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Clinical and Research Applications of Carotid Intima-Media Thickness

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Abstract

Cardiovascular imaging modalities such as coronary computed tomography, carotid ultrasonography, and cardiovascular magnetic resonance imaging are increasingly being utilized to measure cardiovascular disease progression. Imaging measures, most notably carotid intima-media thickness (CIMT), are being applied as surrogate markers for clinical endpoints such as myocardial infarction and death in clinical trials. Clinicians and their patients are faced with the challenge of evaluating these imaging measures for their efficacy and practicality in clinical practice, as well as in clinical trials. We conclude from a review of clinical trials and guidelines that CIMT measurement may be useful in evaluating cardiovascular disease risk in select patient populations but may not always be an appropriate surrogate for clinical endpoints. While CIMT has clear advantages over alternative cardiovascular imaging modalities, ultimately prospective trials comparing the effectiveness of CIMT as a predictive tool of cardiovascular risk with that of other novel markers would best direct clinical recommendations for this imaging measure.

Keywords

Carotid intima-media thickness; Atherosclerosis; Carotid arteries

Introduction

Advances in cardiovascular imaging have the potential to improve early detection of atherosclerotic vascular disease and quantify its progression. Clinicians and their patients are challenged with how best to integrate these emerging modalities into clinical practice and understand their implications as surrogate markers for clinical endpoints in trials. The use of carotid intima-media thickness (CIMT) as a surrogate marker of clinical events such as myocardial infarction exemplifies this challenge. The recent publication of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial has provoked debate over the use of CIMT as a surrogate endpoint in clinical trials and has called into question the use of a drug currently taken by millions of patients worldwide.[1] This article examines the utility of CIMT as a proxy for cardiovascular disease events and provides

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a framework for interpreting the results of the ENHANCE trial and other studies using CIMT as the primary endpoint.

CIMT Measurement

The American Society of Echocardiography (ASE) 2008 Consensus Statement on Carotid Intima-Media Thickness defines CIMT as the combined thickness of the intimal and medial layers of the far arterial wall of the carotid artery.[2] Carotid plaque is defined as focal arterial wall thickening that is at least 50% greater than the surrounding wall or a focal region of CIMT > 1.5 mm.[2] While standard carotid duplex ultrasonography is primarily used to identify occlusive carotid plaque (advanced atherosclerosis), CIMT assessment measures arterial wall thickening (pre-atherosclerosis) and non-occlusive plaque formation (subclinical atherosclerosis).

The ASE 2008 Consensus Statement has set forth guidelines for the measurement of CIMT (see Table 1 for full guidelines).[2] Carotid ultrasound imaging should follow a scanning and reporting protocol similar to those used in large research studies such as the Atherosclerosis Risk in Communities (ARIC) study,[3] using: a state-of-the-art ultrasound system; a standardized definition for carotid plaque; CIMT measurements taken exclusively from the far wall of the common carotid artery, with scanning of other portions of the carotid arteries only to search for carotid plaque; B-mode imaging in preference to M-mode imaging; 3-to-5 beat cine-loop and electrocardiographic R-wave gated still frames to optimize accuracy of CIMT measurements.

Normal CIMT values have been defined based on age and gender distribution curves within a general healthy population, as reported in the ARIC study (Table 2).[4] The ASE consensus statement concludes that CIMT values that are ≥ 75th percentile suggest risk higher than that predicted by the Framingham Risk Estimate (FRE), and should be regarded as “high” values.[2] Values that fall within the 25th to 75th percentile ranges are considered “average” and should not affect traditional risk estimates. Values that are ≤ 25th percentile are “low” and suggest risk lower than that predicted by the FRE.

CIMT and Cardiovascular Disease Risk

CIMT is associated with risk of stroke, myocardial infarction, and death from coronary causes in several large observational studies.[5] In the ARIC study, investigators examined the association between CIMT and coronary heart disease over 4 to 7 years in 12,841 individuals (57% women), aged 45–64, who were clinically free of disease at baseline.[4] Hazard ratios for coronary heart disease comparing individuals with mean CIMT ≥ 1 mm to individuals with mean CIMT < 1 mm, after adjustment for age, race, and study center, were 5.07 for women (95% CI, 3.08 – 8.36) and 1.85 for men (95% CI, 1.28 – 2.69). A systematic review and meta-analysis of eight large population-based observational studies (including over 37,000 patients) of CIMT and cardiovascular disease risk concluded that for an absolute CIMT difference of 0.1 mm, the future risk of myocardial infarction increased by 10%–15%, and the stroke risk increased by 13%–18%.[5]

