Measurement of Carotid Intima-Medial Thickness as an Assessment of Subclinical Atherosclerosis using Ultrasound

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DESCRIPTION

Coronary heart disease (CHD) accounts for 30.8% of all deaths in the United States. Established major risk factors for CHD have been identified by the National Cholesterol Education Program (NCEP) Expert Panel. These risk factors include elevated serum levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol, and reduced levels of high-density lipoprotein cholesterol. Other risk factors include a history of cigarette smoking, hypertension, family history of premature CHD, and age.

The third report of the National Cholesterol Education Program Adult Treatment Panel established various treatment strategies to modify the risk of CHD, with emphasis on target goals of low-density lipoprotein cholesterol. Pathology studies have demonstrated that levels of traditional risk factors are associated with the extent and severity of atherosclerosis. The third report of the National Cholesterol Education Program Adult Treatment Panel recommended use of the Framingham criteria to further stratify those patients with two or more risk factors for more intensive lipid management. However, at every level of risk factor exposure, there is substantial variation in the amount of atherosclerosis, presumably related to genetic susceptibility and the influence of other risk factors. Thus, there has been interest in identifying a technique that can improve the ability to diagnose those at risk of developing CHD, as well as to measure disease progression, particularly for those at intermediate risk.

The carotid arteries can be well-visualized by ultrasonography, and ultrasonographic measurement of the carotid intima-media thickness (CIMT) has been investigated as a technique to identify and monitor subclinical arthrosclerosis. B-mode ultrasound is most commonly used to measure CIMT. The intima-media thickness (IMT) is measured and averaged over several sites in each carotid artery. Imaging of the far wall of each common carotid artery yields more accurate and reproducible IMT measurements than imaging of the near wall. Two echogenic lines are produced, representing the lumen-intima interface and the media-adventitia interface. The distance between these two lines constitutes the IMT.

Measurement of carotid intima-media (or intimal-medial) thickness (CIMT) is primarily meant to assess risk for future disease, and therefore can be evaluated as a prognostic measure. Assessment of a prognostic measure typically focuses on 3 categories of evidence: 1) technical reliable; 2) clinically valid (i.e. a test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response [beneficial or adverse]); and 3) clinically useful (i.e. demonstration that use of the prognostic information clinically can alter clinical management and/or improve net health outcomes compared with patient management without use of the prognostic tool). In some cases, it is important to evaluate whether the test provides incremental information above the standard workup to determine whether the test has utility in clinical practice.

Clinical Context and Test Purpose

The purpose of CIMT testing in patients who are undergoing cardiac risk assessment is to inform decision whether to monitor and/or intervene to treat those at increased cardiac risk.

Patients

The relevant patient population of interest is individuals undergoing cardiac risk assessment.

Comparators
Individual risk for cardiac events may be determined from multivariate risk models, such as the Framingham Risk Score.

Outcomes
The general outcomes of interest in CIMT measurement are to characterize the disease activity accurately and predict major adverse cardiac events, including stroke, myocardial infarction, and heart failure.

Timing
Five to ten-year studies are of particular interest due to prolonged natural history of cardiovascular disease.

Setting
The primary setting for CIMT measurement is an outpatient clinic.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Literature

