it may migrate distally, causing silent ischemia. Alternatively, the thrombus may simply heal, leading to progression in the size of the underlying atheroma. This scenario can occur in any artery and eventually present as coronary, renal, intestinal, peripheral, or cerebral disease.\(^6,8\)

However, not every atheroma leads to a clinical event. Thus, identifying vulnerable plaques that are at a higher risk for causing a CV event is an important area of research.

Accurate risk assessment is important so that patients may receive the appropriate level of treatment and minimize CVD-related morbidity, mortality, and associated health care costs. Accurate risk assessment is especially important for middle-aged adults, as recent studies show that they are approximately 2 to 3 times more likely to experience a CV event as they are to die of non-CV causes.\(^9\) The CVD risk categories outlined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and its 2004 update are based on the presence of existing coronary heart disease (CHD) and on the traditional Framingham Risk Score (FRS). The FRS components include age, hypertension, smoking, and total and high-density lipoprotein cholesterol (HDL-C) levels.\(^6,6\) Diabetes is also a significant risk factor in the NCEP ATP III system.

However, knowledge about CVD risk assessment has moved well beyond these established risk factors. A comprehensive update (NCEP ATP IV), which is expected to address the gap between guidelines and the current state of information, should be released soon.\(^10\) Additional risk assessments that have been suggested as supplements to the NCEP ATP III guidelines include the Reynolds Risk Score (RRS),\(^10\) which is a global risk algorithm developed in 2007. The RRS incorporates FRS factors in addition to family history, inflammatory markers (eg, increased high-sensitivity C-reactive protein [CRP] levels), and glycated hemoglobin levels.\(^11\) In clinical practice, treatment decisions are often derived from pooling multiple risk factors. However, the absence of such risk factors does not exclude the presence of atherosclerotic plaque, which must be present in order for a CV event to occur. As a result, even the more accurate RRS cannot identify all patients who will experience a CV event within 10 years.\(^11\)

It is imperative to go beyond the limitations of traditional risk factor paradigms by directly evaluating the presence or absence of vascular disease, which is the most definitive indicator of a future CV event. This is important because patients without major CVD risk factors may have clinically silent atherosclerosis that predisposes them to experiencing a CV event. This was clearly demonstrated in the Carotid and Femoral Ultrasound Morphology Screening and Cardiovascular Events in Low Risk Subjects: A 10-Year Follow-Up Study (CAFES-CAVES),\(^12\) in which the degree of atherosclerosis (assessed by carotid-intima media thickness [CIMT]) in low-risk, asymptomatic patients was strongly correlated with the 10-year incidence of CV events.\(^12\) The Society of Atherosclerosis Imaging and Prevention (SAIP)\(^13\) and the Screening for Heart Attack Prevention and Education (SHAPE) Task Force\(^14\) have endorsed the use of CIMT. The CIMT measurement, in particular, offers a practical, noninvasive approach to complement risk factor assessment by identifying subclinical atherosclerosis and carotid plaque formation. The main goal of this combined risk evaluation approach is to better enable the practitioner to make a well-informed therapeutic decision for each patient. As an additional benefit, simply undergoing CIMT testing appears to motivate improvements in patient behaviors, at least in the short-term.\(^15\)

Despite a wealth of evidence demonstrating the importance of CIMT testing as a disease identifier, whether and how CIMT should be used clinically to predict CVD risk or determine therapeutic effectiveness remains a topic of considerable debate. This article clarifies these issues using current data to illustrate the advantages and limitations of CIMT testing for use as a diagnostic standard for CVD and as an efficacy endpoint for therapies intended to prevent CV events.
Materials and Methods
An electronic search of the scientific literature was performed with PubMed. The following keyword terms were used: (carotid intima-media thickness OR CIMT) AND (statins OR fibrates OR niacin OR antihypertensive drugs OR vitamin B OR atherosclerosis) AND (B-mode ultrasound OR magnetic resonance imaging). Results were limited to the English language, clinical trials, humans, reviews, and publication date between 2002 and 2012, yielding 119 articles of potential interest. Of these, articles that did not directly relate to CIMT testing, CIMT and CVD, and CIMT as an efficacy endpoint in clinical trials were excluded. The remainder, as well as additional pertinent materials from their references, formed the basis of this article.

Appropriate Situations for CIMT Testing
Recently, the SAIP, in collaboration with the International Atherosclerosis Society, reviewed the appropriateness of using CIMT testing in 33 common clinical scenarios in which it could be conducted (Table 1). These clinical scenarios included risk assessment for individuals with and without known CHD, as well as serial testing to monitor CHD risk status. It was concluded by the SAIP that the use of CIMT testing was generally appropriate for assessment of CHD among intermediate-risk patients, patients with metabolic syndrome, and older patients (women, > 55 years; men, > 45 years), but the SAIP did not recommend serial testing at this time. Use of CIMT testing in low- and high-risk patients was mostly seen as inappropriate. Although these guidelines provide a good reference to determine when clinicians should use CIMT testing, the criteria remain dynamic as CIMT testing continues to evolve.

