

# Carotid intima-media thickness for the practicing lipidologist

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Atherosclerosis;  
Statins

**BACKGROUND:** It is well known that cardiovascular disease is the number one killer of men and women in the United States and in many parts of the developed world. However, early detection of atherosclerosis remains a challenging area of research and development.

Stress echo and myocardial perfusion studies were not designed to be screening tests and the majority of literature using these tests is in populations with a high probability of disease. It must be emphasized that negative stress echo and stress MPI tests only imply a lack of flow limiting disease; they do not indicate lack of atherosclerotic disease. It is important to remember that when these tests are “negative,” the implication is favorable short-term prognosis rather than any implication regarding lack of disease.

In contrast, carotid intima-media thickness (CIMT) scanning protocols can detect atherosclerotic disease in early and asymptomatic stages. For a number of reasons reviewed in this article, CIMT may be a more optimal screening and risk-stratifying technology: CIMT directly visualizes vasculature unlike biomarkers such as LDL cholesterol, hsCRP, or PLA2.

**METHODS:** We performed medline searches for original articles and reviews of carotid IMT from 1985 to the present. We particularly emphasized large multi-center epidemiologic studies of the natural history of patients with carotid IMT measurements.

**CONCLUSION:** There is substantial evidence that CIMT is a suitable surrogate for the coronary tree. CIMT is also (along with coronary calcium scoring) recognized by the American Heart Association as a surrogate marker for coronary artery disease. A recent commentary by Stein, et al reviewed the comparison of CIMT to coronary calcium scoring, with favorable findings for CIMT especially in the healthy young and middle-aged populations, as well as women and African American individuals where coronary calcification has more limited utility. Recent findings of the Multi-Ethnic Study of Atherosclerosis indicate further that increased CIMT predicted CVD events in individuals without coronary calcification.

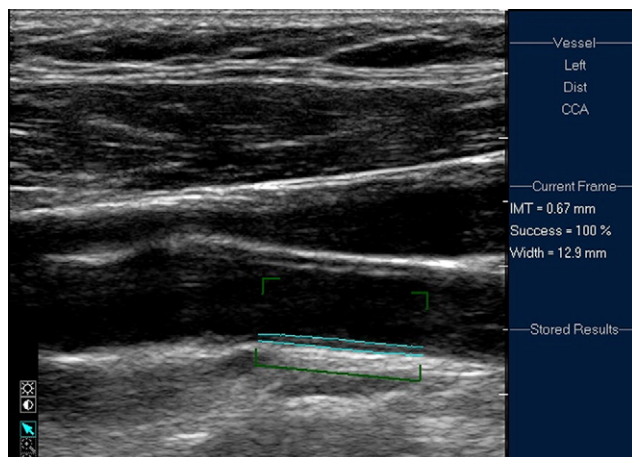
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Cardiovascular disease (CVD) is the number one killer of men and women in the United States, accounting for

more than 910,640 deaths per year—approximately 37.5% of all deaths in 2003. Furthermore, one third of all adults have some form of CVD. The financial burden of CVD in this country is impressive, with estimated direct and indirect costs at \$448.5 billion in 2008.<sup>1,2</sup> The

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**Figure 1** Shown is an example of measuring CIMT with a normal measurement, in this case 0.67 mm. Note the percent success is rated at 100%. The degree of success means the number of times that the software detects the intimal edge divided by the total number of measurements. By a mandate from the Food and Drug Administration, the percent success must be 95% or greater to be valid.

prevention of CVD would have a significant impact on morbidity, mortality, and also reduce cost. Hence it is now clear that a priority is to place greater emphasis on CVD prevention.

Many tests used to detect coronary artery disease at an earlier stage (for example stress echocardiography and stress myocardial perfusion imaging [MPI]) were not designed to be screening tests. They are instead primarily tests to evaluate patients with symptoms. In fact stress echo and stress MPI, along with coronary angiography, are most useful in patients with relatively advanced forms of disease. It must be emphasized that negative stress echo and stress MPI tests only imply a lack of *flow limiting* disease; they do not indicate lack of atherosclerotic disease. It is important to remember that when these tests are “negative,” the implication is favorable short-term prognosis rather than any implication regarding lack of disease.

In contrast, carotid intima-media thickness (CIMT) scanning protocols can detect atherosclerotic disease in early and asymptomatic stages. For a number of reasons reviewed in this article, CIMT may be a more optimal screening and risk-stratifying technology: 1) CIMT directly visualizes vasculature unlike indirect biomarkers such as low-density lipoprotein (LDL) cholesterol or even the more advanced biomarkers like high-sensitivity C-reactive protein or lipoprotein-associated phospholipase A2 (Lp-PLA2). 2) CIMT with plaque interrogation can be performed in any basic ultrasound ambulatory setting with favorable speed and cost factors after appropriate training. 3) CIMT can be easily quantified via automated boundary detection software, and the carotid interrogation is radiation free and thus safer than other imaging tests such as coronary calcium scoring or CT coronary angiography.