Systematic Reviews and Meta-Analyses
(2021) Bytyçi et al published a meta-analysis of 89 studies and found that CIMT was significantly higher in patients with CAD versus controls ($p<.001$).7, A moderate correlation was found between CIMT and severity of CAD ($r = 0.60$; 95% CI, 0.47 to 0.70; $p<.001$) and the number of diseased vessels ($r = 0.49$; 95% CI, 0.36 to 0.59; $p<.001$). CIMT $\geq$ 1.0 mm had a summary sensitivity of 77% (range, 70% to 85%), summary specificity of 72% (range, 59% to 82%), positive predictive value of 82% (range, 80% to 83%), negative predictive value of 66% (range, 64% to 68%), and an accuracy of 76% (range, 74% to 77%) for predicting significant CAD. The results of this meta-analysis support the concept that atherosclerosis affects both carotid and coronary systems, although not always in identical phenotypic manner. These findings highlight the potential beneficial examination of carotid arteries whenever CAD is suspected. This systematic review and meta-analysis assessed the results of all studies using different imaging techniques to investigate the relationship between carotid and coronary atherosclerosis, the two most commonly affected systems by atherosclerosis. The large data set analyzed provided many comparisons and relationships that strengthened the relevance of the finding about pathological similarities of the two arterial systems. This meta-analysis is based on only four available clinical trials and the rest were observational/ cohort studies, however, the accuracy of the studies was high. The inclusion of all noninvasive imaging modalities might have contributed to the modest relationships we found because of their known limitations. It did not evaluate clinical outcome because of extended inclusion criteria and large data analysis as well as lack of

outcome data. Future studies may be required to determine the optimal cutoff of CP features in predicting CAD as well as cardiac events.

(2020) Kumar et al conducted a meta-analysis to clarify the association between CCA-IMT with the risk of stroke. The study included 19 studies; sixteen studies involving 3475 ischemic stroke (IS) cases and 11,826 controls; six studies with 902 large vessel disease (LVD) and 548 small vessel diseases (SVD) of IS subtypes; five studies with 228 intracerebral hemorrhage (ICH) and 1032 IS cases. The authors reported the results noted an association between increased CCA-IMT with risk of IS as compared to control subjects [SMD = 1.46, 95% CI = 0.90-2.02]. There was an increased risk of LVD as compared to the SVD subtype of IS [SMD = 0.36, 95% CI = 0.19-0.52] and more chance of occurrence of IS rather than ICH [SMD = 0.71, 95% CI = 0.28-1.41]. The authors concluded that carotid intima thickness measurements are associated with the risk of stroke and may be used as a diagnostic marker for predicting the risk of stroke events. Prospective studies embedded with larger sample size are needed to validate the findings

(2020) Tschiderer et al published a meta-analysis of seven prospective studies involving a total of 9341 participants, examining the extent to which CIMT predicts the incidence of carotid plaque in individuals free of carotid plaque at baseline. Individuals were recruited between 1987 and 2012, average age at baseline was 54 years, and 63% were female. Studies reported on 1288 incident first-ever carotid plaques, occurring over an average maximum follow-up of 8.7 years. When individuals in the top fourth of baseline carotid intima-media thickness distribution were compared with those in the bottom fourth, the pooled relative risk for incidence of first-ever carotid plaque was 1.78 (95% confidence interval: 1.53-2.07, P < .001, I 2 = 2.8%). The strength of association was not modified by mean baseline age, proportion of female participants, length of follow-up, year of baseline, and geographical location of the studies. In general population studies, elevated baseline carotid intima-media thickness is associated with incidence of carotid plaque in individuals free of carotid plaque at baseline. One limitation of the current analysis lies in the differences of cIMT and carotid plaque assessment. Furthermore, all studies involved participants of the general population. Hence, results might not be applicable to other populations (e.g., individuals at high cardiovascular risk). In addition, a significant weakness is the reliance on published information rather than original data. The use of literature-based results did not allow to investigate the effect of interim CVD events, which could have a potential impact on development of future carotid plaque due to initiation or modification of treatments or due to changes in lifestyle. An individual-participant-data meta-analysis would enable consistent strategies in data analysis and would thereby enhance comparability between studies.