CIMT Testing in the Clinic
Carotid intima-media thickness testing gauges the extent of atherosclerosis by measuring the combined thickness of the intimal and medial layers of the carotid artery. Although there is still no clear standard protocol for obtaining a CIMT image, the American Society of Echocardiogra-

Table 1. CIMT Testing Clinical Scenarios and Appropriateness Ratings Generated by the SAIP and the IAS

<table>
<thead>
<tr>
<th>CIMT Testing</th>
<th>No Known CHD*</th>
<th>Known CHD</th>
<th>Serial Imaging for Monitoring CHD Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Initial detection (intermediate risk)</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>- ≥ 2 risk factors (intermediate risk)</td>
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<td></td>
<td></td>
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<tr>
<td>- Metabolic syndrome (≥ 30 y)</td>
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<td></td>
<td></td>
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<tr>
<td>- Diabetes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Family history of premature CHD (low to intermediate risk)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- CAC score of 0 (FRS, 11%–20%)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Initial detection of CHD (low risk)</td>
<td></td>
<td></td>
<td>- Primary prevention (annually)</td>
</tr>
<tr>
<td>- CAC score of 0 (FRS &lt; 5%)b</td>
<td></td>
<td></td>
<td>- Secondary prevention (annually)</td>
</tr>
<tr>
<td>- Asymptomatic with focal carotid plaque ultrasound</td>
<td></td>
<td></td>
<td>- Prior normal CIMT</td>
</tr>
<tr>
<td>- Asymptomatic with &gt; 50% stenosis on carotid ultrasound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Initial detection (high risk)</td>
<td></td>
<td></td>
<td>- Primary prevention (after ≥ 2 y)</td>
</tr>
<tr>
<td>- ≥ 2 risk factors (low and high risk)</td>
<td></td>
<td></td>
<td>- Secondary prevention (after ≥ 2 y)</td>
</tr>
<tr>
<td>- Men aged ≥ 45 y; women aged &gt; 55 y</td>
<td></td>
<td></td>
<td>- Prior abnormal CIMT</td>
</tr>
<tr>
<td>- Family history of premature CHD (low risk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Abnormal CAC score (ie, &gt; 100 or &gt; 75th percentile for age and sex)</td>
<td></td>
<td></td>
<td>- Have reached treatment goals for CHD risk factors</td>
</tr>
<tr>
<td>- CAC score of 0 (FRS, 5%–10%)b</td>
<td></td>
<td></td>
<td>- Have not reached treatment goals for CHD risk factors</td>
</tr>
</tbody>
</table>

*aDifferent patient criteria in parentheses.

bFRS: high risk, CHD or CHD risk equivalents, 10-year CHD risk > 20%; moderate risk, ≥ 2 CHD risk factors, 10-year CHD risk 10%–20%; low risk, 0–1 CHD risk factor, 10-year CHD risk < 10%.4

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; CIMT, carotid intima-media thickness; FRS, Framingham Risk Score; IAS, International Atherosclerosis Society; SAIP, Society of Atherosclerosis Imaging and Prevention.
phy provided a suggested protocol in 2008. Typically, during CIMT testing, a B-mode ultrasound transducer is placed on top of the skin above the extracranial segments of each of the carotid arteries. A correct image will show a double line, representing 2 echogenic structures known as the lumen–intima interface and media–adventitia interface of the near and far wall of the carotid artery. Border-detection programs will calculate a CIMT value by tracing the far-wall interfaces from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface (Figure 1A, B). Because CIMT testing requires accurate identification and measurement of subpixel echogenic structures, technical challenges have limited its use to research settings with trained sonographers using complicated protocols and bulky ultrasound machines. However, a multicenter study has suggested that non-sonographers using a handheld ultrasound device can obtain images of the carotid arteries that are of good

Figure 1. A) B-mode ultrasound of the right common artery with its midsegment highlighted. The arrow indicates the intima-media layer being measured.


B) Ultrasound images of thickened, irregular (top) and normal (bottom) carotid artery intima-media thickness.

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enough quality to accurately measure CIMT and determine CVD risk.\textsuperscript{19} Nonetheless, interobserver variability remains a potential source of problems with obtaining consistent measurements. Magnetic resonance imaging measurement of CIMT (Figure 1C) is an alternative to B-mode ultrasound that is highly reproducible and yields equivalent results\textsuperscript{20} but is seldom used in the clinical setting owing to its high cost and limited availability.

Regardless of the measurement device, CIMT is calculated either from 1 measurement of a predetermined site or by the average of multiple areas from the same artery.\textsuperscript{16,17} Generally, these latter measurements are reported as mean-mean (average of segmental mean values) and/or mean-maximum (average of segmental maximum values or maximum) absolute values (in mm) or percentiles.\textsuperscript{16}

**Interpretation of CIMT Measurements**

The average CIMT value is a measure of atherosclerosis and other causes of thickening, whereas regions of markedly greater thickness indicate the presence of plaques. The American Society of Echocardiography identifies an atherosclerotic plaque as CIMT $\geq 1.5$ mm or $\geq 50\%$ of the surrounding vessel wall,\textsuperscript{16} but this definition may exclude clinically significant CVD. For example, Kabluck-Ziembicka et al\textsuperscript{21} reported that individuals with a mean CIMT $\geq 1.15$ mm had a 94\% chance of having significant coronary artery disease (CAD). On average, in 1 large study, the 25th and 75th percentiles for CIMT in men were 0.65 mm and 0.84 mm, respectively; for women, the values were 0.58 mm and 0.74 mm, respectively.\textsuperscript{22} Generally, a CIMT value that is above the 75th percentile is considered
CIMT Testing in CVD Risk Assessment