There is substantial evidence that CIMT is a suitable surrogate for the coronary tree.<sup>3–5</sup> CIMT is also (along with

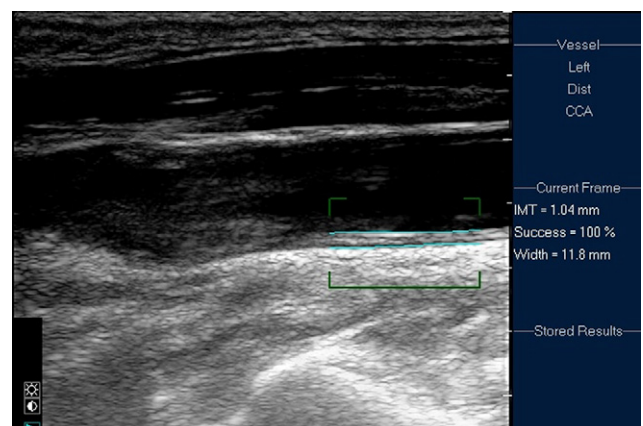
coronary calcium scoring) recognized by the American Heart Association as a surrogate marker for coronary artery disease.<sup>6,7</sup> A recent commentary by Stein et al<sup>8</sup> reviewed the strengths of CIMT compared to coronary calcium scoring. CIMT has particular advantages in the healthy young and middle-aged populations, as well as women and African American individuals. In contradistinction, coronary calcium scoring has limited value in these populations due to lack of or minimal coronary calcium. Recent findings of the Multi-Ethnic Study of Atherosclerosis indicate further that increased CIMT predicted CVD events in individuals without coronary calcification.<sup>9</sup> Many practitioners believe CIMT can be integrated into an existing practice of cardiac ultrasound with attention to quality control and detail.<sup>10</sup>

## CIMT: definition

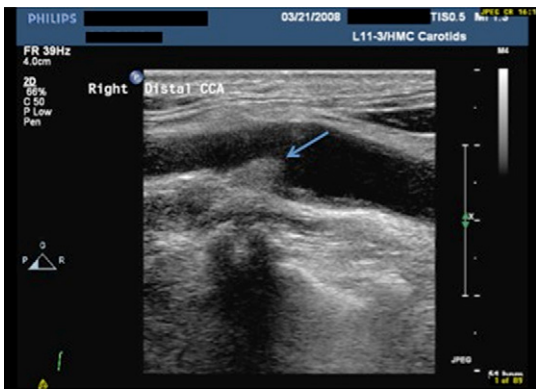
First described by Pignoli in 1986, IMT is defined as the measured distance between the luminal-intimal interface and the media-adventitial interface of the *common* carotid artery (CCA; see Figure 1).<sup>11</sup> More specifically, IMT is the double-line pattern visualized by B-mode vascular ultrasound formed by the two parallel lines of: 1) the junction of the vessel lumen with the intima and 2) the junction of the media with the adventitia.<sup>12</sup>

## CIMT methodology: Mannheim consensus and beyond

In 2004 a consensus panel gathered in Mannheim, Germany, to review the imaging and measurement of CIMT. Discrepancies appeared in the literature after the reporting of five major clinical trials that were based on IMT results, where each trial executed the scanning and measurement(s) with the use of different protocols. The five large trials reported somewhat-different associations between IMT and risk of stroke or myocardial infarction (MI)



**Figure 2** Example of measuring CIMT with an abnormal measurement, in this case, 1.0 mm.



**Figure 3** Shown is an example of CCA with plaque formation (arrow) in the distal CCA.

depending on whether the IMT was measured from the common carotid or internal carotid arteries.

More specifically, the Cardiovascular Health Study (CHS) reported that the relative risk of MI appeared greater with increasing internal CIMT compared with common CIMT, but the opposite appeared true for stroke risk.<sup>13</sup> In fact, the CHS found that IMT measurements in subjects varied three times as much in the internal carotid as compared with the common carotid.<sup>14</sup> Meanwhile, other IMT regression trials (ACAPS, ASAP, and BCAPS) would have reported negative outcomes if only the far wall common CIMT was measured.<sup>15–17</sup>

How can such variability between clinical trials be explained? The answer is that there clearly is more variability in the internal carotid as opposed to the common carotid. Although CIMT is easier to perform and less variable in its results, it is only part of the data needed to predict future relative risk. Important information is also contained in the arterial wall of the bulb and internal carotid segments, and the predictive information can be further enhanced by interrogating for early ultrasonographically defined plaque.<sup>18</sup>

The Mannheim Consensus<sup>19</sup> ultimately recommended that the most reliable IMT measurements are obtained from the distal 2 cm of the CCA, proximal to the bifurcation (Figs. 1 and 2), and preferably in a wall region that is free of plaque. The advantages of using this region of the CCA are that it usually lies close to the surface and runs relatively parallel to the skin. Plaque formation is less common in the CCA than either the bulb or the internal carotid artery (ICA), making it easier to find a plaque free area to measure the IMT. The ICA, on the other hand, is less superficial, does not run parallel to the skin of the neck, and is often high in the neck near the angle of the jaw. These factors make the ICA much more difficult to image in patients, and impossible in some, which helps explain why the incorporation of ICA measurement into overall IMT data leads to more variability in the reported results.