(2020) Willeit et al preformed a meta-analysis of randomized clinical trials to explore CIMT progression as a surrogate marker for different types of CVD end points defined as myocardial infarction, stroke, revascularization procedures, or fatal CVD. The study included 119 randomized controlled trials that involved 100,667 patients with a mean follow-up of 3.7 years. Of those patients, 12,038 developed the combined CVD end point. A 10 μm/y slower CIMT progression was associated with a relative risk of 0.91

(95% CI, 0.87–0.94) for the principal outcome of CVD. The interventions reduced the CVD risk and resulted in relative risk of 0.92 (95% CI:0.87-0.97) independent of their effects on CIMT progression. The authors estimated that interventions reducing CIMT progression by 10, 20, 30, or 40 μm/y would yield relative risks of 0.84 (0.75-0.93), 0.76 (0.67- 0.85), 0.69 (0.59-0.79), or 0.63 (0.52-0.74), respectively. The authors concluded that the effects of interventions on CIMT progression and on CVD risk are associated. Study limitations were identified. The type of therapeutic intervention was different across the included trials which may affect the CIMT surrogate value and the individuals had different comorbidities.

(2018) Lorenz et al conducted a meta-analysis to assess the relation between CIMT change and events in individuals at high cardiovascular risk (results from the PROG-IMT collaboration above). From 31 cohorts with two CIMT scans (n = 89070) on average 3.6 years apart and clinical follow-up, subcohorts were drawn: A) individuals with at least three cardiovascular risk factors without previous CVD events; B) individuals with carotid plaques without previous CVD events; and C) individuals with previous CVD events. Cox regression models were fit to estimate the hazard ratio (HR) of the combined endpoint (myocardial infarction, stroke or vascular death) per standard deviation (SD) of CIMT change, adjusted for CVD risk factors. These HRs were pooled across studies. In groups A, B and C it was observed 3483, 2845 and 1165 endpoint events, respectively. The average common CIMT was 0.79mm (SD 0.16mm), and annual common CIMT change was 0.01mm (SD 0.07mm), both in group A. The pooled HR per SD of annual common CIMT change (0.02 to 0.43mm) was 0.99 (95% confidence interval: 0.95-1.02) in group A, 0.98 (0.93-1.04) in group B, and 0.95 (0.89-1.04) in group C. The HR per SD of common CIMT (average of the first and the second CIMT scan, 0.09 to 0.75mm) was 1.15 (1.07-1.23) in group A, 1.13 (1.05-1.22) in group B, and 1.12 (1.05-1.20) in group C. The authors concluded that although common CIMT is associated with future CVD event risk, this is not apparently true for common CIMT change over time; it is theorized that reasons may include the complexity of atherosclerotic process, and technical limits of current CIMT measurement.

(2013) Van den Oord et al completed a systematic review and meta-analysis by provided a review of the evidence on the association of CIMT with future cardiovascular events and the additional value of CIMT (carotid intima-medial thickness) to traditional cardiovascular risk prediction models. The association of CIMT with future cardiovascular events and the additional value of CIMT were calculated using random effects analysis. The literature search yielded 1196 articles of which 15 articles provided sufficient data for the meta-analysis. A 1 SD increase in CIMT was predictive for myocardial infarction (HR 1.26, 95% CI 1.20-1.31) and for stroke (HR 1.31, 95% CI 1.26-1.36). A 0.1 mm increase in CIMT was predictive for myocardial infarction (HR 1.15, 95% CI 1.12-1.18) and for stroke (HR 1.17, 95% CI 1.15-1.21). The overall performance of risk prediction models did not significantly increase after addition of CIMT data. The areas under the curve increased from 0.726 to 0.729 (p = 0.8). The authors concluded, the addition of CIMT did not statistically improve risk prediction over traditional cardiovascular risk factors.