Age, sex, and race influence the interpretation of CIMT findings. The CIMT values are generally lower in white men and women than in black men and women (Figure 2). An individual’s CIMT increases at an average rate of < 0.0033 mm per year of age, even without evidence of atherosclerosis. Moreover, a study investigating the association between CAD and mean CIMT in 558 patients showed that a CIMT > 1.069 mm was strongly predictive of CAD in women, whereas the predictive CIMT value in men was > 1.153 mm. Because the absolute values of CIMT can vary depending on the particular patient population and techniques used for measurement, CIMT risk categorization may be determined using percentiles. Whether absolute results or percentiles are used, they should be interpreted based on standard values that have been adjusted for demographic factors.

Value and Utility of CIMT Testing in CVD Risk Assessment

Use of CIMT testing refines and expands on other markers of CVD risk to optimize prevention. The measurements obtained from CIMT testing often correlate with traditional CVD risk factors (eg, metabolic syndrome, age, hypertension, diabetes, hyperlipidemia, and smoking) and emerging risk factors (eg, lipoprotein(a), oxidized low-density lipoprotein cholesterol [LDL-C], homocysteine, and CRP). For example, Scuteri et al retrospectively reviewed the Baltimore Longitudinal Study of Aging (BLSA) and found a 16% greater increase in CIMT in patients with metabolic syndrome compared with patients without metabolic syndrome. Moreover, in both the Framingham Heart Study and the Rotterdam Coronary Calcification Study, CIMT was shown to correlate with CRP and predict CVD progression. However, the true benefit of CIMT testing is its ability to identify atherosclerosis and risk for CV events beyond these other factors. The inadequacies of risk factor assessment alone in CVD prognosis were highlighted in a meta-analysis investigating the prevalence of 4 conventional CVD risk factors (smoking, diabetes, hypertension, and hyperlipidemia) in 14 trials with > 122 000 patients with known CVD. The meta-analysis performed by Khot et al showed that 15.4% of women and 19.4% of men with CVD, and > 20% of women aged > 75 years and men aged > 65 years, had none of these conventional risk factors.

Increased CIMT is associated not only with traditional risk factors, but also with elevated incidence of CV events. Several studies, including the Atherosclerosis Risk In Communities (ARIC) study, the Rotterdam Coronary Calcification Study, the Cardiovascular Health Study (CHS), and the Carotid Atherosclerosis Progression Study (CAPS), as well as several smaller studies, have shown that CIMT is significantly related to the incidence of CV events, even after adjustment for traditional risk factors. However, a recent longitudinal, population-based analysis spanning 13 years found that traditional risk factors (eg, age, sex, and smoking) predicted increases in total plaque area but not increases in CIMT. This is consistent with a meta-analysis by Inaba et al, which found that CVD risk is more closely related to the extent of arterial plaques than to average CIMT, although there is also evidence from a subanalysis of the ARIC study that the relative importance of CIMT and plaque may vary with sex. Nonetheless, the value of adding CIMT to traditional risk factors for predicting CV events was confirmed by Polak et al. Moreover, another study found that the risk for ischemic stroke in normotensive patients was 3-fold higher when a patient had carotid artery atherosclerosis (mean CIMT ≥ 0.81 mm or the presence of a plaque [defined as CIMT > 1.2 mm in any segment]), even when risk was adjusted for age, sex, blood pressure, cholesterol ratios, fasting blood glucose level, and smoking.

In fact, atherosclerosis in the carotid artery is actually more predictive of a CV event than atherosclerosis in the coronary artery. Most recently, the Carotid Intima Media Thickness (IMT) and IMT-Progression as Predictors of Vascular Events in a High Risk European Population (IMPROVE) cohort study in 3703 Europeans with ≥ 3 vascular risk factors found that combining CIMT measurements with Framingham risk factors resulted in a net reclassification improvement of up to 11.3% compared with using Framingham risk factors alone. When the diameters of the carotid arteries and the presence of plaque were incorporated into the analysis, the net reclassification index increased to 13%. Considered as a group, these studies provide compelling evidence to indicate that CIMT and plaque are associated with the risk for developing CVD and experiencing CV events. Thus, use of these measurements in combination with traditional risk factors is expected to help classify patients into appropriate risk categories and improve CVD risk prediction.

Limitations of CIMT Testing in CVD Risk Assessment

Although CIMT testing has many advantages, it also has limitations, as does any surrogate measure of CVD risk. A main challenge is the absence of a generally accepted pro-
tocool. Measurement and interpretation of CIMT may also be perceived as being technically complicated and time-consuming, thus requiring specialized training. However, the process of CIMT measurement has been simplified and streamlined by advances in computer programs that detect the carotid intima border. Using such systems, even novice readers were able to note CIMT measurements that were comparable (mean difference, 0.022 mm) with those from a reference imaging group. Results from experienced readers were even more similar (mean difference, 0.011 mm) to the reference measurements. Reproducibility of repeated measurements for the same reader over time was good, with mean absolute differences of −0.040 and 0.003 for novice and experienced readers, respectively.