While the data supporting CIMT association with coronary artery disease is strongest for individuals between the ages of 42 and 74, a few studies have demonstrated a strong relationship between risk factor burden and CIMT in younger individuals (18 to 42 years old).[6, 7] The Bogalusa Heart Study, a community-based epidemiological study of the early natural history of cardiovascular disease in children and young adults from the semirural, biracial community of Bogalusa, Louisiana, demonstrated an association of CIMT with an increased number of cardiovascular risk factors (smoking, high total cholesterol to HDL cholesterol ratio, high systolic blood pressure, large waist circumference, and high insulin level).[8, 9] Further,

increased CIMT is seen in individuals with familial hypercholesterolemia and the metabolic syndrome.[9–11]

Given the relationship between CIMT and traditional cardiovascular risk factors, it is important to consider whether CIMT offers incremental information beyond the risk factors. After adjustment for many possible confounders—age, race, study center, LDL cholesterol, HDL cholesterol, body mass index, sports activity, cigarette-years, hypertension, diabetes mellitus, ethanol use, and fibrinogen—the ARIC study showed hazard ratios for coronary heart disease comparing mean CIMT more vs. less than 1 mm to be 2.62 for women (95% CI, 1.55 – 4.46) and 1.20 for (95% CI, 0.81 – 1.77) (compare to numbers above, adjusted only for age, race, and study center), suggesting that CIMT may add prognostic information to risk prediction based on traditional risk factors, particularly in women.[4]

Even though CIMT is predictive of coronary heart disease, it is not clear how much the pathobiological processes underlying the 2 phenomena overlap. A novel locus on chromosome 9p has been identified as the strongest common genetic risk factor for myocardial infarction and coronary artery disease, and the same locus is associated with coronary artery calcification.[12, 13] However, this locus does not appear to be associated with CIMT,[14, 15] underscoring that CIMT is at least partly distinct from coronary atherosclerosis and thus will not fully mirror cardiovascular disease events, either in the context of a predictor of risk or that of a surrogate endpoint.

CIMT Versus Other Imaging Measures

Coronary artery calcification (CAC) measurement and cardiovascular magnetic resonance imaging (CMR) are 2 additional non-invasive imaging modalities used to assess atherosclerotic disease progression. A recent study from the Multi-Ethnic Study of Atherosclerosis (MESA) compared CAC to CIMT in predicting cardiovascular disease incidence in 6,698 individuals, aged 45 to 84, who were asymptomatic and free of cardiovascular disease at baseline.[16] The study found that compared to CIMT, CAC was more strongly associated with incident cardiovascular disease in the overall population. In the subgroup analysis of individuals with intermediate FRE scores, CAC was also more predictive than CIMT, with multivariable-adjusted hazard ratios of 1.8 (95% CI, 1.4 – 2.2) for the former and 1.4 (95% CI, 1.1 – 1.6) for the latter. In contrast, CIMT was found to be a modestly better predictor of stroke, perhaps the result of the difference between vascular territories targeted by the 2 measures. The major disadvantage of measurement of CAC compared to CIMT is exposure to ionizing radiation.

CMR provides high-resolution, 3-dimensional capabilities to measure atherosclerotic plaque burden in arterial walls. CMR has been used to assess atherosclerotic disease progression in the carotid arteries, aorta, and coronary arteries.[17] The technique also provides detailed information about plaque composition, which may eventually play a role in predicting plaque vulnerability to rupture.[18] Multiple studies of statin therapies have demonstrated both regression and decreased progression of atherosclerotic plaque as measured by CMR.[19–21] Compared to CIMT measurement, the major advantage of CMR is the ability to directly image the coronary arteries and perhaps characterize unstable plaques; the major disadvantage is the high cost of the study compared to ultrasonography.[22]

CIMT as an Endpoint in Trials

Observational studies and interventional trials using adverse cardiovascular events such as myocardial infarction and death from cardiovascular causes as endpoints often require large populations, years of follow-up, and considerable financial resources. With the establishment of an association between CIMT and cardiovascular disease risk, an increasing number of trials are utilizing CIMT as a surrogate endpoint for clinical events. The clear advantage is that CIMT

allows investigators to monitor for changes in a study's endpoint with a therapy—progression or regression of CIMT—significantly earlier and with fewer participants than would be required with clinical endpoints such as myocardial infarction, reducing the time and expenses spent on the study. Compared to other imaging modalities, such as CAC, CMR, quantitative coronary angiography (QCA), and intravascular ultrasonography (IVUS) of the coronary arteries, CIMT measurement has the advantages of being non-invasive, radiation-free, relatively easy to acquire regardless of patient anatomy, relatively inexpensive, and reliant on widely available equipment.