(2012) Den Ruijter et al completed a meta-analysis to determine whether common CIMT (carotid intima-media thickness) has added value in 10-year risk prediction of first-time myocardial infarctions or strokes, above that of the Framingham Risk Score. Studies were included if participants were drawn from the general population, common CIMT was measured at baseline, and individuals were followed up for first-time myocardial infarction or stroke. It included 14 population-based cohorts contributing data for 45,828 individuals. During a median follow-up of 11 years, 4007 first-time myocardial infarctions or strokes occurred. They refitted the risk factors of the Framingham Risk Score and then extended the model with common CIMT measurements to estimate the absolute 10-year risks to develop a first-time myocardial infarction or stroke in both models. The C statistic of both models was similar (0.757; 95% CI, 0.749-0.764; and 0.759; 95% CI, 0.752-0.766). The net reclassification improvement with the addition of common CIMT was small (0.8%; 95% CI, 0.1%-1.6%). In those at intermediate risk, the net reclassification improvement was 3.6% in all individuals (95% CI, 2.7%-4.6%) and no differences between men and women. The authors concluded, the added value of common CIMT in 10-year risk prediction of cardiovascular events, in addition to the Framingham Risk Score, was small and unlikely to be of clinical importance.

(2012) Lorenz et al completed a meta-analysis on carotid intima-media thickness (CIMT) to predict cardiovascular events in the general population, the PROG-IMT collaborative project. They identified general population studies that assessed CIMT at least twice and followed up participants for myocardial infarction, stroke, or death. The study teams collaborated in an individual participant data meta-analysis. Excluding individuals with previous myocardial infarction or stroke, we assessed the association between CIMT progression and the risk of cardiovascular events (myocardial infarction, stroke, vascular death, or a combination of these) for each study with Cox regression. The log hazard ratios (HRs) per SD difference were pooled by random effects meta-analysis. Of the 21 eligible studies, 16 with 36,984 participants were included. During a mean follow-up of 7 years, 1519 myocardial infarctions, 1339 strokes, and 2028 combined endpoints (myocardial infarction, stroke, vascular death) occurred. Yearly CIMT progression was derived from two ultrasound visits 2-7 years (median 4 years) apart. For mean common carotid artery intima-media thickness progression, the overall HR of the combined endpoint was 0.97 (95% CI 0·94-1·00) when adjusted for age, sex, and mean common carotid artery intima-media thickness, and 0.98 (0·95-1·01) when also adjusted for vascular risk factors. Although they detected no associations with CIMT progression in sensitivity analyses, the mean CIMT of the two ultrasound scans was positively and robustly associated with cardiovascular risk (HR for the combined endpoint 1·16, 95% CI 1.10-1.22, adjusted for age, sex, mean common carotid artery intima-media thickness progression, and vascular risk factors). In three studies including 3439 participants who had four ultrasound scans, CIMT progression did not correlate between occasions (reproducibility correlations between r= -0.06 and r= -0.02). The authors concluded, the association between CIMT progression assessed from two ultrasound scans and cardiovascular risk in the general population remains unproven.

Summary
Evidence from prospective cohort studies has established that carotid intima-media thickness (CIMT) is an independent risk factor for CAD. However, systematic reviews and meta-analyses have shown that the use of CIMT data to reclassify patients into clinically relevant categories is modest and may not be clinically important. The uncertainty concerning the ability to reclassify patients into clinically relevant categories limits the potential for CIMT to improve health outcomes.

Prospective Cohort Studies
(2017) Geisel et al compared coronary artery calcification, carotid intima-media thickness (CIMT) and ankle-branchial index for predicting 10-year incident cardiovascular events in the general population, 3108 subjects (mean age 59.2 ± 7.7, 47.1% male). Associations with incident major CV events (coronary event, stroke, CV death; n = 223) were assessed during a follow-up period of 10.3 ± 2.8 years with Cox proportional regressions in the total cohort and stratified by Framingham risk score (FRS) groups. Discrimination ability was evaluated with Harrell's C. All three markers were associated with CV events (hazard ratio [95% confidence interval (CI)]: CAC: 1.31 (1.23-1.39) per 1-unit increase in log (CAC + 1) vs. CIMT: 1.27 (1.13-1.43) per 1 SD vs. ABI: 1.30 (1.14-1.49) per 1 SD, in FRS adjusted models). Considering reclassification, CAC led to highest reclassification in the total cohort, while also for CIMT and ABI significant improvement in net-reclassification was observed [NRI (95% CI): CAC: 0.55 (0.42-0.69); CIMT: 0.32 (0.19-0.45); ABI: 0.19 (0.10-0.28)]. The authors concluded, CIMT did not significantly improve the prediction of cardiac risk for patients with an intermediate Framingham Risk Score.