Another concern that may be raised is whether measurement of carotid atherosclerosis with CIMT is relevant for assessing coronary atherosclerosis, as CAD causes the majority of CVD deaths. Reassuringly, a systematic review found positive correlations between CIMT and CAD in 29 of 33 studies analyzed; although it is not yet clear whether the moderate degree of observed correlations (coefficients ranging from 0.12–0.51) reflected differences in the carotid and coronary vascular beds or technical limitations of CIMT testing methods. Nonetheless, it should be noted again that plaque in the carotid artery is predictive of worse CV outcomes than plaque in the coronary artery alone.

A final caveat in interpreting CIMT measurements is that thickening can be associated not only with atherosclerosis, but also with inflammatory disorders, such as diabetes and rheumatoid arthritis. Increases in CIMT in patients with these conditions may be due to the combined effect of atherosclerosis and chronic inflammation, or to the inflammation alone. In the latter case, treating the inflammation should result in CIMT regression. Progression of CIMT has also been associated with occupational stress and daily activity demands. In addition to stress and inflammation-related increases in CIMT, age-related CIMT increases can also be difficult to differentiate pathologically from atherosclerosis-related increases.

### CIMT Testing Compared With Other Methods of Detecting Atherosclerosis

Coronary angiography, which has long been the gold standard in CHD diagnosis, visualizes blood flow and detects blockages in the coronary artery using dye and radiograph imaging. Although intervention studies clearly show the benefit of this technique in the determination of future risk, it has significant drawbacks (Table 2). These include low resolution, imaging of the vessel lumen only (not the wall, which is the actual site of atherosclerotic disease), invasiveness, patient exposure to radiation (often making it inappropriate for monitoring over time), and inability to reliably identify underlying atherosclerotic disease. Coronary artery calcium (CAC) scoring is another method that is often used to assess CHD risk. When CAC scoring is used, cardiac computed tomography quantifies the amount of calcified coronary artery plaques. Although CAC scoring is noninvasive and directly images plaque, it still exposes the patient to significant doses of radiation and therefore is unsuitable for long-term monitoring. Similar

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**Table 2. Advantages and Disadvantages of Coronary Angiography, CAC Scoring, CIMT Testing, and Stress Testing**

<table>
<thead>
<tr>
<th>CHD Risk Assessment Tool</th>
<th>Major Advantages</th>
<th>Major Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>Widely available and often used; well known as a marker of atherosclerosis progression</td>
<td>Invasive; radiation and contrast exposure; gives image of lumen only; unsuitable for serial examinations</td>
</tr>
<tr>
<td>CAC scoring (CT scan)</td>
<td>Widely available and often used; images calcified plaque</td>
<td>Significant radiation exposure; unsuitable for serial examinations</td>
</tr>
<tr>
<td>CIMT testing</td>
<td>Simple to perform; cost-effective; can be frequently performed without any adverse effects; images actual site of atherosclerosis; suitable for serial examinations</td>
<td>Limited to carotid arteries; identifies changes not only due to atherosclerosis (eg, age and inflammation); clear standardized protocol lacking</td>
</tr>
<tr>
<td>Stress testing (with or without imaging by echocardiographic, nuclear, and MR methods)</td>
<td>Cost-effective (for echocardiography, high-volume PET, or no imaging); high contrast and resolution without ionizing radiation (MR); suitable for serial examinations; can be performed with exercise or pharmacologically</td>
<td>May be difficult in thin or obese patients and in patients with large breasts or lung disease (echocardiography, SPECT); response to exercise varies so that a standard maximal level of exercise cannot be defined; physical stress may be associated with risk to patients</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAC, coronary artery calcium; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CT, computed tomography; MR, magnetic resonance; PET, positron emission tomography; SPECT, stress myocardial perfusion single-photon emission computed tomography.
to CAC scoring, CIMT testing is noninvasive and images the arterial wall; however, CIMT testing has the additional advantage of being able to be repeated frequently without adverse effects on the patient.

Numerous studies have compared coronary angiography or CAC scoring by CIMT testing. Stenosis $\geq$ 50%, detected with coronary angiography, was strongly correlated with CIMT. Moreover, an increase in CIMT was associated with the presence and extent of CAD identified by coronary angiography. The relationship between CAC scoring and CIMT testing appears to be more complex. Initially, the Rotterdam Coronary Calcification Study showed that CAC and CIMT testing technology advances and becomes easier to use in the clinic, it may begin to supplant other techniques as the imaging method of choice for CVD risk stratification.

**CIMT as an Efficacy Endpoint in Clinical Trials**

As discussed, several studies have shown that CIMT is related to the incidence of CV events. Using CIMT measurement as a biomarker for atherosclerosis progression may accelerate drug development by facilitating efficacy assessments before the occurrence of endpoints such as MI, stroke, and death.