The Mannheim Consensus also defined plaque, which was described as a focal extrusion into the arterial lumen at

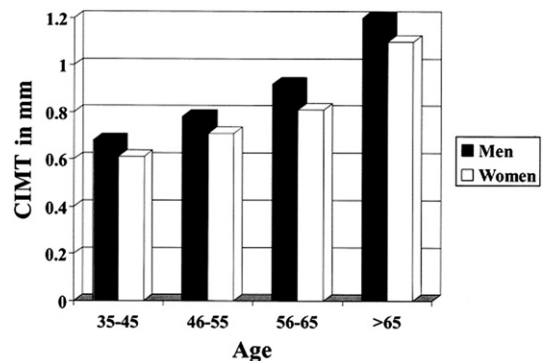
least 0.5 mm or 50% of the surrounding IMT value, or a thickness of >1.5 mm when measured in the same fashion as IMT (measured from the media adventitia interface to the intima-lumen interface; Fig. 3).<sup>19</sup> Limiting the carotid plaque interrogation to the CCA segment only, although technically easier than searching the bulb and internal segments, is not recommended<sup>10</sup> because it risks missing significant atherosclerosis in the distal segments where atherosclerosis actually progresses more rapidly. Furthermore, although the two processes—increasing IMT and plaque formation—share some common risk factors, their overlap is not identical, and their predictive power for cardiac and cerebral events differ. Indeed Brook et al<sup>20</sup> recently reported that the presence of carotid plaque (and particularly plaque surface area) is superior to CIMT alone for predicting the presence of coronary artery disease.

From a technical standpoint, the Mannheim consensus recommended B-mode transducers with a minimum frequency of 7 MHz, ideally greater than 10 MHz for optimal scanning characteristics. An optimal focus depth of 30–40 mm should be employed and frame rates greater than 15 Hz should be obtained. A minimum of 10-mm arterial length should be captured within the longitudinal scanning view. Today, high-end B-mode ultrasound systems far exceed the Mannheim recommendations.

## Normal CIMT

Before the development of symptomatic vascular disease in the coronary or carotid, the arterial wall can develop atherosclerosis. The intima-medial layer thickens and plaque forms long before there is significant stenosis. With continued remodeling, the vessel lumen may actually become slightly larger before it begins to narrow, emphasizing the limitation of angiography for detection of this process.<sup>21</sup> Plaque development is even seen in children and young adults, although not always in the presence of traditional risk factors.<sup>22</sup> Carotid ultrasound can detect all of these findings.

The average CIMT varies by age in large cross-sectional screens from 0.5 mm (500 microns) in the youngest to



**Figure 4** Bar graph showing the 75th percentile of CIMT on the basis of age and sex (Reprinted with permission from Redberg et al<sup>27</sup>).

**Table 1** Summary of prospective studies in which the authors examined the relationship between CIMT and cardiovascular and cerebrovascular events

Authors/studies	F/U, yrs	Event type recorded	Type of pt (n)	Unit of CIMT measurement, mm	Independent prognostic value/adjusted RR (95% CI)
Aboyans	3.5	MI, CVA, CV death, PVD surgery, coronary revascularization	CABG (609)	<0.9 vs. >0.9	No independent predictor
Benedetto	2.7	CV death	ESRD (138)	0.1	Yes 1.24 (1.06–1.44)
Bots/Rotterdam	2.7	MI and stroke	≥55 yrs (7983)	0.16	Stroke 1.41 (1.25–1.82) MI 1.43 (1.16–1.78)
Chambless/ARIC	4–7	MI, coronary death	General (12841)	0.19 CCA	Yes, M 1.32 (1.16–1.78) W 1.92 (1.66–2.22)
Chambless/ARIC	4–7	Nonfatal and fatal stroke	General (14214)	<0. vs. >1.0 mm	Yes, M 1.52 (1.28–1.80) W 1.72 (1.49–1.99)
Folsom	10.2	MI, coronary revascularization, CHD death	Diabetics (1500)	1.0	Yes, M 2.3 (not given) W 4.7 (not given)
Held, et al	3	Nonfatal MI or death	Angina (558)	<0.81 vs. >1.02	Yes 1.28 (0.59–2.78)*
Hodis/CLAS	8.8	Coronary death, nonfatal MI	CABG (146)	0.13 absolute CIMT 0.03 mm/yr	Yes, 1.4 (1.1–1.8) 2.2 (1.4–3.6)
Hollander/Rotterdam	6.1	Stroke	≥55 yrs (7983)	0.16	Yes, 1.28 (1.15–1.44)
Kato	5	CV mortality	ESRD (219)	0.1	Yes, 1.41 (1.12–1.78)
Kitamura	4.5	Stroke	60–74 yrs (1289)	≤0.77 vs. >1.08	Yes, 3.0 (1.1–8.3)
Lacroix	0.9	Worsening, recurrence of cardiac sx	PTCA pts (123)	≤0.7 vs. >0.7	No independent predictor
O'Leary/CHS	6.2	MI and stroke	≥65 yrs (4476)	0.2 CCA	Yes, 1.35 (1.25–1.45)
Lorenz	4.2	MI, stroke and mortality	19–90 yrs (5056)	0.16 CCA	Stroke 1.11 (0.97–1.28) MI 1.16 (1.05–1.27)
Murakami	3.2	All-cause and vascular mortality	>75 yrs (298)	0.2	Left 1.40 (1.05–1.85) Right 2.23 (1.27–3.91)
Nishizawa	2.5	CV mortality	ESRD (438)	<1.0 vs. 1.0–2.0	Yes, 3.17 (1.41–7.18)
Rosvall	7	MI or coronary death	46–68 yrs, no CVD (5163)	≤0.69 vs. >0.80	Yes, 1.50 (0.81–2.59)
Rosvall	7	Stroke	46–68 yrs, no CVD (5163)	≤0.69 vs. >0.80	Yes 2.54 (1.20–5.40)
Solomon/KIHD	1–3	Fatal and nonfatal MI	General population(1288)	IMT > 1	Yes, 1.1 (1.06–1.16)
Yamasaki	3.1	Angina pectoris and MI	DM type II (287)	>1	Yes, 4.9 (1.7–14.1)

CABG, coronary artery bypass grafting; CCA, common carotid artery; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CV, cerebrovascular; CVA, cerebrovascular attack; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease.