(2017) Villines et al prospectively assessed a cohort of 3801 African American (AA) patients free of CVD at baseline. At the baseline examination (2000 to 2004) of the Jackson Heart Study, AA adults 21 to 94 years of age (mean 54) underwent bilateral far-wall CIMT measurement (mean 0.76 mm). Incident CVD events were then assessed over 7 to 11 years of follow-up (2000 to 2011) from samples of 2,463 women (107 CVD events) and 1,338 men (64 CVD events) who were free of clinical CVD at baseline. Each 0.2-mm increase in CIMT was associated with age-adjusted incident CVD hazard ratios of 1.4 (95% confidence interval 1.2, 1.5) for women and 1.3 (1.1, 1.6) for men. Classification accuracy improved only slightly when comparing multivariable models that used traditional risk factors alone with models that added CIMT: C-statistics 0.837 (0.794, 0.881) versus 0.842 (0.798, 0.886) in women and 0.754 (0.683, 0.826) versus 0.763 (0.701, 0.825) in men. Similarly, risk reclassification was only mildly improved by adding CIMT: Net Reclassification Index 0.13 (p = 0.05) and 0.05 (p = 0.50) for women and men, respectively; Integrated Discrimination Improvement 0.02 (p = 0.02) and 0.01 (p = 0.26) for women and men, respectively. Risk reclassification improved only slightly when adding CIMT to a model that included only traditional risk factors for CVD.

(2015) Baber et al reported on the BioImage Study (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) sought to identify imaging biomarkers that predict near-term (3-year) atherothrombotic events. The BioImage Study enrolled

5,808 asymptomatic U.S. adults (mean age: 69 years, 56.5% female) in a prospective cohort evaluating the role of vascular imaging on cardiovascular risk prediction. All patients were evaluated by CAC (coronary artery calcium) score and novel 3-dimensional carotid ultrasound. Plaque areas from both carotid arteries were summed as the carotid plaque burden (cPB). The primary endpoint was the composite of major adverse cardiac events (MACE) (cardiovascular death, myocardial infarction, and ischemic stroke). A broader secondary MACE endpoint also included all-cause death, unstable angina, and coronary revascularization. Over a median follow-up of 2.7 years, MACE occurred in 216 patients (4.2%), of which 82 (1.5%) were primary events. After adjustment for risk factors, and compared with individuals without any cPB, hazard ratios for MACE were 0.78 (95% confidence interval [CI]: 0.31 to 1.91), 1.45 (95% CI: 0.67 to 3.14), and 2.36 (95% CI: 1.13 to 4.92) with increasing cPB tertile, with similar results for CAC. Net reclassification significantly improved with either cPB (0.23) or CAC (0.25). MACE rates increased simultaneously with higher levels of both cPB and CAC. The authors concluded, detection of subclinical carotid or coronary atherosclerosis improves risk predictions and reclassification compared with conventional risk factors, with comparable results for either modality.

(2010) Lorenz et al reported on 10-year follow-up of 4904 subjects from the Carotid Atherosclerosis Progression Study (CAPS) without pre-existing vascular disease included cardiovascular events and total mortality. Using Cox models and reclassification statistics, they investigated the usefulness of CIMT (carotid intima-medial thickness) in individual risk prediction beyond the Framingham and the SCORE models, using risk strata of 0-5, 5-10, 10-20, and $\geq$ 20% over 10 years. Carotid intima media thickness was significantly and independently predictive for cardiovascular events. Compared with a model using the Framingham risk factors, a second model that included the common CIMT led to the reclassification of 357 subjects (8.1%). In 107 subjects (30.0%), this reclassification was correct as confirmed with the actual outcome over 10 years. Net reclassification improvement was -1.41% (P = NS); integrated discrimination improvement was 0.04% (P = NS). More subjects were shifted to lower than to higher risk categories by the inclusion of CIMT. Analyses including other endpoint definitions, other carotid segments, and the SCORE risk model for baseline prediction did not result in consistently better risk prediction with CIMT. The authors concluded, despite CIMT being predictive for cardiovascular endpoints, it did not consistently improve the risk classification of individuals.