**Statins**

Statins lower lipid levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis. Numerous clinical studies have established that statin monotherapy reduces or even reverses the progression of CIMT (Table 3), as described in a review by Riccioni. More recent research has focused on statins combined with other cholesterol-lowering agents. In older studies, no positive effect on CIMT was observed when ezetimibe was added to a statin, but the same strategy significantly decreased CIMT in the Vytorin on Carotid Intima-Media Thickness and Overall Arterial Rigidity (VYCTOR) study, which involved high-risk patients in Mexico. Likewise, addition of niacin to a statin had beneficial effects on CIMT in several studies. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) study, the addition of niacin to a statin resulted in a significant reduction in mean CIMT ($-0.0102 \pm 0.0026$ mm; $P < 0.001$), whereas addition of ezetimibe to a statin did not ($-0.0016 \pm 0.0024$ mm; $P = 0.88$). A comparable study to ARBITER 6-HALTS was conducted by Taylor et al. with similar results.
<table>
<thead>
<tr>
<th>Study</th>
<th>N; Age, y; CVD Risk Factors</th>
<th>Intervention</th>
<th>Duration</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin Monotherapy</strong></td>
<td></td>
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<tr>
<td>ASAP67; 2002</td>
<td>325; 30–70; familial hypercholesterolemia</td>
<td>Atorvastatin 80 mg, simvastatin 40 mg</td>
<td>2 y</td>
<td>- Atorvastatin reduced CIMT progression more than simvastatin (0.031 mm [P = 0.0017] vs 0.036 mm [P = 0.005]; P = 0.001 between groups). - CIMT change correlated with percentage of LDL-C level reduction (P = 0.001)</td>
</tr>
<tr>
<td>van Wissen et al68; 2005</td>
<td>255; 30–70; familial hypercholesterolemia</td>
<td>Atorvastatin 80 mg</td>
<td>2-y extension of ASAP</td>
<td>- Patients taking atorvastatin for 4 y had a complete arrest in CIMT progression (0.89 to 0.90 mm; P = 0.58). - Patients switched to atorvastatin from simvastatin had a significant regression of CIMT (0.95 to 0.92 mm; P = 0.01)</td>
</tr>
<tr>
<td>ARBITER69; 2002</td>
<td>161; mean, 60; met NCEP ATP II criteria for lipid-lowering therapy</td>
<td>Atorvastatin 80 mg, pravastatin 40 mg</td>
<td>1 y</td>
<td>- Atorvastatin decreased CIMT by a mean ± SD of 0.034 ± 0.021 mm; pravastatin did not change CIMT (0.025 ± 0.017 mm; P = 0.03 between groups). - Changes correlated with LDL-C and total cholesterol levels.</td>
</tr>
<tr>
<td>METEOR70; 2007</td>
<td>984; mean, 57; FRS, 10% CIMT 1.2 to 3.5 mm, elevated LDL-C</td>
<td>Rosuvastatin 40 mg, placebo</td>
<td>2 y</td>
<td>- Rosuvastatin reduced maximum CIMT progression compared with placebo (–0.0014 vs 0.0131 mm/y; P &lt; 0.001)</td>
</tr>
<tr>
<td>Yu et al71; 2007</td>
<td>112; 66; angiographic CVD evidence</td>
<td>Atorvastatin 10 mg, atorvastatin 80 mg</td>
<td>26 wk</td>
<td>- Atorvastatin 80 mg reduced CIMT (left, 1.24 ± 0.48 mm vs 1.15 ± 0.35 mm; P = 0.02; right, 1.12 ± 0.41 mm vs 1.01 ± 0.26 mm; P = 0.01). - Atorvastatin 10 mg resulted in no change (left, 1.25 ± 0.55 mm vs 1.20 ± 0.51 mm; P = NS; right, 1.18 ± 0.54 mm vs 1.15 ± 0.41 mm; P = NS). - Changes correlated with hsCRP, LDL-C, and total cholesterol levels.</td>
</tr>
<tr>
<td><strong>Statin Combination Therapy</strong></td>
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<tr>
<td>SANDS73; 2008</td>
<td>252; &gt; 40; T2DM with no CV events, LDL-C ≤ 70 mg/dL, non–HDL-C ≤ 100 mg/dL, SBP &lt; 115 mm Hg</td>
<td>Statin ± ezetimibe</td>
<td>3 y</td>
<td>- Aggressive LDL-C reduction resulted in similar CIMT regression ± ezetimibe (–0.025 to –0.012 mm)</td>
</tr>
<tr>
<td>Kastelein et al74; 2008</td>
<td>720; 30–75; familial hypercholesterolemia</td>
<td>Simvastatin + ezetimibe or simvastatin + placebo</td>
<td>2 y</td>
<td>- No significant difference between groups</td>
</tr>
<tr>
<td>VYCTOR75; 2009</td>
<td>90; 40–72; high-risk patients</td>
<td>Pravastatin + ezetimibe or simvastatin ± ezetimibe</td>
<td>1 y</td>
<td>- Dual therapy has a beneficial effect on CIMT (pravastatin: changed from 1.33 ± 0.32 mm to 0.93 ± 0.13 mm; simvastatin + ezetimibe: changed from 1.30 ± 0.29 mm to 0.90 ± 0.11 mm; simvastatin alone: changed from 1.23 ± 0.28 mm to 0.92 ± 0.01 mm; all P &lt; 0.01; intragroup analysis). - Changes correlated with changes in LDL-C and total cholesterol levels.</td>
</tr>
<tr>
<td>ARBITER 276; 2004</td>
<td>167; mean, 67; history of CVD and already receiving statins</td>
<td>Statin + niacin or placebo</td>
<td>1 y</td>
<td>- Combination therapy resulted in an NS progression in CIMT (P = 0.23), whereas CIMT significantly increased (mean, 0.044 mm) in the monotherapy group (P &lt; 0.001). - CIMT changes correlated with CV events (3.8% of patients on combination therapy and 9.6% on monotherapy experienced CV events).</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>N; Age, y; CVD Risk Factors</th>
<th>Intervention</th>