Table adapted with permission from Bots et al<sup>40</sup> and Dijk et al.<sup>24</sup>

\*After adjustment for risk factors such as age, smoking, previous MI, HTN, DM, and lipids, the association was not statistically significant RR 0.78 (0.36–1.71).

0.8 mm (800 microns) in the elderly. The thickness also varies by race and gender so that expected “normal” curves are best established for each major racial group by gender.

Baseline values of CIMT have been established based on cross-sectional scanning of the general, healthy population across all age distributions. The upper range of normal is often taken as the 75th percentile of IMT distribution for a given age, gender, and race/ethnicity of an individual and values above this threshold are indicative of increased cardiovascular risk.<sup>23,24</sup>

Because of different scanning protocols in the past, the absolute values of intima-media thickening reported from different sources, rather than normalized “percentile” figures, can at first seem inconsistent. Findings from the large epidemiologic study of Atherosclerosis Risk In Communities (ARIC trial), for example, report that IMT based on a protocol that incorporates all 3 carotid segments into the IMT calculation, above threshold value of 1.0 mm confers increased absolute risk of coronary heart disease.<sup>25</sup> Others have suggested the “normal” IMT range to be 0.5 to 1.2 mm.<sup>26</sup> Figure 4 shows data from Redberg regarding the 75<sup>th</sup> percentile CIMT on the basis of age and sex.<sup>27</sup> More recently, the ASE guidelines have published tables that include race in addition to age and sex.<sup>10</sup> We recommend using the ASE guidelines 75th percentile corrected for these variables as the upper limit for CIMT values to be considered “normal.”

## Change in CIMT over time

It is important to distinguish studies that report risk-predictive power for IMT established by single measurements in cross-sectional or epidemiologic populations from the clinical reports that have evaluated change in IMT over time. Most of the literature of the past 30 years is focused on single measurements for risk stratification, usually in asymptomatic populations, and well-established data exist in support of increasing cardiovascular risk with increasing IMT and/or findings of plaque burden.

Cross-sectional studies have reported apparent age-related increases in common CIMT of about 0.010 mm (10  $\mu$ m) per year in seemingly healthy men and about 0.014 mm (14  $\mu$ m) per year in seemingly healthy women, whereas in the ICA it is 10  $\mu$ m for both sexes.<sup>28</sup> Patients with known CAD, however, exhibit a tripling of CIMT progression rates over patients without known CAD, some 30  $\mu$ m/yr versus 10  $\mu$ m/year, respectively.<sup>29</sup>

## Baseline CIMT and correlation with stroke and MI: cross-sectional studies

There have been numerous investigations of the correlation of increased CIMT to the risk of stroke and MI (Table 1). A concise review of these older studies is provided by O’Leary and Polak.<sup>30</sup> Not surprisingly, an

increased single measurement of IMT correlates well with both outcomes. A typical example is the Kuopio Ischemic Heart Disease Risk Factor Study. This study quantified an increased MI risk of 11% for each 0.1-mm increase in CIMT.<sup>31</sup>

A recent meta-analysis by Lorenz et al<sup>32</sup> summarized the prediction of clinical cardiovascular events with IMT and found age and sex-adjusted overall relative risk of MI was 1.26 (95% confidence interval [CI] 1.21 to 1.30) per 1-standard deviation CCA IMT difference and 1.15 (95% CI 1.12 to 1.17) per 1-standard deviation CCA IMT difference. The same measures for stroke were 1.32 (1.27 to 1.38) and 1.18 (1.16 to 1.21), respectively.<sup>32</sup> Another large European prospective study<sup>33</sup> incorporating CIMT, plaque evaluation, and data from the common femoral IMT demonstrated significant predictive value of interrogating the vascular system for pre-clinical disease in low risk subjects.

Recently, the Multi-Ethnic Study of Atherosclerosis (MESA Study),<sup>9</sup> The Tromso Study,<sup>34</sup> and The Northern Manhattan Study<sup>35</sup> all confirmed the increased hazard ratios of the asymptomatic presence of increased CIMT and/or carotid plaque (defined as focal thickening >1.5 mm) as giving significantly increased hazard ratios for clinical end points.

Older well-known prospective cohort studies defining IMT and cardiovascular outcomes are the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study (CHS), and the Rotterdam study.<sup>26,36,37</sup> The largest of these, the Atherosclerosis Risk in Communities (ARIC) study, demonstrated strong correlation of CIMT and cardiovascular events in greater than 10,000 individuals, both male and female, with a mean follow up of 5.2 years. The age-adjusted risk of coronary heart disease increased with increasing CIMT and remained statistically significant despite adjustment for other risk factors. For a 0.19-mm increase in common CIMT, the relative risk for cardiac events was 1.36 (95% CI 1.23 to 1.51) in men and 1.69 (95% CI 1.50 to 1.90) in women, thus increasing the risk for coronary heart disease (CHD) 32% and 92%, respectively.<sup>25</sup> The risk for cerebrovascular disease was reported separately, demonstrating a graded relationship to CIMT. In fact, CIMT proved to be an even more powerful predictor of ischemic cerebrovascular accidents (CVA). The follow up for this data was 6-9 years, longer than the initial study, and the data demonstrated that the risk of CVA was 8.5 (95% CI 3.5 to 20.7) times greater in women with CIMT >1 mm in contrast to their age-matched counterparts with CIMT <0.6 mm. This relationship was more overt than for men, whose risk was 3.6 times greater (95% CI 1.5 to 9.2).<sup>36</sup>