(2010) Raiko et al compared CAD risk scoring tools for identification of CHD risk with CIMT (carotid intima-medial thickness) results in 2204 healthy adults, ages 24 to 39 years from the Cardiovascular Risk in Young Finns study. The CVD risk scoring tools evaluated included the Framingham Risk Score, Reynolds Risk Score, Systematic Coronary Risk Evaluation (SCORE), PROCAM, and FINRISK. In this population-based follow-up study, the authors found all CVD risk scores performed equally well in predicting subclinical atherosclerosis, as measured by high CIMT 6 years later.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

(2011) Johnson et al prospectively studied the effects of office based carotid ultrasound screening (CUS) on physician decision-making and patient health related behaviors (HRBs). Physicians from 5 non-academic, community practices recruited patients ≥40 years old with ≥1 CVD risk factor. Abnormal carotid ultrasound screening (AbnlCUS) was defined as carotid intima-media thickness >75th percentile or carotid plaque presence. Subjects completed questionnaires before and immediately after CUS, then 30 days later to determine self-reported behavioral changes. Odds ratios (OR) for changes in physician management and patient HRBs were determined from multivariate hierarchical logistic regression models. There were 355 subjects (mean [standard deviation] 53.6 [7.9] years old, 2.3 [0.9] risk factors, 58% women); 266 (74.9%) had AbnlCUS. Presence of AbnlCUS altered physicians' prescription of aspirin ($p<0.001$) and cholesterol medications ($p<0.001$). Immediately after CUS, subjects reported increased ability to change HRBs ($p=0.002$), regardless of their test results. Subjects with AbnlCUS reported increased CVD risk perception (OR 4.14, $p<0.001$), intentions to exercise (OR 2.28, $p=0.008$), make dietary changes (OR 2.95, $p<0.001$), and quit smoking (OR 4.98, $p=0.022$). After 30 days, 34% increased exercise frequency and 37% reported weight loss; but these changes were not predicted by the CUS results. AbnlCUS modestly predicted reduced dietary sodium (OR 1.45, $p=0.002$) and increased fiber (OR 1.55, $p=0.022$) intake. Although this study performed a prospective intervention and each physician and patient served as their own control, it was not a randomized clinical trial, so a strategy of CUS was not compared to standard care or to CVD risk counseling alone. Randomized trials are needed to determine the long-term clinical effects of atherosclerosis screening on health-related behaviors and clinical outcomes; however, our observations suggest that the results of screening on patient behaviors are modest, at best. Such trials should be guided by behavioral theory to best identify patients who are most likely to respond to imaging feedback.

Summary
There is no direct evidence on the clinical utility of measuring carotid intima-media thickness (CIMT) for cardiac risk stratification. The available evidence on reclassification into clinically relevant categories does not indicate that use of CIMT will improve net health outcomes.

Miscellaneous
(Updated 2019; Reviewed through 11/2021) UptoDate noted numerous prospective epidemiological studies have shown that CIMT is a predictor of future cardiovascular events, independent of traditional risk factors. In addition, three systematic reviews and meta-analyses have reviewed the one-time and serial use of CIMT for CVD risk prediction.