Is CIMT a legitimate proxy endpoint for cardiovascular events? Espeland et al. examined whether CIMT fulfills established clinical and statistical criteria for surrogate endpoints.[23] The analysis was based on 7 placebo-controlled trials of statins, published between 1994 and 2002, that reported both CIMT and cardiovascular outcomes.[23] Two sets of criteria were used to evaluate surrogacy: Boissel et al. defined surrogacy with the 3 parameters of efficiency, linkage, and congruency;[24] Prentice's 4 criteria comprised the impact of the intervention on the endpoint, the impact on CIMT, the link between CIMT and cardiovascular events, and conditional independence between statin therapy and cardiovascular events given CIMT.[25] CIMT was judged to meet all 3 of the Boissel criteria but only the first 3 of the 4 Prentice criteria, with the exception of one meta-analysis study that was felt to support the fourth criterion.[26] Based on these analyses, the authors concluded that CIMT progression met accepted definitions of a surrogate marker for cardiovascular endpoints in statin trials.[23] The possibility remains that while statins reduce CIMT progression and cardiovascular events in tandem fashion, making the former a good surrogate for the latter, other lipid-modifying medications may not.

Two significant trials involving lipid-lowering therapy and CIMT that have since been published include The Measuring Effect on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial[27] and, more recently, the ENHANCE trial.[1] METEOR evaluated the effect of rosuvastatin on CIMT over 2 years in 984 asymptomatic low-risk individuals (middle-aged individuals with FRE ≤ 10%) with evidence of subclinical atherosclerosis. Rosuvastatin resulted in a nonsignificant regression of CIMT (−0.0014 mm/yr), in contrast to the progression of CIMT seen in the placebo arm (+0.0131 mm/yr; $P < 0.001$ for rosuvastatin vs. placebo).[27] The rosuvastatin group also experienced a 49% reduction in LDL cholesterol. While METEOR was not a clinical outcomes-based trial, the effect on CIMT was consistent with an expectation for improvement in clinical outcomes based on other statin-based trials. This expectation was borne out with the early termination of the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, in which an overwhelming clinical benefit was seen with rosuvastatin in primary prevention patients.[28]

The ENHANCE trial was published shortly after the release of the ASE Consensus Statement and has become one of the most provocative trials in cardiology.[1] The investigators conducted a double-blind, randomized trial over 2 years comparing the effects of simvastatin paired with a placebo vs. the combination of simvastatin and ezetimibe in patients with familial hypercholesterolemia. The primary endpoint was the change in the mean CIMT thickness (average of the means of the far-wall intima-media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries). The mean CIMT thickness was 0.0058 mm in the simvastatin-only group and 0.0111 mm in the simvastatin plus ezetimibe group, with a difference in means of 0.0053 mm ($P = 0.29$). The apparent 47% increase in CIMT in the combination group compared to the simvastatin-only group—which was not statistically significant—led to public statements by thought leaders in cardiology and by the mass media denouncing the use of ezetimibe as potentially increasing risk of cardiovascular disease.

ENHANCE undoubtedly drew much attention because it was one of the first trials to demonstrate an apparently negative—albeit not statistically significant—effect of a lipid-lowering agent on a surrogate for cardiovascular disease events. What has not received as much attention as the negative CIMT findings of ENHANCE is the unambiguous improved reduction in LDL cholesterol in the combination group compared to the simvastatin-only group (16% increased reduction in LDL cholesterol).[1] Reduction of these markers in statin trials have been consistently associated with reduction of rates of cardiovascular events.[29] Thus, ENHANCE showed a discordance between 2 widely used surrogates for cardiovascular events—LDL cholesterol and CIMT—and it remains unclear which is the "correct" surrogate in this trial.

ENHANCE demonstrated both the need for standardization of CIMT protocols and the potentially serious consequences for clinical practice if surrogate markers are inappropriately utilized. To exclude ezetimibe based on nonsignificant changes in CIMT alone in a study where about 80% of subjects were on prior lipid-lowering therapy—particularly when significant LDL cholesterol reductions were seen with the drug—seems premature. Ultimately, the ongoing clinical outcomes-based trial evaluating the combination therapy versus simvastatin alone in reducing post-acute-coronary-syndrome cardiovascular events [Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)] will more definitively establish whether ezetimibe has meaningful clinical efficacy,[30] as well as whether CIMT or LDL cholesterol was the "correct" surrogate in ENHANCE.