The Cholesterol Lowering Atherosclerosis Study determined in a population of men aged 40 to 59 with known CAD that for each 0.03-mm increase per year in common CIMT, relative risk for nonfatal MI or coronary death was 2.2 (95% CI 1.4 to 3.6), with a relative risk for combined coronary events of 3.1 (CI 2.1 to 4.5). Therefore, for each 0.13-mm increment increase in CIMT, the risk for coronary

events increased 1.4-fold for any coronary event, and this change in CINT was an independent predictor of coronary events.<sup>23</sup>

CHS further examined the relationship between CINT and cardiovascular outcomes. This study examined a total of 4476 subjects over 6.2 years. The CHS group determined that an increase in 1 standard deviation in common CINT, internal carotid, and combined thickness was associated with a relative risk of 1.33 (95% CI 1.20 to 1.47) for the combined end point of MI or CVA, when adjusted for age, sex, and other traditional factors.<sup>13</sup> Thus, these increases in CINT were associated with 33% to 44% increases in combined event risk. The authors compared the relative strength of association between events and CINT as compared with the association between events and other traditional risk factors. This comparison demonstrated that CINT is a strong predictor of cardiovascular events.<sup>13</sup>

Increased CINT is associated with other well-known cardiovascular risk factors, including diabetes,<sup>37</sup> smoking, hypertension, hypercholesterolemia,<sup>38</sup> and the metabolic syndrome.<sup>39</sup> Bots demonstrated a graded relationship between the number of traditional risk factors and increased CINT.<sup>40</sup> Crouse in the *Journal of Lipid Research* compiled an extensive list of both traditional and nontraditional risk factors associated with CINT.<sup>41</sup>

The Bogalusa Heart Study is a long-term epidemiologic study of a cohort of young adults (mean age 32 years; 71% white, 39% male) from the semi-rural, biracial community of Bogalusa, Louisiana.<sup>26</sup> In this study, age, race (black more than white), high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and insulin were independent predictors of increased IMT in the common carotid and bulb segments. Sex (male more so than female) and body mass index were independent predictors of increased IMT in the internal carotid segment. Insulin and HDL cholesterol were inversely related to CINT.<sup>26</sup>

The role of CINT as an *independent* predictor for vascular events in patients with known disease, reflecting its usefulness as a surrogate marker in these populations, was questioned in a handful of studies.<sup>41–43</sup> Although in aggregate the data suggest that there is a graded relationship between increasing CINT and vascular risk, the relationship of CINT with clinical end points of MI or stroke might be reduced when this relationship is corrected for standard risk factors of age, dyslipidemia, smoking, previous MI, hypertension, and diabetes. However, the SMART study recently demonstrated a relationship between CINT and new vascular events even in patients with known, clinically significant and symptomatic coronary, cerebrovascular, or peripheral arterial disease.<sup>24</sup> The authors showed increased CINT was associated with a greater risk of vascular events, *independent* of classical vascular risk factors. The SMART study reinforced the relationship between CINT and the occurrence of new vascular events, primarily stroke. This finding mirrored the strength in the association of CINT with stroke specifically in other studies with broader inclusion criteria.<sup>20,38–40,44–46</sup>

## CINT as an end point in clinical trials

In 2002 the Food and Drug Administration recognized the progression of CINT as measured by B-mode ultrasound as a marker of atherosclerosis.<sup>47</sup> CINT has been used as an end point in clinical trials evaluating the efficacy of lipid, glycemic, and blood pressure control. In light of the strong and significant relationship between lipoprotein levels and carotid intima-media thickness,<sup>45</sup> we infer that reduction of lipoprotein levels and subsequent regression or slowed progression of atherosclerosis as visualized by CINT leads to reduction in ischemic events. However, a randomized controlled trial evaluating decreasing CINT risk progression on hard CVD events has not yet been reported, and no clinical trial has yet drawn a strong statistical relationship between changes in CINT induced by changes in LDL and subsequent reduction in major coronary events.

Examples of lipid-lowering studies and subsequent results are shown in [Table 2](#). The first of the trials to use B-mode ultrasound to follow changes in CINT as a marker for pharmacologic intervention on regression of atherosclerotic burden was the Cholesterol Lowering Atherosclerosis Study in 1993.<sup>23</sup> In this trial, the investigators compared cholestipol-niacin combination therapy versus placebo in a total of 146 men with known CAD after coronary artery bypass grafting and demonstrated less progression of CINT in the treatment arm. This trial was followed by a series of additional trials in which the investigators predominantly looked at the effects of statins, either in placebo-controlled trials or in head-to-head trials and consistently demonstrated slowed progression of CINT in the treatment arm.<sup>48–62</sup>

Two critical studies in which the investigators used CINT as a surrogate end point for treatment were ARBITER 1 and 2. In the ARBITER 1 trial, CINT was used to show that a high-potency synthetic statin, atorvastatin, resulted in more regression of plaque compared with pravastatin, a lower potency, naturally derived statin.<sup>49</sup> The ARBITER trials and the ASAP trial<sup>16</sup> were the first studies to report “more regression” with intervention rather than simply “less progression.”