- One-time CIMT measurement – In a systematic review and meta-analysis on the individual data of 14 studies of 45,828 asymptomatic individuals who underwent one-time CIMT measurement at baseline (median follow-up 10.8 years), the hazard ratio (per 0.10 mm adjusted mean common CIMT difference) for first myocardial infarction and stroke was 1.09 (95% CI, 1.07-1.12), for first myocardial infarction 1.08 (95% CI, 1.05-1.10), and for first stroke 1.12 (95% CI, 1.10-1.15) [10]. CIMT measures of other carotid artery segments and the presence of plaque showed similar relationships with future cardiovascular events.
    - While a one-time CIMT measurement can provide some predictive value for CVD risk assessment, they do not routinely perform CIMT measurement in most patients, preferring to use a standard cardiovascular risk assessment model based on traditional cardiac risk factors.

- Serial CIMT measurements – In a systematic review and meta-analysis on the individual data of 16 studies of 36,984 patients without known CVD who underwent serial CIMT measurement (mean follow-up seven years), in which the yearly progression rates were calculated for various CIMT measures (mean and maximum CIMT values of the common, bifurcation, and internal carotid arteries), there was no association between progression of CIMT and future events. These findings are corroborated by a more recent meta-analysis including 31 studies of 89,070 patients showing a consistent association between CIMT and the combined endpoint of myocardial infarction, stroke, and vascular death, while there was no association between CIMT change and vascular event risk. While there are various potential methodological as well as biological explanations, there is no proof of a relation between CIMT progression and future cardiovascular events.

Because of this, they do not recommend the use of serial CIMT measurements for the purpose of CVD risk assessment. (*Accessed December 2021)*

Summary of Evidence
For individuals who are undergoing cardiac risk assessment who receive ultrasonic measurement of carotid intima-media (or intimal-medial) thickness (CIMT), the evidence includes prospective cohort studies, systematic reviews, and meta-analyses. The results of these studies and reviews/meta-analyses have demonstrated the predictive value of CIMT is uncertain, and the predictive ability for any level of population risk cannot be determined with precision. Also, available studies do not define how use of CIMT in clinical practice improves outcomes. There is no scientific literature that directly tests the hypothesis that measurement of CIMT results in improved patient outcomes and no specific guidance on how measurements of CIMT should be incorporated into risk

assessment and risk management. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American College of Cardiology (ACC)/American Heart Association (AHA)
(2019) The American College of Cardiology (ACC)/American Heart Association (AHA) issued updated the 2017 guideline on the primary prevention of cardiovascular disease.

- This guideline does not include or indicate the use of CIMT as a routine measurement in clinical practice for the prevention of cardiovascular disease.

(*Accessed December 2021*)

(2013) The American College of Cardiology (ACC)/American Heart Association (AHA) issued a guideline on the assessment of cardiovascular risk which indicates, CIMT is not recommended for routine measurement in clinical practice for risk assessment for first atherosclerotic cardiovascular disease (ASCVD) event. (Grade N (No Recommendation for or against); Level of Evidence B (Limited populations evaluated; data derived from a single randomized trial or nonrandomized studies); ACC/AHA Class III (No benefit – procedure/test not helpful). (*Accessed December 2021*)

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)
(2010) The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) issued a practice guideline for the assessment of cardiovascular risk in asymptomatic adults which indicates, the measurement of carotid artery intima-media thickness is reasonable for assessment of cardiovascular risk assessment in asymptomatic adults at intermediate risk. The guidelines note an increased CIMT reading may be used as a guide in determining clinical utility, but evidence has not demonstrated improvements in outcomes when incorporating CIMT measurement into treatment decision making. Additionally, the guidelines state "clinical tools integrating carotid IMT within global risk scoring system are not available. The incremental value of carotid IMT and cost effectiveness beyond that available from standard risk assessments to improve overall patient outcomes is not established." (*Accessed December 2021*)