CIMT in Clinical Practice

While one big challenge faced by preventive cardiologists and their patients is how best to interpret the results of trials using CIMT as the primary endpoint, another challenge is how to integrate new imaging measures such as CIMT into clinical practice. The ASE concluded that measuring CIMT and identifying carotid plaque may be useful in evaluating cardiovascular disease risk in the following patient populations:[2]

- Individuals with intermediate cardiovascular disease risk (6%–20% 10-year risk of myocardial infarction by the FRE), to further define their cardiovascular disease risk and to guide therapy
- Patients with family history of premature cardiovascular disease in a first-degree relative
- Individuals younger than 60 years of age with severe single risk factor abnormalities (i.e., genetic dyslipidemias), who would otherwise not be candidates for pharmacotherapy
- Women younger than 60 years of age with ≥ 2 cardiovascular disease risk factors

The consensus statement also suggests that CIMT can be used if the "burden of subclinical vascular disease" is unclear or if evaluation for the degree of aggressiveness of therapy is needed.[2] CIMT measurement has not been recommended for patients in whom the results would not change treatment, such as in patients with established coronary atherosclerotic disease.

It is important to recognize that current recommendations for the clinical use of CIMT are based on observational studies. Further, the role of CIMT in an environment where a number of other novel markers, such as coronary artery calcium, hsCRP, and genetic polymorphisms, are being similarly advocated for clinical use remains unclear. Ultimately prospective trials comparing the effectiveness of CIMT as a predictive tool of cardiovascular risk with that of other novel markers would best direct clinical recommendations for this imaging measure.

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Table 1

American Society of Echocardiography 2008 Consensus Statement guidelines for carotid intima-media thickness (CIMT) measurement.[2]

Instrumentation and Image Display:

- The carotid arteries should be interrogated using a state-of-the-art ultrasound system with a linear-array transducer operating at fundamental frequency of at least 7 MHz. The typical pixel size with imaging at 4cm depth is approximately 0.11 mm.
- B-mode imaging is preferred over M-mode imaging (M-mode provides measurement of only a single point of thickness, rather than a segmental measurement).
- Digital images should be stored directly from the ultrasound system, rather than digitized video captures.

CIMT Imaging Protocol:

- Ultrasound images of the distal 1 cm of the far wall of each common carotid artery should be obtained and compared with values from a normative data set (Table 1).
- These measurements should be supplemented by a thorough scan of the extracranial carotid arteries for presence of carotid plaques.
- Transverse B-mode scan (3–5 beat cine-loop in each segment) from proximal common carotid artery (CCA) through middle of the internal carotid artery.
- Internal and external carotid artery Doppler recordings (one frame of each) at proximal 1 cm of each branch.
- Longitudinal plaque screen scan (3–5 beat cine-loop from at least 3 different angles in each segment) at near and far walls of CCA, bulb, and internal carotid artery (ICA) segments.
- CIMT imaging (3–5 beat cine-loop and optimized R-wave gated still frames at each angle) at distal 1 cm of each CCA.
- Mean CIMT values from the far walls of the right and left CCAs (mean-mean) should be reported.

Table 2

Carotid intima-media thickness values, adjusted for age, field center, race, and sex, adapted from the Atherosclerosis Risk in Communities Study.[4]

Variable	Intima media thickness (IMT) (mm)	
	Females	Males
All-site mean*		
Mean	0.68 (0.65, 0.71)**	0.77 (0.73, 0.81)
95th percentile	0.9800	1.1400
Third tertile	0.7057	0.8043
Second tertile	0.6070	0.6783
Carotid bifurcation		
Mean	0.78 (0.73, 083)	0.90 (0.85, 0.95)
Third tertile	0.8069	0.9358
Second tertile	0.6816	0.7729
Common carotid artery		
Mean	0.60 (0.62, 0.70)	0.74 (0.69, 0.79)
Third tertile	0.6296	0.6983
Second tertile	0.5425	0.5931
Internal carotid artery		
Mean	0.66 (0.62, 0.70)	0.74 (0.69, 0.79)
Third tertile	0.6794	0.7730
Second tertile	0.5733	0.6381

* mean IMT of the far wall for 1-cm lengths of the carotid bifurcation, internal and common carotid arteries, right and left

** mean IMT (95% confidence interval)