In the ARBITER 2 trial, researchers examined secondary prevention in patients already treated with atorvastatin by adding niacin to the atorvastatin arm. Atorvastatin plus niacin resulted in enhanced regression compared with atorvastatin alone. Although the trial was not powered to detect significant differences in event rates, the trend was towards reduction of events.<sup>50</sup> A subgroup of ARBITER 2 patients continued an additional 12 months of combined statin and open-label Niaspan or switched to this pharmacologic intervention from statin plus placebo. These patients showed an increase in HDL cholesterol in patients who switched to Niaspan, and consequent atherosclerosis regression, with a mean reduction in CINT of 0.04 mm from baseline after 12 to 24 months of treatment with Niaspan.<sup>51</sup> The remainder of the studies and their results are summarized in [Table 2](#).

**Table 2** Lipid-lowering therapy on the progression of carotid atherosclerosis in randomized controlled trials, modified from American Society of Echocardiography with additions of Meteor, Enhance, and Arbitr 6

Authors/ studies	Treatment	Study length	Type of pt (n)	Site	CIMT results	Findings
Probstfield/ ACAPS	Lovastatin vs. placebo	3 years	Dyslipidemia, early carotid atherosclerosis (919)	CCA, bulb, ICA	Mean IMT: $-0.009 \pm 0.003$ mm/yr $P = .01$	Less progression with treatment
Hodis/CLAS	Colestipol-niacin vs. placebo	2 years	Men with previous CABG (146)	CCA	Mean IMT: treatment $0.64 \pm 0.13$ mm vs. placebo $0.64 \pm 0.13$ mm $P = .06$ , rate of change CIMT: treatment: $-0.024$ mm/yr vs. placebo: $0.021$ mm/yr	Less progression with treatment
Taylor/ ARBITER	Atorvastatin vs. pravastatin	1 year	ATP criteria for lipid lowering (161)	Far wall, CCA	Mean common atorvastatin: $-0.034 \pm 0.021$ mm vs. pravastatin: $+0.025 \pm 0.003$ mm $P = .03$	More regression with atorvastatin
Taylor/ ARBITER 2	Atorvastatin + Niaspan vs. atorvastatin + placebo	1 year	CAD, low HDL (167)	Far wall, CCA	Mean common niacin: $0.014 \pm 0.104$ mm vs. placebo: $+0.044 \pm 0.01$ mm $P = <.001$ , overall $P = .23$	Slowed progression with extended release niacin
Sawayama/ FAST	Probuocol vs. pravastatin vs. diet	2 years	Assx mg/dL (246)	CCA	Mean IMT (probuocol: $-13.9\%$ and pravastatin: $-13.9\%$ and $P < .01$ and $P < .01$ , respectively)	Less progression with probuocol or pravastatin than with diet
Byington/ PLAC-II	Pravastatin vs. placebo	3 years	CAD, elevated LDL (151)	CCA, bulb, ICA	Mean IMT $-0.0161$ , $P = .05$	Less progression with pravastatin
Smilde/ASAP	Atorvastatin vs. simvastatin	2 years	Familial Hypercholesterolemia, elevated LDL (325)	CCA, bulb, ICA	Mean IMT atorvastatin: $-0.031$ mm vs. simvastatin: $+0.036$ mm $P < .0001$	Less progression with atorvastatin
MacMahon/ LIPID	Pravastatin vs. placebo	4 years	MI or unstable angina and elevated TC (522)	CCA	Mean IMT: $-0.014$ mm/yr (0.11) over 4 years $P < .0001$	Less progression with pravastatin than placebo
Hedblad/ BCAPS	Metoprolol CR/XL and fluvastatin vs. placebo	3 years	Assx carotid plaque (793)	CCA, bulb, ICA	IMT (max), bulb and mean IMT (common) IMT (max) metoprolol: $-0.023$ mm/yr; Rate of mean IMT fluvastatin: $-0.009$ mm/y	Less progression with metoprolol XL, less progression with fluvastatin vs. placebo
Salonen/ KAPS	Pravastatin vs. placebo	3 years	Men, LDL $\geq 154$ mg/dL and TC $< 290$ mg/dL (447)	CCA, bulb	Mean IMT pravastatin: $+0.017$ mm/yr vs. placebo: $+0.031$ mm/yr $P = .005$	Less progression with pravastatin than placebo
De Groot/ REGRESS	Pravastatin vs. placebo	2 years	Men with angiographic CAD, TC 155–310 mg/dL	CCA, bulb, ICA	Mean IMT Pravastatin: $-0.05 \pm 0.22$ mm vs. no change in placebo, $P = .0085^*$	Less progression with pravastatin than placebo
Mercuri/ CAIUS	Pravastatin vs. placebo	3 years	Elevated LDL, one $1.3 < \text{IMT} < 3.5$ mm in the carotids (305)	CCA, bulb, ICA	Mean max IMT: $-0.0082 \pm 0.0031$ mm/yr	Less progression with pravastatin than placebo
Hodis/MARS	Lovastatin vs. placebo plus diet therapy	$\leq 4$ years	Angiographic CAD, TC 190–295 mg/dL (188)	CCA	Mean IMT lovastatin: $-0.028$ mm/yr vs. placebo: $-0.015$ mm/yr	Less progression with lovastatin than placebo