American Society of Echocardiography (ASE)
(2020) The ASE submitted a guideline and standard and the writing panel selected CIMT threshold value signifying plaque that is slightly more conservative than the Mannheim consensus by recommending $\geq$ 1.5 mm (vs >1.5 mm) as the cut-off CIMT threshold value for the presence of diffuse plaque. This newly established Plaque Grading Consensus, described in detail below, now allows for the identification and characterization of protuberant plaque lesions smaller than the CIMT threshold value for identifying diffuse plaque. In other words, we recognize that plaque lesions smaller than 1.5 mm can be highly resolved with today's technology. Advances in ultrasound now allow for identification of such small lesions in exquisite detail, allowing for both

quantification and even potential analysis of composition. Thus, this modern grading system sets a framework for continued outcomes-based research across the spectrum of plaque lesion shapes, sizes, and types.

- Recommendation #1: We recommend that carotid arterial plaque visualized by ultrasound (with or without use of an ultrasound enhancing agent [UEA]) be defined in one of the following 2 ways: 1) any focal thickening thought to be atherosclerotic in origin and encroaching into the lumen of any segment of the carotid artery (protuberant-type plaque) or 2) in the case of diffuse vessel wall atherosclerosis, when carotid intima-media thickness (CIMT) measures $\geq$ 1.5 mm in any segment of the carotid artery (diffuse-type plaque).
- Recommendation #2: We recommend the evaluation of both protuberant and diffuse types of carotid arterial plaque for cardiovascular risk stratification and the serial assessment of atherosclerosis.
- Recommendation #3: We recommend that first, the carotid arterial wall be visually scanned for the presence of protuberant plaque, and if absent, then carotid intima-media thickness (CIMT) measurement be performed to identify the presence of diffuse plaque (defined as CIMT $\geq$ 1.5 mm). If performed, CIMT should be measured as described in the ASE Consensus Statement on the Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Risk

(*Accessed December 2021*)

U.S. Preventative Services Task Force (USPSTF)

- (July 2018) The U.S. Preventative Services Task Force (USPSTF) updated their recommendation regarding cardiovascular disease risk assessment with nontraditional risk factors. This current recommendation states the following:

- Summary of Recommendation
  The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events.

- This recommendation currently does not include or address the use of carotid intima-medial thickness regarding cardiovascular disease risk assessment. (*Accessed December 2021*)

Regulatory Status

Device	FDA 510(k) Approval	Description
SonoCalc® (SonoSite)	February 2003	This software was substantially equivalent to existing image display products for use in the automatic measurement of the IMT of the carotid artery from images obtained from ultrasound

		systems. Subsequently, several other devices have been approved through the 510(k) process. FDA product code: LLZ.

This is not an all-inclusive list

PRIOR APPROVAL

Not applicable.

POLICY

Ultrasonographic measurement of carotid intima-media thickness (CIMT) as a technique of identifying subclinical atherosclerosis is considered **investigational** for use in the screening, diagnosis, or management of atherosclerotic disease.

Based on peer reviewed medical literature the available studies do not define how the use of carotid intima-media thickness (CIMT) in clinical practice improves outcomes. Also, there is no scientific literature that directly tests the hypothesis that measurement of carotid intima-media thickness (CIMT) results in improved patient outcomes and no specific guidance on how measurements of carotid intima-media thickness (CIMT) should be incorporated into risk assessment and risk management. The evidence is insufficient to determine the effects of this technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 93895 Quantitative carotid intima media thickness and carotid atheroma evaluation, bilateral

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POLICY HISTORY		
Date	**Reason**	**Action**
January 2022	Annual Review	Policy Renewed
January 2021	Annual Review	Policy Renewed
January 2020	Annual Review	Policy Renewed
January 2019	Annual Review	Policy Renewed
January 2018	Annual Review	Policy Renewed
January 2017	Annual Review	Policy Renewed
January 2016	Annual Review	Policy Renewed
January 2015	Annual Review	Policy Revised
February 2014	Annual Review	Policy Revised
March 2013	Annual Review	Policy Renewed
June 2012	Literature Review	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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