<th>Duration</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER 3(^\text{77}); 2006</td>
<td>130; mean, 67; completed ARBITER 2</td>
<td>Statin + niacin</td>
<td>1 y</td>
<td>- Subjects who switched from placebo to niacin therapy had a regression of CIMT (−0.095 ± 0.019 mm; (P &lt; 0.001) vs placebo phase). - CIMT changes correlated with changes in HDL-C, LDL-C, and triglyceride levels.</td>
</tr>
<tr>
<td>ARBITER 6-HALTS(^\text{56}; 2010)</td>
<td>315; 65 y; CHD or CHD equivalent on long-term statin therapy</td>
<td>Niacin (2000 mg) or ezetimibe (10 mg) + statin</td>
<td>14 mo</td>
<td>- Treatment with niacin resulted in significant regression of CIMT (−0.0102 ± 0.0026 mm; (P &lt; 0.001)), whereas treatment with ezetimibe had no effect (−0.0016 ± 0.0024 mm; (P = 0.88); (P &lt; 0.016) between groups)</td>
</tr>
<tr>
<td>Taylor et al(^\text{79}; 2009)</td>
<td>208; 65; CHD or CHD equivalent on long-term statin therapy</td>
<td>Niacin (2000 mg) or ezetimibe (10 mg) + statin</td>
<td>14 mo</td>
<td>- Treatment with niacin resulted in significant regression of mean CIMT (−0.0142 ± 0.0041 mm; (P = 0.001)), whereas treatment with ezetimibe had no effect (0.0007 ± 0.0035 mm; (P = 0.84); (P = 0.01) between groups)</td>
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<tr>
<td>Antihypertensive and Antidiabetic Drugs</td>
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<td></td>
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<tr>
<td>STARR(^\text{86}; 2009)</td>
<td>1425; mean, 54; prediabetes</td>
<td>Rosiglitazone or ramipril</td>
<td>3 y</td>
<td>- Rosiglitazone significantly reduced CIMT (−0.0043 ± 0.0017 mm/y; (P = 0.01)) compared with placebo. - Ramipril had no effect on CIMT (−0.0020 ± 0.0017 mm/y; (P = 0.26)).</td>
</tr>
<tr>
<td>Napoli et al(^\text{80}; 2008)</td>
<td>48; mean, 43; newly diagnosed mild hypertension</td>
<td>Enalapril or zofenopril</td>
<td>5 y</td>
<td>- A significant reduction in CIMT occurred in the zofenopril group but not in the enalapril group ((P &lt; 0.01))</td>
</tr>
<tr>
<td>Mazzone et al(^\text{85}; 2006)</td>
<td>462; mean, 60; T2DM</td>
<td>Pioglitazone or glimepiride</td>
<td>72 wk</td>
<td>- Pioglitazone slowed mean CIMT progression compared with glimepiride (−0.001 vs 0.012 mm; (P = 0.02)).</td>
</tr>
<tr>
<td>MITEC(^\text{81}; 2009)</td>
<td>209; 40–74; mild-to-moderate hypertension with treated T2DM</td>
<td>Candesartan or amlodipine</td>
<td>36 mo</td>
<td>- CIMT regression was observed in 56.5% of patients receiving candesartan and in 59% of those receiving amlodipine ((P = 0.820) between groups)</td>
</tr>
<tr>
<td>ELSA(^\text{82}; 2002) (data reanalysis 2009)</td>
<td>2334; mean, 56; mild hypertension</td>
<td>Lacidipine or atenolol</td>
<td>3.75 y</td>
<td>- Lacidipine significantly reduced the progression of CIMT compared with atenolol. - Data re-analysis failed to show a predictive role of treatment-dependent CIMT changes.</td>
</tr>
<tr>
<td>AAA(^\text{83}; 2009)</td>
<td>104; mean, 68; Japanese patients with T2DM</td>
<td>Amlodipine or ARB</td>
<td>56.9 wk</td>
<td>- CIMT decreased more with amlodipine than ARBs (−0.046 vs 0.080 mm; (P &lt; 0.05)).</td>
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<tr>
<td>Other Lipid-Altering Drugs and Vitamin B Supplements</td>
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<tr>
<td>Zhu et al(^\text{87}; 2006)</td>
<td>225; mean, 60.3; hypertension and mild hyperlipidemia</td>
<td>Micronized fenofibrate 160 mg or placebo</td>
<td>2 y</td>
<td>- Fenofibrates prevented the progression of CIMT ((P &lt; 0.05)) and carotid atherosclerosis, and reduced the risk of stroke. - Changes correlated with changes in HDL-C, LDL-C, and triglyceride levels.</td>
</tr>
<tr>
<td>FIELD(^\text{88}; 2008)</td>
<td>170; 50–75; T2DM</td>
<td>Micronized fenofibrate 200 mg or placebo</td>
<td>5 y</td>
<td>- Fenofibrate treatment was not associated with regression of CIMT, augmentation index, or inflammatory markers</td>
</tr>
<tr>
<td>Chironi et al(^\text{89}; 2005)</td>
<td>373; mean, 56; dyslipidemia</td>
<td>Fibrate or statin for ≥ 3 mo</td>
<td>NA (matched cohorts)</td>
<td>- CIMT was greater with fenofibrate than with statins (0.65 vs 0.61 mm; (P &lt; 0.01)).</td>
</tr>
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</table>
The trials presented here and in Table 3 clearly show that statin monotherapy prevents the progression and induces the regression of CIMT in patients who are at risk for CVD; however, long-term treatment and aggressive drug therapy may be necessary to see this effect. The effects of statin monotherapy on CIMT are consistent with the well-known ability of statins to reduce the rate of CV events, implying that CIMT is a valid endpoint in the assessment of the efficacy of statin therapy. The combination studies suggest that the addition of niacin, but possibly not ezetimibe, to a statin slows CIMT progression and may promote CIMT regression. Further
research is necessary to clarify the effects of ezetimibe plus a statin on CIMT.