*(continued on next page)*

Table 2 Continued

Authors/ studies	Treatment	Study length	Type of pt (n)	Site	CIMT results	Findings
Taylor/ ARBITER3	Atorvastatin + Niaspan continued vs. atorvastatin + Niaspan from placebo	1 year	Patients continued from ARBITER 2	Far wall CCA	Mean CIMT $-0.04$ mm from baseline in all patients	Slowed progression with extended release niacin
METEOR	Rosuvastatin vs placebo	2 years	Patients with age (mean, 57 years) as only CAD risk factor or FRS $<10\%$ , CIMT 1.2-3.5 mm		Mean CIMT of common carotid 0.0004. Max CIMT change $-0.0014$ for rosuvastatin group vs. 0.0131 for placebo group.	Slowed progression, but did not meet criteria for regression
ENHANCE	Simvastatin vs Simvastatin plus ezetimibe	2 years	Mean age 46 with familial hypercholesterolemia, and low (7.2 and 3.9%) incidence of MI	6 sites, left and right CCA, ICA, and carotid bulb, far wall	Mean CIMT difference at 24 mo: Simvastatin alone: $0.0058 \pm$ $0.0037$ Simvastatin plus ezetimibe: $0.0111 \pm 0.0038$ , $P = .29$	No difference in change in CIMT
ARBITER 6	Statin plus niacin vs. Statin plus ezetimibe	14 months (terminate early)	Mean age 65 in patients with established coronary artery disease or equivalent	Far wall of right and left CCA	Mean CIMT difference at 14 mo Statin plus niacin: $-0.0142 \pm$ $0.0041$ Statin plus ezetimibe: $-0.0007$ $\pm 0.0035$ , $P = .01$	No change from baseline with ezetimibe, regression with niacin

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCA, common carotid artery; CIMT, carotid intima-media thickness; HDL, high-density lipoprotein; ICA, internal carotid artery; LDL, low-density lipoprotein; MI, myocardial infarction; TC, total cholesterol.

Table adapted with permission from Gottdiener et al. American Society of Echocardiography Recommendations for Use of Echocardiography in Clinical Trials J Am Soc Echocardiography 2004;17:1086.

\*The mean values for maximal IMT decreased by 0.005 mm in the pravastatin vs. 0.001 mm in placebo with a  $P < .0001$ .

As representative examples of CIMT and blood pressure lowering, two studies used CIMT to demonstrate the antiatherosclerotic benefits of beta blockade. First, the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque study (BCAPS) showed significant reduction in the progression of CIMT in asymptomatic patients treated with metoprolol CR/XL versus placebo over 1 year and was sustained over 3 years.<sup>52</sup> The Effects of Long-Term Treatment of Metoprolol CR/XL on Surrogate Variables for Atherosclerotic Disease (ELVA) trial randomized patients with hypercholesterolemia to metoprolol CR/XL 100 mg once daily or placebo once daily, both with concomitant fluvastatin therapy. The combined beta blockade and statin had a significantly lower rate of progression of CIMT versus statin alone. This result demonstrated that beta-blockers and statins affect different mechanisms in the atherosclerotic process and have additive effects.<sup>17</sup> Additionally, the ELSA, PREVENT, and SECURE trials all found similar reductions in progression of lesions with the use of calcium channel blockers and ACE inhibitors.<sup>53–55</sup> There have been other antihypertension trials in which the researchers administered diuretics; however, it is difficult to distinguish changes in CIMT caused by alterations in intravascular volume versus the long-term effects of blood pressure control on atherosclerosis.

In contrast to the previous studies, the METEOR trial (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin) enrolled low-risk, asymptomatic patients with early signs of atherosclerosis, with either age as the only risk factor or a 10-year Framingham risk score of less than 10%. This trial was designed to evaluate the effects of rosuvastatin on CIMT progression in asymptomatic patients with evidence of mild dyslipidemia and subclinical atherosclerosis.<sup>56</sup> This novel study defined atherosclerosis as CIMT  $\geq 1.2$  mm and  $<3.5$  mm with the primary end point defined as the change in CIMT from baseline. Treatment with rosuvastatin was associated with a statistically significant reduction in the rate of progression of CIMT both overall and for the individual carotid segments, whereas the placebo group showed progression. The change in maximum CIMT for the 12 carotid sites was  $-0.0014$  (95% CI  $-0.0041$  to  $0.0014$ ) mm/yr for the rosuvastatin group vs.  $0.0131$  (95% CI  $0.0087$  to  $0.0174$ ) mm/yr for the placebo group ( $P < .001$ ).<sup>57</sup> Although no reduction of clinical events was demonstrated, the message from this trial is that aggressive statin therapy slows the progression of atherosclerosis even in people with LDL levels that would otherwise not be treated.

The METEOR trial identifies a role for CIMT in the primary prevention of CHD. The findings of this study reflect the insidious nature of subclinical atherosclerotic disease and the presumed benefit from treatment in this demographic. Currently, the most powerful tool for establishing cardiovascular risk is the Framingham risk score and treatment decisions are made based upon estimated risk. Therefore, proposed use of CIMT is to enhance risk assessment beyond Framingham alone.

Of course no discussion of CIMT and clinical trials would be complete without mentioning the ENHANCE trial. The perceived premature release of the ENHANCE trial on January 9, 2008, as a press release by Merck & Co. and Schering Plough before its presentation at the 2008 meeting of the American College of Cardiology resulted in an eruption of controversy in the academic community as well as a congressional investigation.<sup>58</sup> The ENHANCE trial enrolled 720 patients with familial hypercholesterolemia and randomized them to simvastatin 80 mg versus simvastatin plus ezetimibe with a primary end point of CIMT progression from baseline. At the end of the 2-year study period, despite a trend favoring the statin only treatment arm, there was no difference ( $P = .29$ ) between the groups even though progression of CIMT was largely stopped in both arms of the trial.<sup>59</sup> Much has been discussed regarding this result,<sup>60,61</sup> but many experts believe that there could not be an improvement in outcome with more enhanced lipid lowering because the starting CIMT, an average of six segments (0.70 mm, SD 0.13 mm) was nearly normal and strikingly less than in ASAP (0.93 mm, SD 0.20 mm) for instance,<sup>16</sup> and in addition, 80% of the population had been previously treated with statin drugs, hence potentially limiting any additional benefit. Unfortunately, others have taken it to mean that the simvastatin plus ezetimibe combination is harmful. Because there was no statistically significant difference in adverse effects or in CIMT progression, this certainly cannot be concluded from the ENHANCE trial.