**Antihypertensive and Antidiabetic Drugs**

The effect of antihypertensive drugs (including calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) on CIMT has been extensively investigated, often in comparison with antidiabetic drugs (Table 3),\(^{80-83}\) and previously reviewed.\(^{84}\) Despite some variability in efficacy findings both within and between drug classes, the preponderance of evidence suggests that many antihypertensive drugs prevent the progression of CIMT, and in some instances, induce CIMT regression. Carotid intima-media thickness has also been used to determine the efficacy of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk. During an 18-month period, pioglitazone slowed mean CIMT progression of various diabetes therapies at reducing CVD risk.

**Other Lipid-Altering Drugs and Vitamin B Supplements**

The effects of drugs from other classes on CIMT have also been reported (Table 3). Fenofibrate, which increases HDL-C and reduces LDL-C and triglyceride levels, inhibited CIMT progression in patients with essential hypertension and mild hyperlipidemia in a clinical study.\(^{87}\) Although the common and internal CIMT remained unchanged during the trial, the CIMT-to-vessel diameter ratios were significantly reduced from baseline in patients who received fenofibrate \((P < 0.05)\), whereas these ratios increased in the control group.\(^{67}\) In contrast, a substudy of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial showed that CIMT and the augmentation index (a measure of large artery stiffness) increased equally in the fenofibrate and placebo groups over a 5-year period.\(^{88}\) Similar to the FIELD study, a nonrandomized observational study demonstrated a lipid-independent effect toward greater and steeper CIMT progression in patients treated with various fibrates compared with those treated with statins.\(^{89}\) It also should be noted that none of these fenofibrate studies specifically enrolled patients with mixed dyslipidemia, who are known to benefit most from fibrate therapy.\(^{90}\) Additionally, these studies were limited by their small size and relatively low baseline CIMT values, which could account for the lack of observed CIMT regression. An ongoing study, the Evaluation of Fenofoic Acid on Carotid Intima-Media Thickness in Patients With Type IIb Dyslipidemia With Residual Risk in Addition to Atorvastatin Therapy (FIRST) study, has been designed to address these shortcomings.\(^{91}\) The FIRST study will examine the effects of fenofibric acid in combination with a statin on CIMT in 682 patients with controlled LDL-C levels, elevated triglyceride levels, low HDL-C levels, and a baseline CIMT > 0.7 mm on ≥ 1 side.\(^{91}\)

The utility of CIMT as a surrogate marker for CVD risk was apparent in trials of torcetrapib (a cholesteryl ester transfer protein [CETP] inhibitor), although several of the studies were terminated early after preliminary data indicated progression of CIMT corresponding with an increase in CVD events.\(^{92,93}\) The Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor (RADIANCE) 1 and 2 trials showed that CIMT changes were similar in patients with mixed dyslipidemia\(^{92}\) and familial hypercholesterolemia\(^{94}\) who were randomized to treatment with either atorvastatin or atorvastatin plus torcetrapib (Table 3). A pooled analysis showed that mean common CIMT progression increased in patients receiving torcetrapib plus atorvastatin compared with patients receiving atorvastatin monotherapy \((0.0076 ± 0.0011 \text{ mm/y vs } 0.0025 ± 0.0011 \text{ mm/y}; P = 0.0014)\).\(^{95}\) In patients receiving combination therapy, an increase in LDL-C level was associated with less CIMT progression, whereas an increase in systolic blood pressure was associated with greater CIMT progression; HDL-C level increase was not associated with change in CIMT.\(^{95}\) Off-target effects of torcetrapib on blood pressure and electrolytes may have resulted in CIMT progression, as the between-treatment differences were diminished after adjustment for these factors.\(^{95}\)