An even more recent CIMT trial, the ARBITER 6 trial, raises additional questions regarding lipid strategies that are mainly aimed at LDL-lowering, such as ENHANCE.<sup>62</sup> On the background of statin monotherapy and a baseline LDL  $<100$  and HDL  $<50$  in men and  $<55$  in women, ARBITER 6 randomized patients with coronary heart disease or the equivalent to the addition of either ezetimibe 10 mg or extended-release niacin (target dose, 2000 mg per day). The primary outcome was change in mean common CIMT from baseline to 14 months. Baseline CIMT was abnormal in this study at 0.90 mm in both groups. After 14 months of therapy, the mean CIMT thickness regressed in the niacin group ( $-0.0142$  mm  $\pm$  0.0041) but not in subjects treated with ezetimibe ( $-0.0007$  mm  $\pm$  0.0035;  $P = .01$ ). Although not powered to show a difference in clinical outcomes, major cardiovascular events were lower in the niacin group than in the ezetimibe group (1% vs. 5%,  $P = .04$ ).

Because there was no statin plus placebo group, it still cannot be concluded that ezetimibe is harmful but rather that statin plus ezetimibe is not as effective at reduction of CIMT as is statin plus niacin. The clinical outcome result is post hoc and was not part of the prespecified end points. Therefore, to truly determine the clinical outcome difference between statin plus placebo compared with statin plus ezetimibe, we must continue to await the result of the IMPROVE IT trial,<sup>63</sup> an outcomes trial that compares the same treatment arms as used in ENHANCE.

## CIMT and patient compliance

Very recently, the OPACA trial added information regarding the use of carotid imaging for patient motivation/compliance. In this trial, nonsonographer clinicians were given a 2-day training session at the core IMT laboratory. The nonsonographer clinicians were 3 physicians, 2 registered nurses, 2 medical assistants, and 1 emergency medical technician. These care givers were highly motivated to learn the technique of carotid ultrasound and had experience with its use in their respective outpatient clinics. Patients were provided with feedback about the results of their CIMT as well as presence of plaque. In fact, regardless of the result of the ultrasound, patients reported more motivation to change lifestyle, but when increased CIMT or plaque were present, patients reported higher likelihood of taking lipid lowering agents.<sup>64</sup>

## Guidelines for CIMT

Recently guidelines have been published regarding the recommendations for use of CIMT.<sup>10</sup> As would be expected the population of patients that the guideline committee recommended screening were those in the intermediate risk group for development of vascular disease, specifically, Framingham risk score 6% to 20% without established CHD, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, or abdominal aortic aneurysm. In addition, the recommendations include consideration for CIMT in the additional circumstances: 1) family history of premature CVD in a first-degree relative (men <55 years old, women <65 years old); 2) individuals younger than 60 years old with severe abnormalities in a single risk factor (eg, genetic dyslipidemia) who otherwise would not be candidates for pharmacologic therapy; or 3) women younger than 60 years old with a least two CVD risk factors. Finally, the guidelines discourage imaging in patients with established atherosclerotic vascular disease or if the results would not be expected to alter therapy. In particular, serial studies of CIMT to address progression were not currently recommended by the guidelines.

## Conclusions

CIMT is safe, noninvasive, and relatively inexpensive means of assessing subclinical atherosclerosis. Its advantage over coronary calcium scoring and coronary CT angiography is the lack of ionizing radiation and the ability to detect disease at a young age when coronary calcium score is often zero. CIMT is predictive of MI and stroke. The incremental value of CIMT over traditional risk factors is present but modest as demonstrated by a small increase in the area under the curve in receiver operating curves in two studies. The strong association with traditional risk factors questions the additional benefit from information gained from CIMT in discriminating low and high-risk

patients, while emphasizing CIMT importance in intermediate risk patients. However, recent data do show that patient compliance is enhanced when shown CIMT data.<sup>10,64</sup> CIMT has been successfully used as a surrogate end point in lipid-lowering trials and in that regard now has been used to show reduced progression even in a lower-risk group as demonstrated by the METEOR trial with rosuvastatin.<sup>57</sup> The main limitations of CIMT are ultrasound resolution, reproducibility of single measurement, and questionable accuracy of repeated measurements in clinical practice.

Recent enhancements to ultrasound systems and software refinements have largely eliminated the first two issues. Repeated CIMT measurements remains difficult because identification of the identical carotid segment on return visits is challenging. As a result, the use of CIMT in a lipid clinic for intermittent (perhaps annual) follow-up of patients with vascular disease currently is not advocated by guidelines. However, follow-up examinations are performed at some sites and may become an accepted practice in the future as the quality of ultrasound imaging and resultant inter-study variability continue to improve. The use of CIMT in clinical practice should adhere to standardized protocols and strict quality assurance. Furthermore, appropriate training of the sonographer performing the study and the practitioner interpreting the study should also be performed with appropriate updates in technique, technology, interpretation, and limitations.

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