Pactimibe (an acetyl-coenzyme A acetyltransferase inhibitor) showed promising results for the prevention of atherosclerosis in animal models, but similar to torcetrapib, was associated with increased mean CIMT in patients heterozygous for familial hypercholesterolemia (Table 3).\(^{93}\) Additionally, more CV events (death, MI, and stroke) occurred and there were significant increases in LDL-C and total cholesterol levels in patients receiving pactimibe compared with placebo \((P ≤ 0.02)\).\(^{93}\) As with torcetrapib, the clinical data for pactimibe suggest that CIMT progression corresponded with worse CV outcomes.

Information on the impact of other drug interventions on CIMT is limited but does lend additional support to the hypothesis that CIMT can be modulated by therapies that alter other CVD risk factors (Table 3).
Meta-Analyses of CIMT Testing as a Predictor of CV Events

In the absence of complete consistency from individual clinical trial findings, several meta-analyses have been conducted to clarify the potential value of CIMT testing for stratifying CVD risk and monitoring therapeutic effectiveness. Unfortunately, the meta-analyses themselves have not always reached consistent conclusions. A meta-regression analysis that pooled data from 28 clinical trials with nearly 16,000 patients found no relationship between changes in CIMT and nonfatal MIs, particularly in patients with high CIMT values at baseline and in trials that evaluated statin therapy.96 Similarly, an analysis of 41 clinical trials, which included data from >18,000 patients, found that regression or slowing of CIMT progression due to interventions was not accompanied by reduction in CV events.97 A recent meta-analysis that included approximately 37,000 patients and incorporated individual patient-level data from general-population cohort studies (rather than randomized trials) suggested that there was no association between CIMT progression and risk for CV events.98 In contrast to these studies, a meta-analysis by Espeland et al99 concluded that CIMT progression meets the criteria for an effective surrogate endpoint based on efficacy, association with endpoints, and congruency effects. Similarly, another meta-analysis of 8 clinical studies with >37,000 patients and a mean follow-up of 5.5 years determined that an absolute CIMT difference of 0.1 mm increased the future risk of stroke by ≤18% and increased the risk of MI by ≤15%.100 The largest meta-analysis to date (individual data from >45,000 patients in prospective cohort studies) concluded that CIMT testing modestly improved prediction of MI and stroke when added to FRS.101 Consistent with this, an analysis of 5028 subjects from the MESA found that a rate of CIMT increase of 0.05 mm annually was associated with a 23% increase in the risk of stroke.102 As described previously, data from the MESA also showed that CIMT predicted the risk of stroke more effectively than CAC scoring.58 These meta-analyses and other retrospective investigations only add to the growing debate of whether CIMT should be used as an efficacy endpoint in clinical trials. Furthermore, the findings could have been complicated by heterogeneity in how CIMT was measured, how endpoints were defined, and short follow-up in some studies. Prospective studies will be required to finally determine whether CIMT is an acceptable surrogate marker for the risk of CV events. In the following text and in Table 3, the application of CIMT as an efficacy endpoint for various CVD intervention therapies is reviewed.

Summary

Wider use of CIMT testing and better understanding of its use for CVD risk stratification may herald changes in the paradigm for CVD diagnosis and treatment. Due to the growing prevalence of obesity and metabolic syndrome in children and adolescents, early and accurate detection of CVD risk is increasingly important.103 A surrogate risk assessment method, such as CIMT testing, can allow patients to initiate lifestyle and pharmacologic changes early, possibly preventing progression to the high-risk category and reducing the risk of future CV events. Clinicians must explain the purpose of measuring CIMT to their patients, who otherwise may not understand why an ultrasound of arteries in the neck is relevant to the risk of sustaining an MI, stroke, or other CV event.

Carotid intima-media thickness testing is a safe, non-invasive, inexpensive method for detecting subclinical atherosclerotic plaques and carotid artery wall thickening. It independently helps to predict future patient risk for stroke and MI, is correlated with CV risk factors, and has become a widely used surrogate marker for the effect of interventions targeting atherosclerosis in clinical trials. Recent studies show that proper training and standardization of protocols make it feasible to obtain accurate CIMT measurements in the clinic using handheld ultrasound devices and border detection software. In the future, more research is needed to further standardize CIMT testing, to make it even more practical for use in clinics, to better assess its prognostic value in young patients (aged <25 years), and to delineate its additional value for CVD risk prediction in comparison with traditional factors and other atherosclerosis-detection techniques.

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Conflict of Interest Statement

Amy L. Doneen, MSN, ARNP, has served as a key opinion leader for Berkeley HeartLab, Inc. and as a consultant and speaker for Cleveland HeartLab, Inc. Bradley F. Bale, MD, has served as a speaker for Berkeley HeartLab, Inc., Cleveland HeartLab, Inc., Kowa Science Division, and Vasolabs, and as a consultant for Cleveland HeartLab, Inc.
References


CIMT Testing in CVD Risk Assessment


